ヒドラゾンによるシクロプロパンの活性化を駆動力とする含窒素ヘテロ環合成法の開発

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薬品化学

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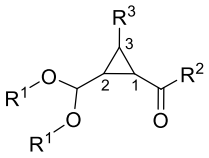
略語表

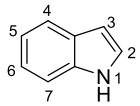
Ac	acetyl
aq.	aqueous
Ar	aromatic, aryl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bn	benzyl
CAN	ammonium cerium (IV) nitrate
CDI	1,1'-carbonyldiimidazole
CMD	concerted metallation-deprotonation
conc.	concentrated
Cp*	cyclopentadienyl
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]-7-undecene
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DFT	density functional theory
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EDG	electron-donating group
EWG	electron-withdrawing group
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
HRMS	high resolution mass spectrum
i	iso
m	multiplet
[M]	metal
Me	methyl

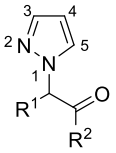
MOM	methoxymethyl
Mp	melting point
Ms	methanesulfonyl
MS	molecular sieve
MW	microwave
n	normal
NBS	*N*-bromosuccinimide
N.D.	not detected
N.R.	no reaction
NMR	nuclear magnetic resonance
Np	naphthyl
p	para
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
Piv	pivaloyl
Pr	propyl
q	quartet
quant.	quantitative
rt	room temperature
s	singlet
t	triplet
t, *tert*	tertiary
t-Amyl	2-methyl-2-butyl
TBS	tributylsilyl
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin-layer chromatography
tol	tolyl
Ts	toluenesulfonyl
p-TsOH	*para* toluenesulfonic acid
PTLC	preparative thin-layer chromatography
UV	ultraviolet

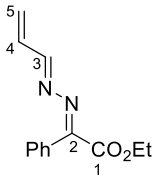
- 各化合物の命名は、原則として Chemical Abstracts の命名法に従ったが、スペクトルデータの記載は、慣用的なものを使用した。

- 本論文中の化合物の Numbering は下記のように統一した。







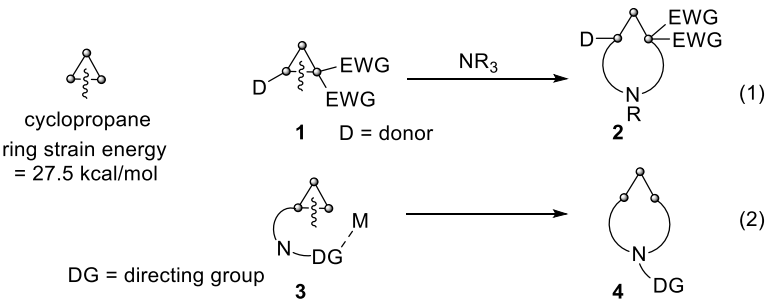


目次

実験

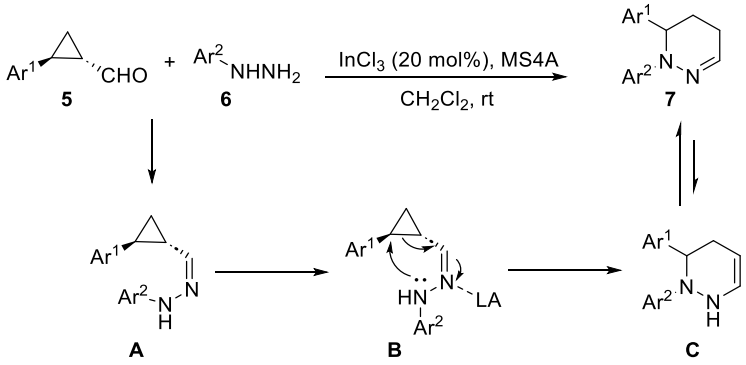
序論

含窒素ヘテロ環は医薬品の約 6 割に含まれている重要な骨格群であり、それらの短工程合成法の開発は創薬研究や医薬品製造の効率を高めるために重要な課題である。含窒素ヘテロ環の効率的な合成法として近年、シクロプロパンの開環反応を利用する手法が注目されている。[1] シクロプロパンは 27.5 kcal/mol のひずみエネルギーを持ち、このひずみエネルギーを解消するシクロプロパンの C-C 結合切断を伴う開環反応は、熱力学的に有利である。[2] そのため、シクロプロパンの開環は穏やかな反応条件で進行し、新たな活性中間体が生成することで、骨格変換を伴う官能基化や環拡大反応に展開できる。[3] このシクロプロパンの開環反応の特徴を利用することで、様々な含窒素ヘテロ環の効率的な合成法が報告されている。[4] シクロプロパンの開環反応を利用した含窒素ヘテロ環合成の代表例として、ドナー・アクセプター型シクロプロパンを用いる手法がある。[5] ドナー・アクセプター型シクロプロパンは電子供与基と電子求引基によって両置換基間の C-C 結合が大きく分極し、ヘテロリティックに切断されやすくなっているため、シクロプロパンの C-C 結合を位置選択的に切断することができる (Scheme 1、式 1)。[6] 分極の大きいドナー・アクセプター型シクロプロパンによる様々な含窒素ヘテロ環合成が報告されている。一方、比較的分極の小さいシクロプロパンに対しては遷移金属を用いる手法があり、シクロプロパンの開環に続く連続反応により含窒素ヘテロ環合成を達成した報告もある (式 2)。[7] これら代表的なシクロプロパンの開環反応では、一般にシクロプロパンを活性化するための官能基を事前に導入する必要があり、また不要な官能基が目的物に残留する場合があるため、導入や除去のための工程数の増大に伴う廃棄物・時間・労力の観点で課題がある。すなわち、上述したドナー・アクセプター型シクロプロパンを用いる際には、一般にアクセプター部位に 2 つの電子求引基が必要であり、多くの報告例において、これらの電子求引基が残されたまま環化生成物として得られる。[5,8] また、遷移金属を用いる手法では、シクロプロパンの位置選択的な開環反応を実現するために配向基が必要であることから、配向基がその後の変換に不要な官能基として残留することがほとんどである。[9]



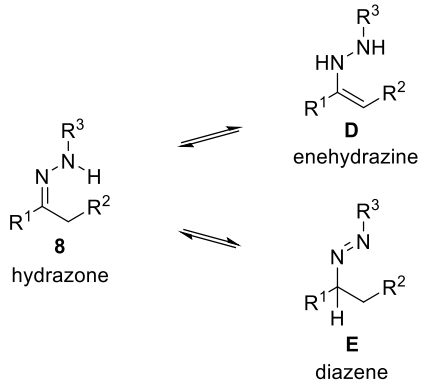
Scheme 1. Synthesis of nitrogen containing heterocyclic compounds via ring opening reaction of cyclopropanes.

そのため、シクロプロパン活性化のための官能基を、さらなる連続反応に巧みに利用することで、含窒素ヘテロ環の一部として取り込む反応が開発されている [10,11]。例えば Banerjee らはシクロプロピルアルデヒド **5** とアリールヒドラジン **6** から生成するシクロプロピルヒドラゾン **A** のシクロプロパンの開環に伴う分子内環化反応、エナミンーイミン互変異性化の連続反応によりテトラヒドロピロロ[1,2-*b*]ピリダジン **7** が合成できることを報告している (Scheme 2)。[12] この反応はルイス酸がヒドラゾン **A** のイミン部位へ配位し、イミンが強い電子求引性を示すことでシクロプロパンを活性化している。更にヒドラゾン部位が含窒素ヘテロ環に取り込まれていることから、シクロプロパン活性化の官能基が更なる連続反応に巧みに利用された反応となっている。



Scheme 2. Lewis acid catalyzed annulation of cyclopropane carbaldehydes and arylhydrazines.

以上の背景から今回著者は、シクロプロパンの活性化に必要な官能基として、以下に示すヒドラゾンの性質を利用することで、ヒドラゾンの窒素原子がヘテロ環内に取り込まれる新たな連続反応が実現できると考えた。ヒドラゾンはカルボニル化合物とヒドラジンの脱水縮合によって容易に合成可能な化学種で、イミン窒素にアミノ基が結合した構造を有している。この構造に起因して、ヒドラゾンは複数の互変異性体を介して特異な反応性を示す (Scheme 3)。ヒドラゾンのイミン構造に由来する互変異性体として、エンヒドラジンが存在する (イミンーエナミン互変異性) (**8** → **D**)。エンヒドラジンに含まれる N-N 結合は C-C, C-H, C-O, C-N といった一般的な有機化合物中に含まれる結合に比べると結合エネルギーが約 1/2 倍であるため、特定の条件下で容易に開裂する。[13] さらに、ヒドラゾンのアミノ窒素の孤立電子対が C=N 結合と共鳴することで、アゾ化合物との互変異性も存在する (アゾーヒドラゾン互変異性) (**8** → **E**)。[14] そのため、ヒドラゾンの C=N 結合は、一般的なイミンの C=N 結合よりも単結合に近い性質を有している。

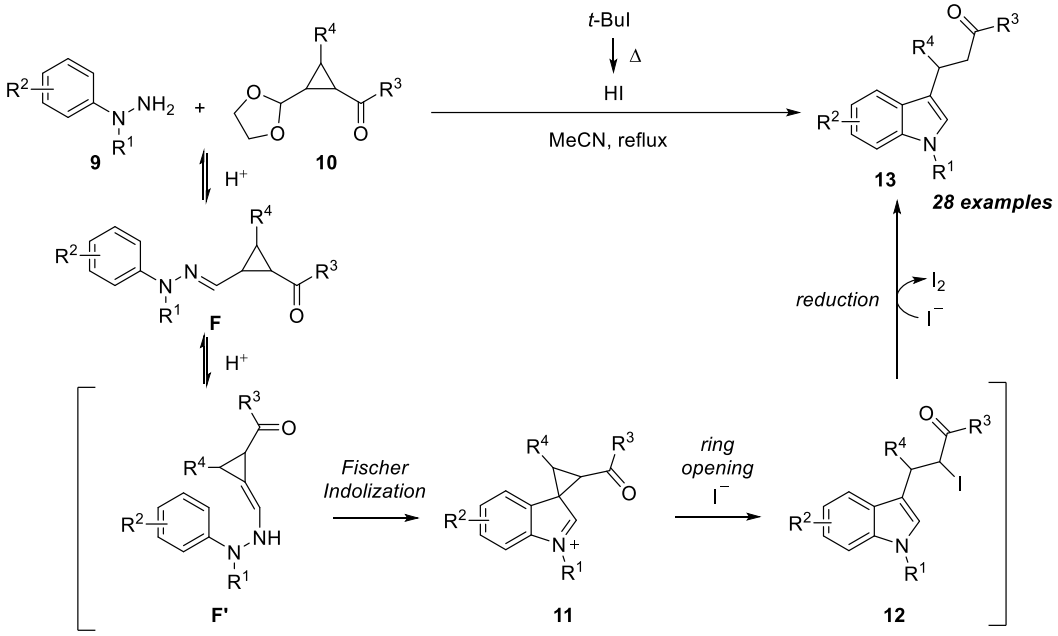


Scheme 3. Tautomers of hydrazones.

このように、ヒドラゾンは特異な性質を有しているにもかかわらず、シクロプロパンの活性化に利用された例は、前述したヒドラゾンを電子求引基として利用する例に限られていた。そこで、ヒドラゾンの互変異性化を利用したシクロプロパンの新規活性化法を開拓することで、工程数や原子効率の観点から優れた連続反応の開発、および含窒素ヘテロ環合成を実現できると期待した。すなわち、エンヒドラジンへの互変異性化を利用する手法では、N-N 結合の開裂を伴う連続反応が進行し、1 つの窒素原子が取り込まれた含窒素ヘテロ環を合成できる。また、ジアゼンへの互変異性化を利用する連続反応では N-N 結合含有ヘテロ環を合成することができると考えた。

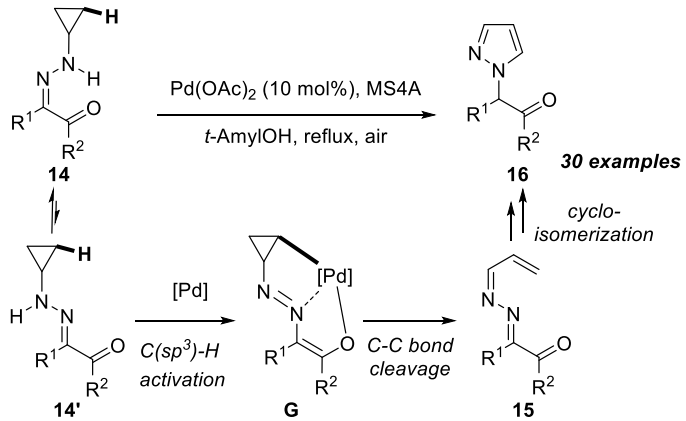
以上の概念に基づき、ヒドラゾンを用いたシクロプロパンの活性化に続く連続反応による含窒素ヘテロ環の新規合成法の開発に取り組み、本論文を 3 章にまとめた。

第 1 章ではまず、ヒドラゾンのエンヒドラジンへの互変異性化に続いてシクロプロパンを活性化する含窒素ヘテロ環合成に取り組んだ (Scheme 4)。すなわち、アリールヒドラジン **9** とシクロプロピルアセタール **10** をアセトニトリル還流中、ヨウ化水素発生源であるヨウ化 *tert*-ブチルで処理することで、3-アルキルインドール **13** が合成できることを見出した。反応機構解析の結果、本反応では、まずアリールヒドラジン **9** とシクロプロピルアセタール **10** からヒドラゾン **F** が生成する。続いてヒドラゾン **F** のエンヒドラジン **F'**への互変異性化を介した Fischer インドール化反応により活性中間体であるスピロシクロプロピルインドレニン **11** が生成すると考えている。その後ヨウ化物イオンのシクロプロパンへの求核攻撃と開環に続く還元反応により 3-アルキルインドール **13** が生成する。本反応はヒドラゾンがシクロプロパンの活性化だけでなく目的のインドールに取り込まれていることが特徴である。



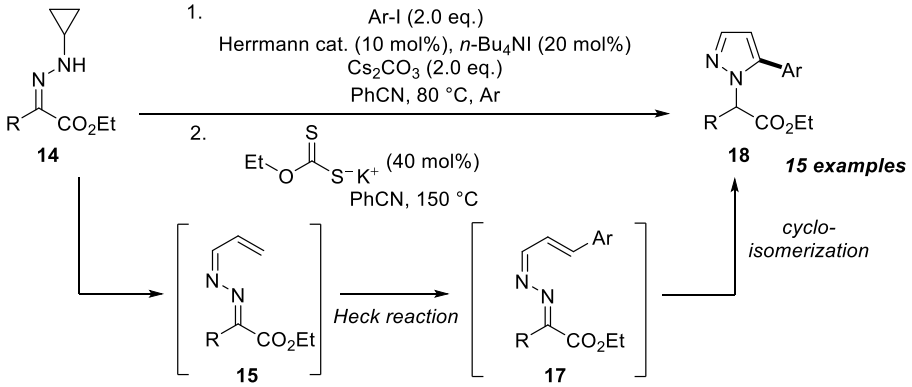
Scheme 4. Reductive indolization of *N*-aryl-*C*-cyclopropylhydrazone.

第 2 章ではヒドラゾンのアゾーヒドラゾン互変異性化する特徴と、イミン窒素の孤立電子対を利用することで、シクロプロパンを活性化する連続反応の開発に取り組んだ(Scheme 5)。すなわち、*N*-シクロプロピルアシルヒドラゾン **14** を酢酸パラジウムで処理することでピラゾール **16** が生成することを見出した。本反応はシクロプロピルヒドラゾン **14** が **14'**へ異性化したのちに、シクロプロパンの C(sp^3)-H 活性化が進行し、メタラサイクル **G** が生成する。さらに、メタラサイクルと縮環することで増大したシクロプロパン環のひずみエネルギーの解消を駆動力とすることで、シクロプロパンの開環に続く連続反応が進行し、アジン **15** が生成する。最後に、環化異性化反応が進行して、ピラゾール **16** が生成する。本反応ではアシルヒドラゾン構造がパラジウム触媒の配向基として機能し、シクロプロパンの開環反応が進行すると考えている。



Scheme 5. Pyrazole synthesis via C-H activation of *N*-cyclopropyl acylhydrazones.

第 2 章では様々な一置換ピラゾールの合成に成功したが、一方で二置換ピラゾールの合成は、原料である二置換シクロプロパンの合成に多くの工程を要することからより効率的な合成法への進化が必要である。そこで第 3 章では、本反応の中間体である共役アジンに Heck 反応で置換基を導入することで、二置換ピラゾールを簡便に合成できると考え、連続反応の開発に取り組んだ (Scheme 6)。すなわち、シクロプロピルヒドラゾン **14** と 2.0 当量のヨードアレーンをベンゾニトリル中、80 °C で 10 mol%の Herrmann 触媒と 20 mol%の *n*-Bu_4NI、2.0 当量の炭酸セシウムを用いて反応させた後、40 mol%のエチルキサントゲン酸カリウムを加え、150 °C で加熱撹拌することで 1-アルキル-5-アリールピラゾール **18** を合成した。本反応は第 2 章の反応と同様にパラジウム触媒によるシクロプロパンの開環が進行し、共役アジン **15** が生成する。続いて、アジン **15** への Heck 反応が進行し、5-アリール共役アジン **17** が生成し、最後に環化異性化反応が進行して 1-アルキル-5-アリールピラゾール **18** が生成する。本反応は 1 つの触媒が 2 つの反応サイクルを回転させるオートタンデム型の反応であることが特徴である。また、合成した 1-アルキル-5-アリールピラゾールは位置選択的または化学選択的に合成するのが難しい化合物群であることから、その効率的な合成法になると期待される。

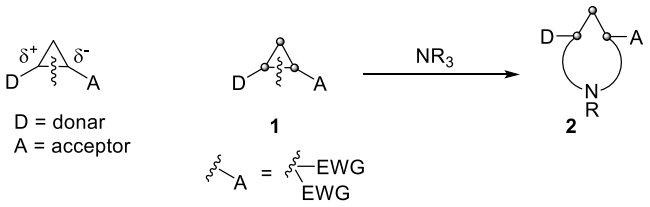


Scheme 6. Heck reaction of *N*-cyclopropyl acylhydrazones.

本論

第 1 章　*N*-アリール-*C*-シクロプロピルヒドラゾンの無水ヨウ化水素による還元的 Fischer インドール合成法の開発

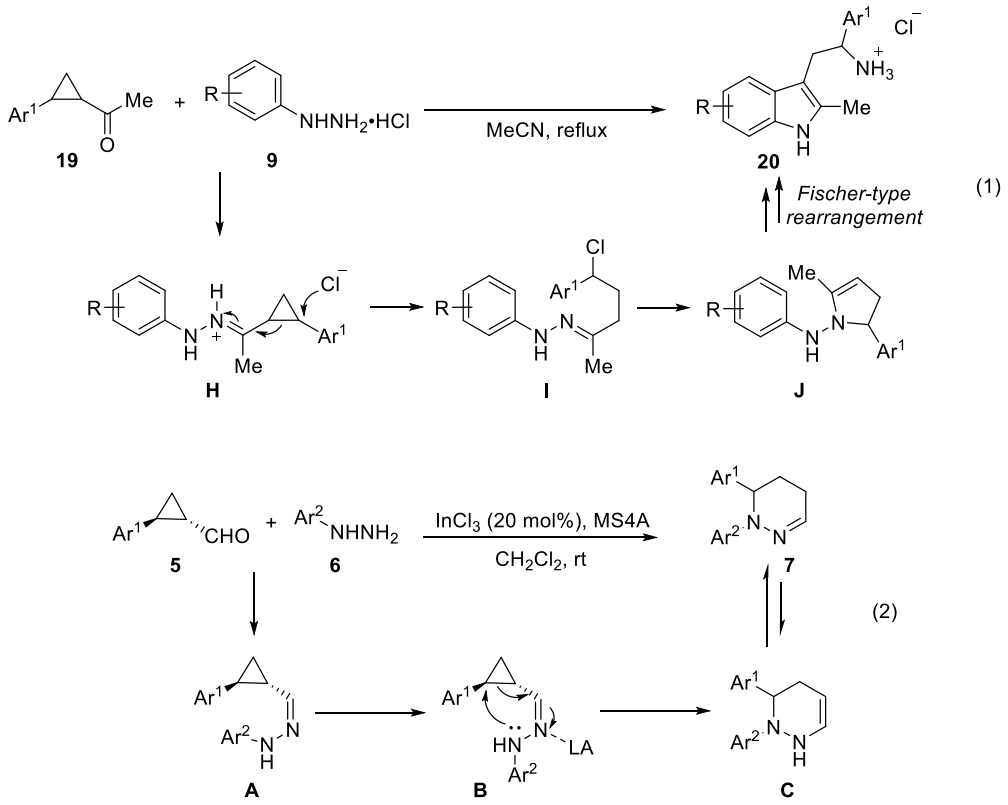
含窒素ヘテロ環は窒素原子と生体分子の活性水素との水素結合を容易に形成することができるため、生物活性物質に多く含まれ、医薬品の約 6 割に含まれている重要な骨格群である。さらに、含窒素ヘテロ環は、メディシナルケミストリーの分野でも注目されており、含窒素ヘテロ環を利用した新規医薬品候補化合物の創製に関する論文が多く報告されている。[15] そのため、含窒素ヘテロ環の短工程合成法の開発は創薬研究や医薬品製造の効率を高めるために重要な課題である。そのような含窒素ヘテロ環合成の効率的な合成法として近年、シクロプロパンの開環反応を利用する手法が注目されている。[1] シクロプロパンは 27.5 kcal/mol のひずみエネルギーをもち、この高いひずみを利用することで、比較的温和な条件で C-C 結合切断を伴う開環反応が進行する。[2] シクロプロパンの開環反応によって骨格変換を伴う官能基化や環拡大反応を可能にし、含窒素ヘテロ環を合成する際の 3 炭素ビルディングブロックとして用いられる。しかし、置換基をもたないものや、アルキル基が置換しただけの単純なシクロプロパンは反応性に乏しく安定であるため、ひずみエネルギーを利用した開環反応に利用するには、シクロプロパンを適切に活性化する必要がある。[3, 16] 中でもドナー・アクセプター型シクロプロパンを用いる手法が代表的であり、含窒素ヘテロ環の合成例も多く報告されている (Scheme 7)。[7] ドナー・アクセプター型シクロプロパンは電子供与基と電子求引基によって両置換基間の C-C 結合が大きく分極し切断されやすくなっているため、シクロプロパンの C-C 結合を位置選択的に切断することができる。[6]



Scheme 7. Synthesis of nitrogen containing heterocyclic compounds using donor-acceptor cyclopropanes.

一方でドナー・アクセプター型シクロプロパンのアクセプター部位には 2 つの電子求引基を有する場合が多く、基質適用範囲に未だ課題があるうえに 2 つの電子求引基が合成上不要な官能基として目的物に残留するため、導入や除去のための工程数の増大に伴う廃棄物・時間・労力の観点でも課題があった。[5, 8] そこで、残留する電子求引基を有効に利用する手法として、電子求引基をシクロプロパンの活性化だけでなく更なる連続反応に利用することで、含窒素ヘテロ環の一部に取り込む反応が開発されている。そのような電子求引

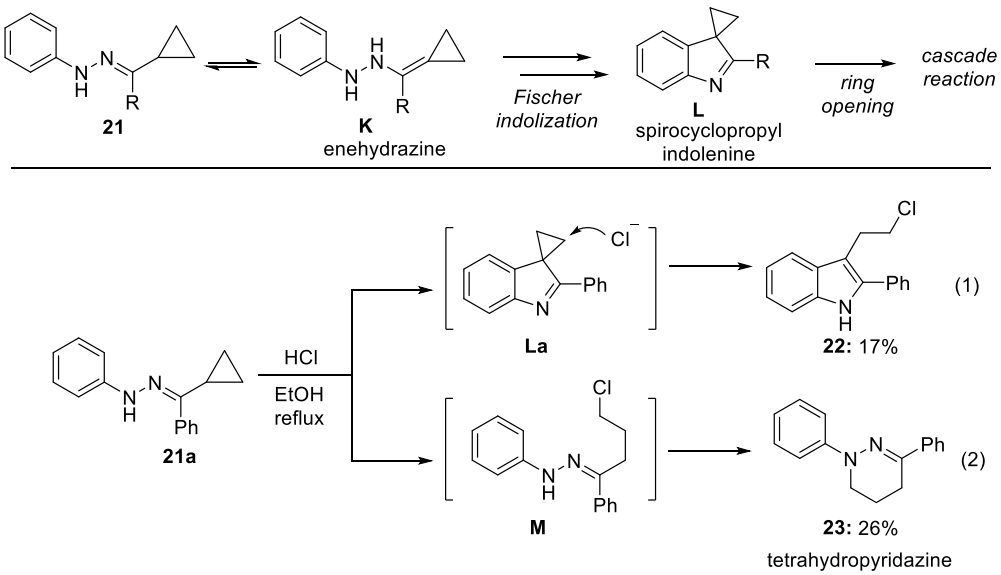
基の 1 つとして、ヒドラゾンが報告されている。Tomilov らはシクロプロピルケトン **19** とアリールヒドラジン塩酸塩 **9** を加熱条件に付すことで、生物活性物質に多く含まれるトリプタミン誘導体 **20** が生成することを報告している (Scheme 8、式 1)。[17] 本反応はシクロプロピルヒドラゾン **H** の塩化物イオンによるシクロプロパンの開環とそれに続く環化反応によりアリールアミノピロリン **J** が生成した後、Fischer 型の転位反応が進行することで、トリプタミン誘導体 **20** が生成している。また、Banerjee らはシクロプロピルアルデヒド **5** とアリールヒドラジン **6** から生成するシクロプロピルヒドラゾン **A** のシクロプロパンの開環に伴う分子内環化反応、エナミン－イミン互変異性化の連続反応によりテトラヒドロピロロ[1,2-*b*]ピリダジン **7** が生成することを報告している (Scheme 8、式 2)。[12] これらの反応では、系中で生成するヒドラゾンが酸性条件で電子求引基として働き、シクロプロパンが活性化されている。さらにヒドラゾンが含窒素ヘテロ環の一部として取り込まれており、ヒドラゾンの性質を巧みに利用することで連続反応を進行させることに成功している。



Scheme 8. Ring opening reaction of *C*-cyclopropylhydrazones.

一方で、ヒドラゾンにはイミン構造に由来する互変異性体として、N-N 結合を含むエンヒドラジンが存在する。N-N 結合は C-C, C-H, C-O, C-N といった一般的な有機化合物中に含まれる結合に比べると結合エネルギーが約 1/2 倍であるので、特定の条件下で容易に開裂する。[13] このようにヒドラゾンがエンヒドラジンへ異性化する性質を利用することで、前述とは異なる新たなシクロプロパンの活性化と連続反応の進行が期待できると考えた。

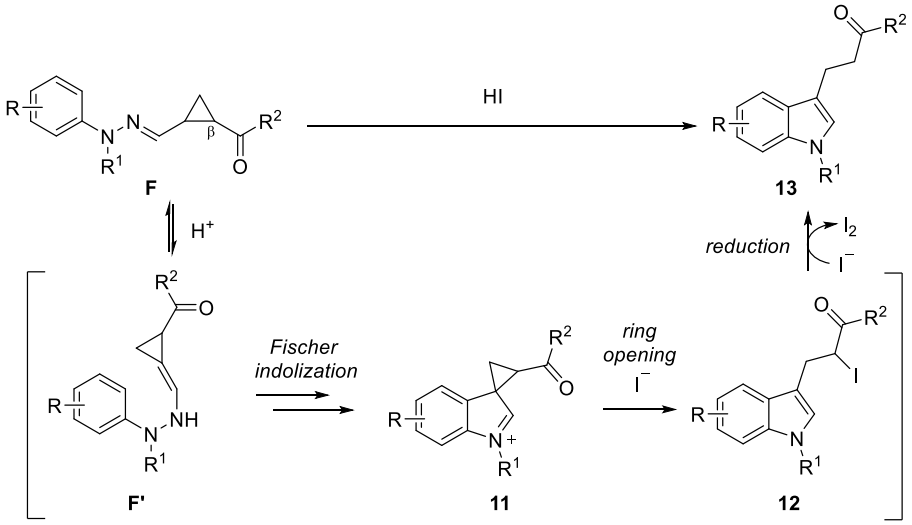
すなわち、イミン炭素上にシクロプロピル基をもつ *N*-アリールヒドラゾン **21** を酸性条件で反応させると、エンヒドラジン **K** への異性化を介した Fischer インドール化が進行することで、活性中間体であるスピロシクロプロピルインドレニン **L** が生成する (Scheme 9)。そして適切な求核剤によるスピロシクロプロピルインドレニン **L** への求核攻撃により、シクロプロパンの開環反応が実現できると考えた。このような Fischer インドール化によりスピロシクロプロピルインドレニンが得られる反応は、Shaw らによって 1 例のみ報告されている。この報告では、*N*-アリール-*C*-シクロプロピルヒドラゾン **21a** をエタノール還流中、塩化水素で処理すると 3-(2-クロロエチル)-2-フェニル-1*H*-インドール **22** が得られている (Scheme 9、式 1)。[18] 本反応では、Fischer インドール化が進行することで、スピロシクロプロピルインドレニン **La** が生成した後、塩化物イオンがシクロプロパン部位に求核攻撃することで、インドレニンの芳香族化を伴ってシクロプロパンが開環し、インドール **22** が生成したと考えられている。しかし、本反応では、塩化物イオンがヒドラゾン **21a** のシクロプロパンへの求核攻撃によりシクロプロパンが開環し、クロロヒドラゾン **M** が生成する。続いてヒドラゾンアミン窒素の塩化物イオンへの求核攻撃による環化反応が進行することで、テトラヒドロピリダジン **23** が同時に生成しているため、収率や化学選択性に課題があった (Scheme 9、式 2)。



Scheme 9. Reaction of *N*-aryl-*C*-cyclopropylhydrazone via spirocyclopropyl indolenine.

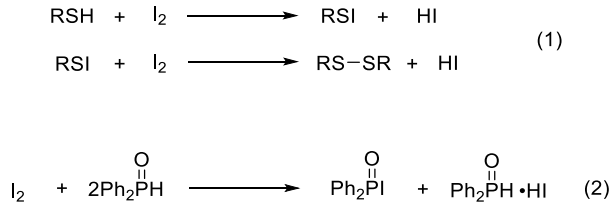
今回著者はヒドラゾン β 位にカルボニル基を導入したシクロプロピルヒドラゾン **F** をヨウ化水素と反応させることで 3-アルキルインドール **13** の合成を計画した (Scheme 10)。本反応はシクロプロピルヒドラゾン **F** のエンヒドラジン **F'**への異性化と Fischer インドール化反応が進行し、スピロシクロプロピルインドレニン中間体 **11** が選択的に生成する。このとき、導入したカルボニル基の電子求引効果によって、C-C 結合の分極率の低下に伴うシクロプロパンの開環反応の抑制が期待される。続いてヨウ化物イオンによる求核攻撃と、

芳香環であるインドール環の形成を伴いながらシクロプロパンの開環が進行し、α-ヨードカルボニル **12** が生成する。最後に α-ヨードカルボニル化合物の還元反応が進行して 2 位に置換基を持たない 3-アルキルインドール **13** が生成すると期待した。



Scheme 10. Reductive Fischer indolization of *N*-aryl-*C*-cyclopropylhydrazone.

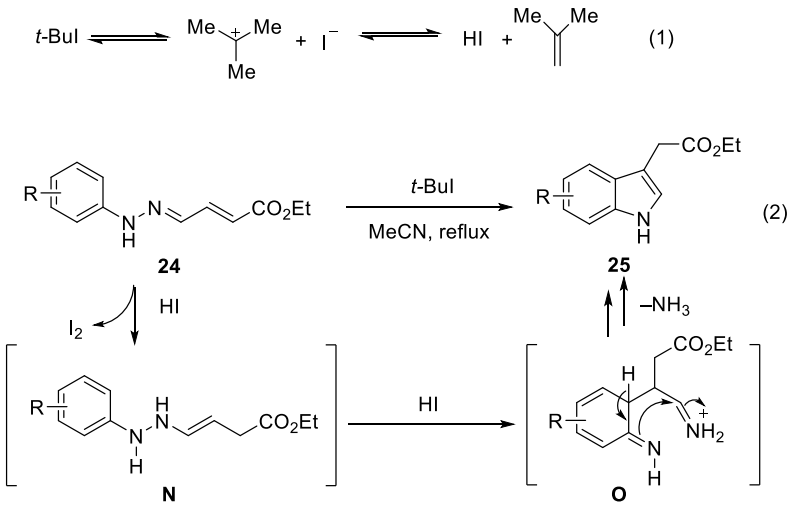
また本反応では含水中で不安定であると予想されるシクロプロピルヒドラゾン **F** やスピロシクロプロピルインドレニン **11** を経由するため、無水条件でヨウ化水素を発生させる条件が適切であると考えた。無水条件でヨウ化水素を発生させる例として、ヨウ素をチオールで還元することでヨウ化水素が発生することが知られている (Scheme 11、式 1)。[19] また、ヨウ素をジフェニルホスフィンオキシドで還元すると、ヨウ化水素－ジフェニルホスフィンオキシド複合体が発生することも知られている (Scheme 11、式 2)。[20] しかし、これらの手法では副生成物であるジスルフィドやジフェニルホスフィン酸の除去操作が必要となる。[21c]



Scheme 11. Methods for generation of anhydrous hydrogen iodide.

一方でヨウ化 *tert*-ブチルは加熱条件下で無水ヨウ化水素とイソブテンに分解する試薬である。そのため、脱水条件が必要な有機合成反応に利用することができるうえに、副生成物のイソブテンは常温で気体であるために、その除去操作が不要である (Scheme 12、式 1)。[21] ヨウ化 *tert*-ブチルの加熱により生じる無水ヨウ化水素を利用した有機合成反応とし

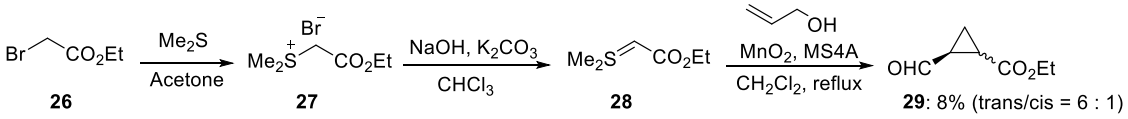
て、当研究室では共役ヒドラゾンの還元的インドール合成法を報告している (Scheme 12、式 2)。[22] 本反応では共役ヒドラゾン **24** がヨウ化水素によって還元されてエンヒドラジン **N** が生成した後、Fischer インドール化反応が進行し、3-アルキルインドール **25** が生成する。本反応はヨウ化 *tert*-ブチルの加熱により生じる無水ヨウ化水素の酸性度と還元力を利用することで効率よく反応が進行している。そこで著者らはこのヨウ化 *tert*-ブチルの有用性に期待し、*N*-アリール-*C*-シクロプロピルヒドラゾンの還元的インドール合成で用いる無水ヨウ化水素の発生源として検討した。



Scheme 12. Generation of anhydrous hydrogen iodide from *tert*-butyl iodide and application reaction.

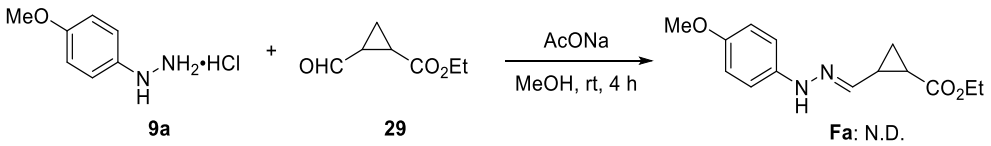
第 1 節　反応条件最適化の検討

はじめに、文献 [23] の方法を参考にシクロプロピルアルデヒド **29** の合成を行った (Scheme 13)。 まず、ブロモ酢酸エチル **26** とジメチルスルフィドの求核置換反応により、ジメチルスルホニウムブロミド **27** を合成した。その後、水酸化ナトリウムと炭酸カリウムを用いてエステル α 位を脱プロトン化し、スルホニウムイリド **28** を合成した。最後に、ジクロロメタン還流中、スルホニウムイリド **28** とアリルアルコールを二酸化マンガンで処理することで、Corey-Chaykovsky 反応が進行し、シクロプロピルアルデヒド **29** を合成した。



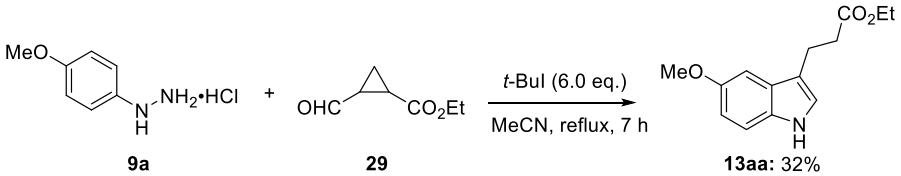
Scheme 13. Preparation of cyclopropyl aldehyde.

続いて、アリールヒドラジン **9a** とシクロプロピルアルデヒド **29** の縮合反応によってヒドラゾン **Fa** を合成する検討を行ったが、目的のヒドラゾンは不安定で単離することができなかった (Scheme 14)。



Scheme 14. Preparation of cyclopropyl hydrazone.

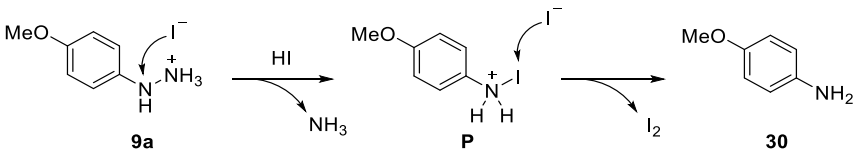
そこでヒドラゾンの生成と、続く連続反応を同一反応系中で進行させることで、ヒドラゾンの単離精製工程が不要になると考え、反応条件を検討することとした (Scheme 15)。まず、1.0 当量の 4-メトキシフェニルヒドラジン **9a** とシクロプロピルアルデヒド **29** をアセトニトリル還流中、無水ヨウ化水素発生源として 6.0 当量のヨウ化 *tert*-ブチルで処理したところ、インドール **13aa** が 32%の収率で得られた。



Scheme 15. One pot reaction of reductive indolization from cyclopropyl aldehyde and arylhydrazine.

低収率に留まった原因について、不安定な **29** が系中で分解されていると考えた。そこで、

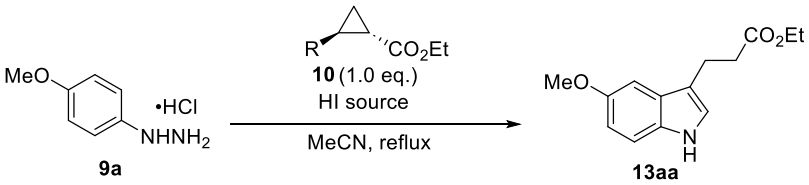
アルデヒドをアセタール保護したシクロプロピルアセタール **10a-d** を用いて、還元的インドール合成を検討した (Table 1)。まず、ジメチルアセタール **10a** や 1,3-ジオキサン **10b** を先述した条件に付すと、アルデヒド **29** を用いた時と比べて収率は低下した (entries 1 and 2)。次に、4,4,5,5,-テトラメチル-1,3-ジオキソラン **10c** を用いた場合、反応は進行せず、原料が回収された。この際、副生成物として 4-メトキシアニリンが 37%の収率で得られた。続いて 1,3-ジオキソラン **10d** を用いたときに収率が 54%に向上した（entry 4)。一方で、ヨウ化 *tert*-ブチルの代わりにヨウ化水素酸を用いた場合、目的物はほとんど得られなかった (entry 5)。このことから当初の想定通り、本反応は無水条件が必要であることが示唆された。続いて、シクロプロピルアセタールのアセタール脱保護に続くヒドラジンとの縮合反応を促進しながらヨウ化水素の生成が期待される試薬として、TMSCl/NaI を用いる条件について検討したが、収率は低下した (entry 6)。[24] 次に様々な溶媒を検討した (entries 7-10)。その結果、アセトニトリルが最適であることが分かった。アセトニトリルはヨウ化 *tert*-ブチルのヨウ化水素への変換を促進することが報告されているため、本反応ではヨウ化水素の速やかな生成が、収率よく反応を進行させるのに重要であることが示唆された。[22] 次に、4-メトキシヒドラジンの当量について検討した。本反応では副生成物として、4-メトキシアニリン **30** が確認された。これは原料の 4-メトキシフェニルヒドラジン **9a** がヨウ化水素によって、アンモニアの脱離を伴いながら求核置換反応が進行し、**P** が生成した後、さらにヨウ化水素による還元反応が進行することで生成していると考えている (Scheme 16)。[25] このことから鍵反応に利用される 4-メトキシフェニルヒドラジンが反応系中で減少するため、シクロプロピルアセタールに対して 4-メトキシフェニルヒドラジンは過剰量必要であると考えた。そこで 6.0 当量のヨウ化 *tert*-ブチル存在下で 4-メトキシフェニルヒドラジンを 1.0 当量から 2.0 当量に増やす検討をした (entry 11)。この際、反応が途中で停止する傾向が見られたので反応開始 15 分後に 3.0 当量のヨウ化 *tert*-ブチルを追加し、さらに 45 分間反応させると、収率は 89%に向上した。次に、**10d** の立体異性体 **10d'**を用いた場合、収率はわずかに低下した (entry 12)。このことからシクロプロパンの立体化学は本反応にほとんど影響を与えないことが示唆された。以上の検討の結果から、アセトニトリル還流中、シクロプロピルアセタールとアリールヒドラジンを 2.0 当量、ヨウ化 *tert*-ブチルを 9.0 当量用いる条件が最も良い結果を与えることが明らかになった。

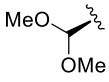
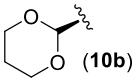
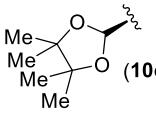
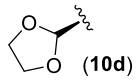
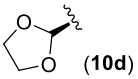
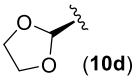
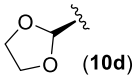
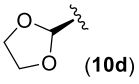
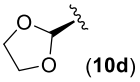
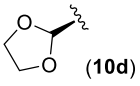
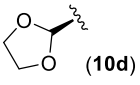
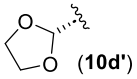


9a **P** **30**

Scheme 16. Proposed reaction mechanism of aniline generation.

Table 1. Optimization of reductive indolization reaction.

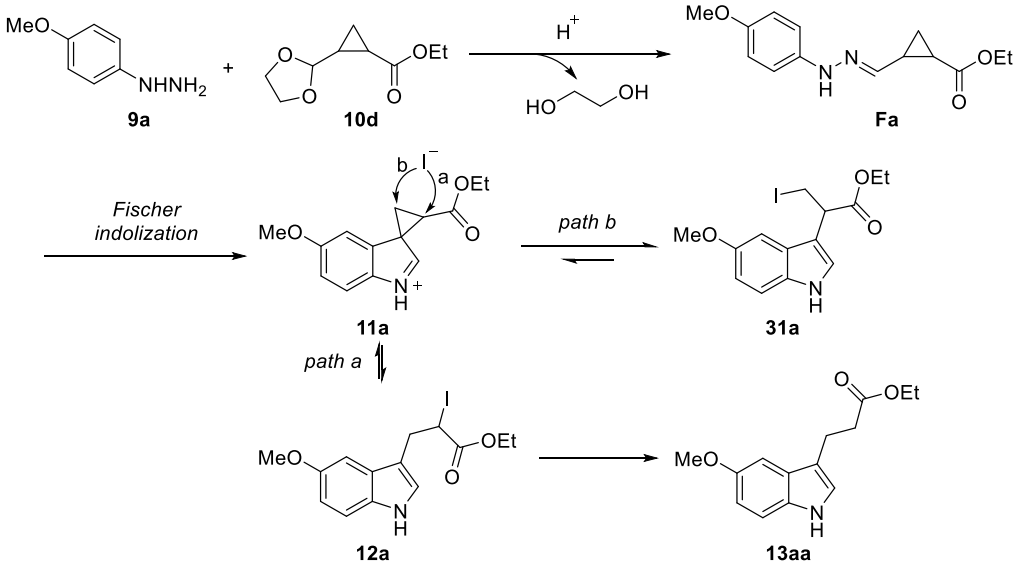


entry	R	HI source	solvent	time	yield (%)
1	 (**10a**)	*t*-BuI (6.0 eq.)	MeCN	40 min	23
2	 (**10b**)	*t*-BuI (6.0 eq.)	MeCN	30 min	20
3	 (**10c**)	*t*-BuI (6.0 eq.)	MeCN	1 h	N.R.
4[a)]	 (**10d**)	*t*-BuI (6.0 eq.)	MeCN	30 min	54
5	 (**10d**)	aq. 57% HI (6.0 eq.)	MeCN	1 h	Trace
6	 (**10d**)	TMSCl/NaI (6.0 eq.)	MeCN	1.5 h	20
7	 (**10d**)	*t*-BuI (6.0+3.0 eq.)	EtOH	3 h	15
8[b)]	 (**10d**)	*t*-BuI (6.0 eq.)	toluene	3 h	N.D.
9[b)]	 (**10d**)	*t*-BuI (6.0 eq.)	DMSO	30 min	N.D.
10[b)]	 (**10d**)	*t*-BuI (6.0 eq.)	THF	2 h	N.D.
11[c)]	 (**10d**)	*t*-BuI (6.0+3.0 eq.)	MeCN	1 h	89
12[c)]	 (**10d'**)	*t*-BuI (6.0+3.0 eq.)	MeCN	1 h	83

a) MS3A was added. b) **9a** (1.2 eq.) was used. c) **9a** (2.0 eq.) was used.

第 2 節　反応経路の考察

本反応の推定反応経路を Scheme 17 に示す。まず、アリールヒドラジン **9a** とシクロプロピルアセタール **10d** からヒドラゾン **Fa** が生成する。その後 Fischer インドール化反応が進行し、スピロインドレニン **11a** が生成する。ヨウ化物イオンが **11a** のエステル β 位に求核攻撃すると、ヨウ化アルキル **31a** が生成する (path b)。**31a** は還元に対する反応性が低く、スピロインドリン **11a** への逆反応が進行する。一方、エステルの α 位に求核攻撃すると、α-ヨードエステル **12a** が生成し、不可逆的に還元されて目的のインドール **13aa** が生成すると考えている (path a)。



Scheme 17. Proposed reaction pathway of reductive indolization.

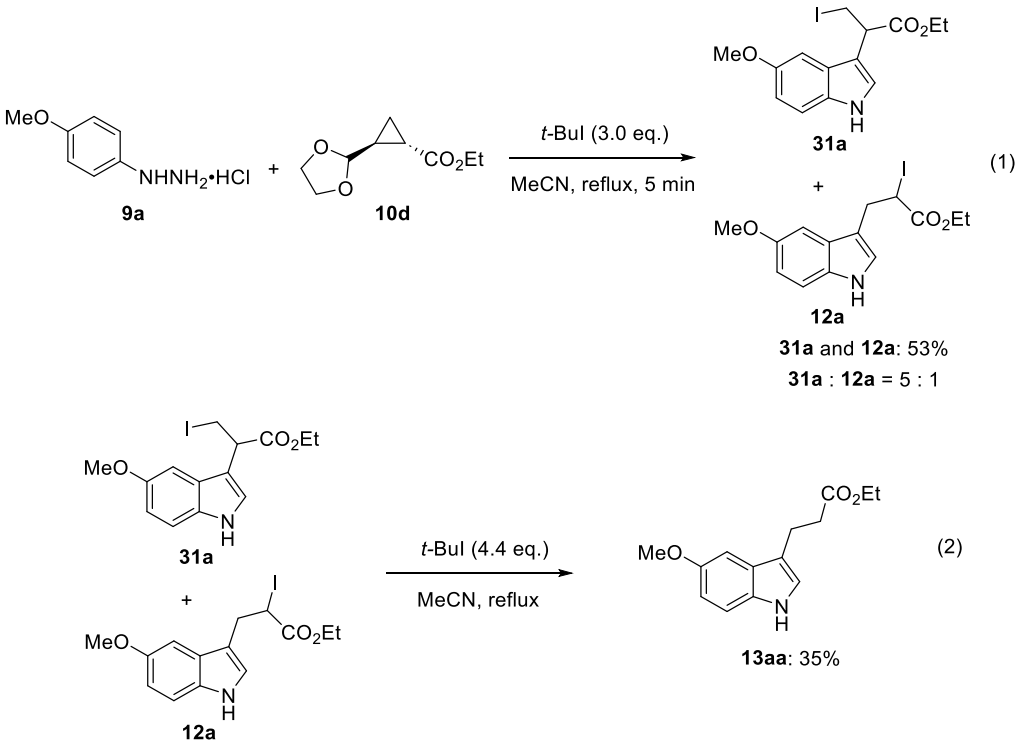
次に、本反応の詳細について以下の段階に分けて詳しく説明する。

1. ヨードエステル中間体 **31a**, **12a** が生成する反応経路 **(9a**, **10d → 31a** ,**12a)**
2. スピロシクロプロピルインドレニン **11a** からインドール **13aa** が生成する反応経路 **(11a→13aa)**

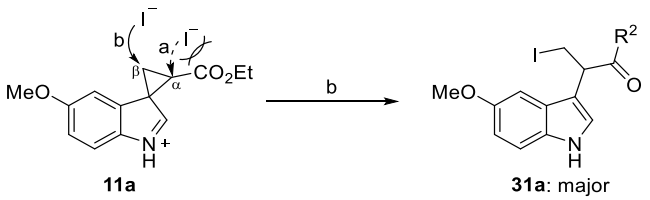
1. <u>ヨードエステル中間体 **31a, 12a** が生成する反応経路</u>

4-メトキシフェニルヒドラジン塩酸塩 **9a** とシクロプロピルアセタール **10d** の等量混合物をアセトニトリル還流中、3.0 当量のヨウ化 *tert*-ブチルと混合して 5 分後に反応を停止させたところ、枝分かれ構造をもつ β-ヨードエステル **31a** と直鎖型の α-ヨードエステル **12a** が 5:1 の比で得られた (Scheme 18、式 1)。さらに、ヨードエステルの混合物をヨウ化 *tert*-ブチルで処理すると、目的のインドール **13aa** が 35%の収率で得られた (式 2)。以上のことから、β-ヨードエステル **31a** と α-ヨードエステル **12a** の混合物が本反応の中間体であること

が示唆された。なお、β-ヨードエステル **31a** の生成比が α-ヨードエステル **12a** に比べて高かった理由について、ヨウ化物イオンがスピロシクロプロパンへ求核攻撃をする際に、立体障害の影響が小さいエステルの β 位での反応が優先したためであると考えている (Scheme 19)。



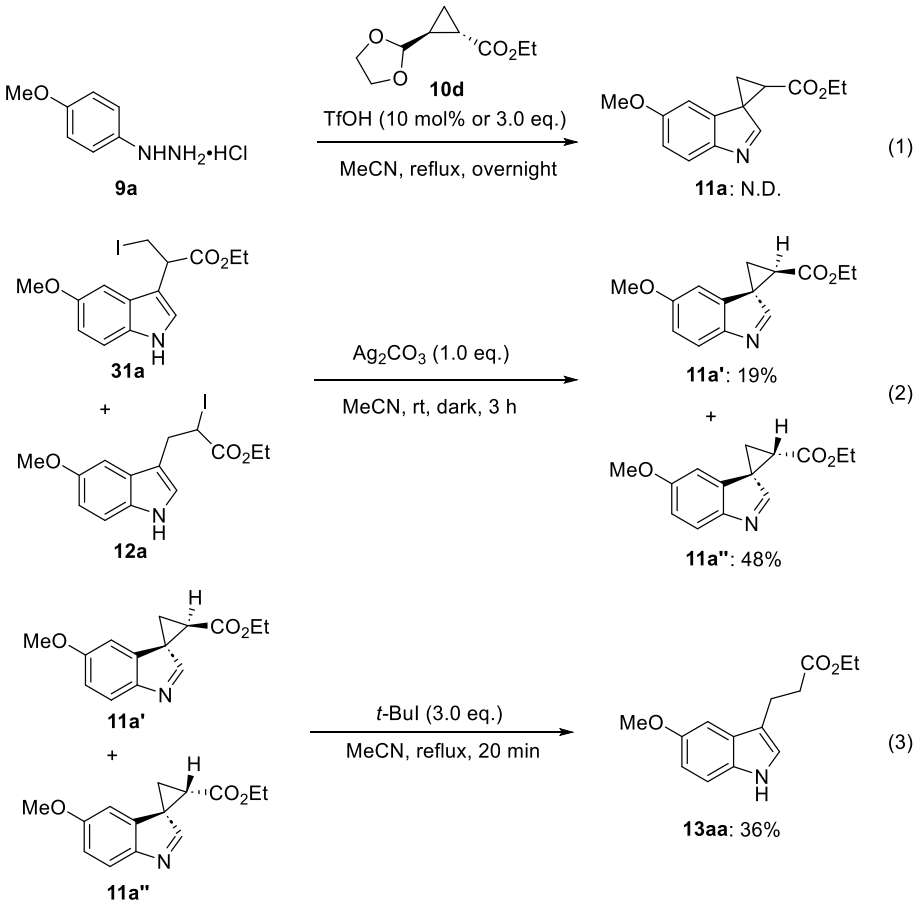
Scheme 18. Detection of iodinated indole intermediates.



Scheme 19. Iodide attack at less hindered position of cyclopropane.

続いて、スピロシクロプロピルインドレニン **11a** が本反応の中間体であることを確認するための実験を行った。まず本反応を 5 分で停止させて、NMR を確認したところ、ヨードエステルの混合物の他にスピロシクロプロピルインドレニン **11a** が生成していることを確認したが、痕跡量であったため、単離できなかった。そこで、スピロシクロプロピルインドレニン **11a** を別法で合成した後に対照実験を検討することとした。まず、スピロシクロプロピルインドレニンの合成を検討した。4-メトキシフェニルヒドラジン塩酸塩 **9a** とシクロプロピルアセタール **10d** をアセトニトリル還流中、10 mol%または 3.0 当量のトリフルオ

ロメタンスルホン酸で処理したが、目的物は得られなかった (Scheme 20、式 1)。これは反応中間体であるヒドラゾンやエンヒドラジンと目的のスピロシクロプロピルインドレニンがトリフルオロメタンスルホン酸存在下の条件では不安定であったためであると考えている。次にヨードエステル中間体の混合物を 1.0 当量の炭酸銀で処理したところ、スピロインドレニン **11a'**と **11a"**がそれぞれ 19%と 48%の収率で得られた (式 2)。そこで、合成したスピロインドレニンのジアステレオマー混合物をアセトニトリル還流中、3.0 当量のヨウ化 *tert*-ブチルで処理すると、目的のインドール **13aa** が 36%の収率で得られた。この結果から、スピロシクロプロピルインドレニンが本反応の中間体であることが示唆された (式 3)。

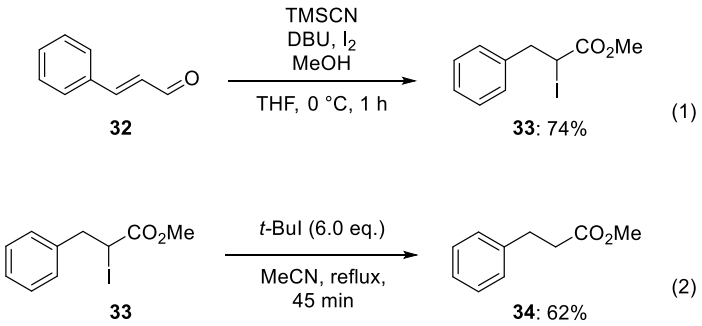


Scheme 20. Synthesis of spiroindolenine and control experiments.

2. スピロシクロプロピルインドレニンからインドールが生成する反応経路

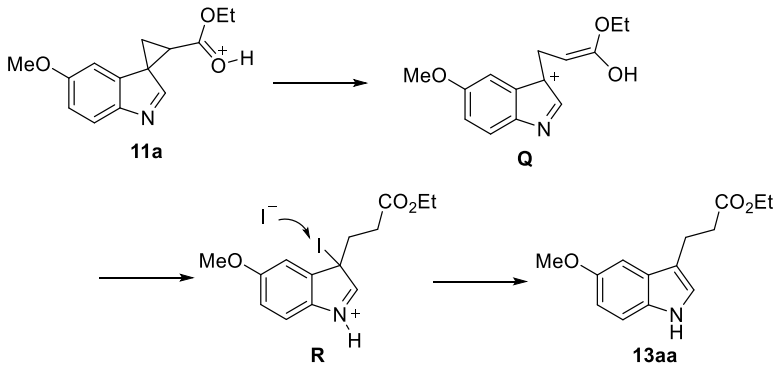
前述した通り、本反応の最終段階では α-ヨードエステル **12a** がヨウ化物イオンによって還元されることでインドール **13aa** が生成していると想定した。そこで、α-ヨードエステルのヨウ化 *tert*-ブチルに対する反応性を確認する目的で、モデル基質を用いて検証することとした。文献[26]の手法を参考に、シンナムアルデヒド **32** を THF 中、0 ℃でトリメチルシリルシアニドと DBU、ヨウ素、メタノールで処理することで α-ヨードエステル **33** を合成した (Scheme 21, 式 1)。この α-ヨードエステル **33** をアセトニトリル還流中、6.0 当量のヨ

ウ化 *tert*-ブチルで処理すると、エステル **34** が 62%で得られた (式 2)。このことから、α-ヨードエステルはヨウ化 *tert*-ブチルから生成するヨウ化水素によって還元されることが明らかになった。従って、本研究の還元的 Fischer インドール合成における中間体 **12a** も同様の反応によって還元されていることが示唆された。



Scheme 21. Control experiment of reduction of α-iodoester.

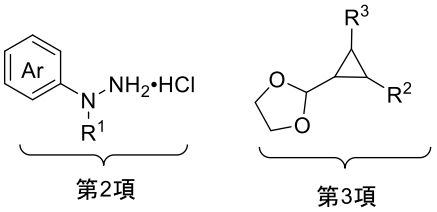
なお、スピロシクロプロピルインドレニン **11a** からインドール **13aa** の生成経路として、プロトン化された **11a** から開環反応が進行し、カルボカチオン **Q** が生成した後、ヨウ化物イオンによるカルボカチオン **Q** への求核付加とインドール **13aa** への芳香族化を伴う還元反応が進行する経路も完全に否定はできない (Scheme 22)。



Scheme 22. Another proposed pathway of the reduction of spiroindolenine.

第 3 節　基質適用範囲に関する検討

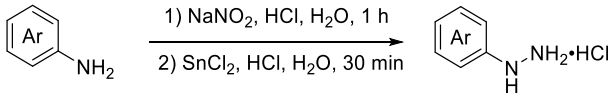
次に著者は還元的インドール合成の基質適用範囲の検討を行った。まず、第 1 章第 3 節第 1 項では原料合成を行った。第 1 章第 3 節第 2 項ではアリールヒドラジン、第 1 章第 3 節第 3 項ではシクロプロピルアセタールの基質適用範囲について検討した。



第 1 項　アリールヒドラジンとシクロプロピルアセタールの合成

初めにヒドラジン塩酸塩 **9c**, **9u**, **9q** を以下のように合成した。まず市販のアニリン **35c**, **35u**, **35q** を亜硝酸ナトリウム、塩化水素で処理することで *N*-ニトロソ化する。続いて、塩化スズを用いて還元することで合成した (Table 2)。

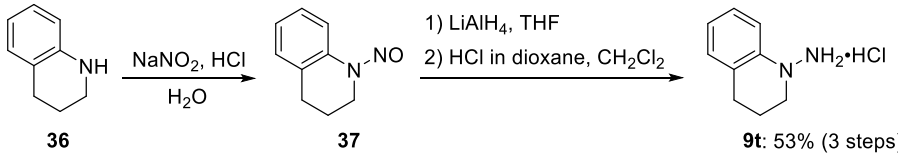
Table 2. Preparation of arylhydrazine hydrochlorides **9c**, **9u**, **9q**.



35c, 35u, 35q **9c, 9u, 9q**

entry	aniline	Ar	hydrazine	yield
1	**35c**	4-$PhOC_6H_4$	**9c**	46%
2	**35u**	3,4-$(OCH_2O)C_6H_3$	**9u**	13%
3	**35q**	3-F-4-$MeOC_6H_3$	**9q**	62%

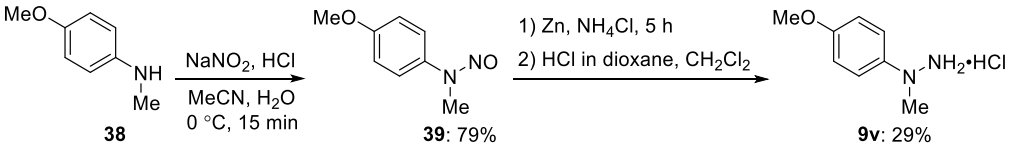
また、市販のテトラヒドロキノリン **36** を亜硝酸ナトリウムと塩化水素で処理することで *N*-ニトロソ化した後、$LiAlH_4$ で還元し、塩化水素 (4M、1,4-ジオキサン溶液) で処理することでヒドラジン塩酸塩 **9t** を合成した (Scheme 23)。



36 **37** **9t**: 53% (3 steps)

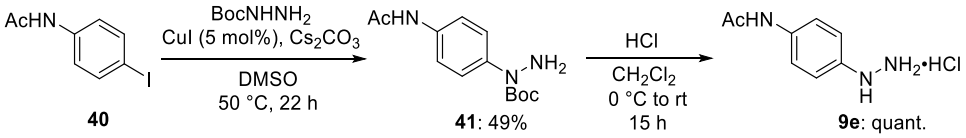
Scheme 23. Preparation of 3,4-dihydroquinonyl (2*H*)-amine hydrochloride **9t**.

N-メチル-4-メトキシアニリン **38** を亜硝酸ナトリウムと塩化水素で処理することで *N*-ニトロソ化した後、亜鉛と塩化アンモニウムで還元し、塩化水素 (4M、1,4-ジオキサン溶液) で処理することでヒドラジン塩酸塩 **9v** を合成した (Scheme 24)。



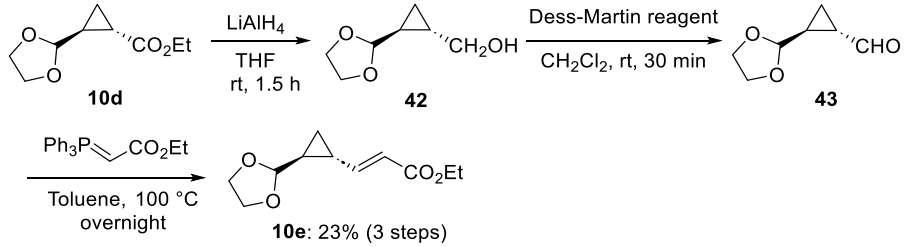
Scheme 24. Preparation of 1-(4-methoxyphenyl)-1-methylhydrazine hydrochloride **9v**.

パラ位にアセトアミドを有するフェニルヒドラジン塩酸塩 **9e** は文献 [22] の方法を参考にして合成した。すなわち、ヨウ化銅を触媒として用いる *N*-(4-ヨードフェニル)アセトアミド **40** と *N*-Boc ヒドラジンのカップリング反応によりアリールヒドラジン **41** を得た。続いて **41** をジクロロメタン中、塩化水素 (4M、1,4-ジオキサン溶液) で処理することで、Boc 基の脱保護を行い、ヒドラジン塩酸塩 **9e** を合成した (Scheme 25)。



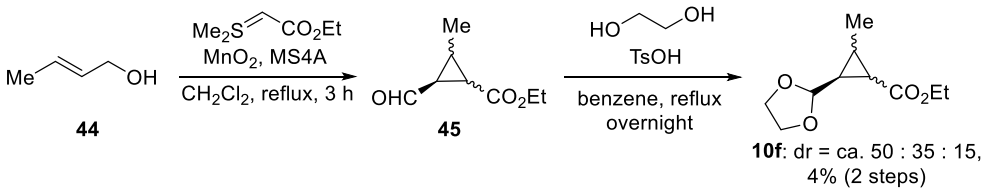
Scheme 25. Preparation of *N*-(4-hydrazinylphenyl)acetamide hydrochloride **9e**.

次に様々なシクロプロピルアセタールの基質合成を以下のように行った。まず、α,β-不飽和エステルをもつシクロプロピルアセタール **10e** の合成を行った (Scheme 26)。エステル **10d** を THF 中、$LiAlH_4$ で処理することで還元し、アルコール **42** を得た。続いてジクロロメタン中、Dess-Martin 試薬で処理することでアルデヒド **43** へと酸化した。最後にトルエン中、ホスホニウムイリドで処理することで、Wittig 反応が進行し、α,β-不飽和エステル **10e** を合成した。



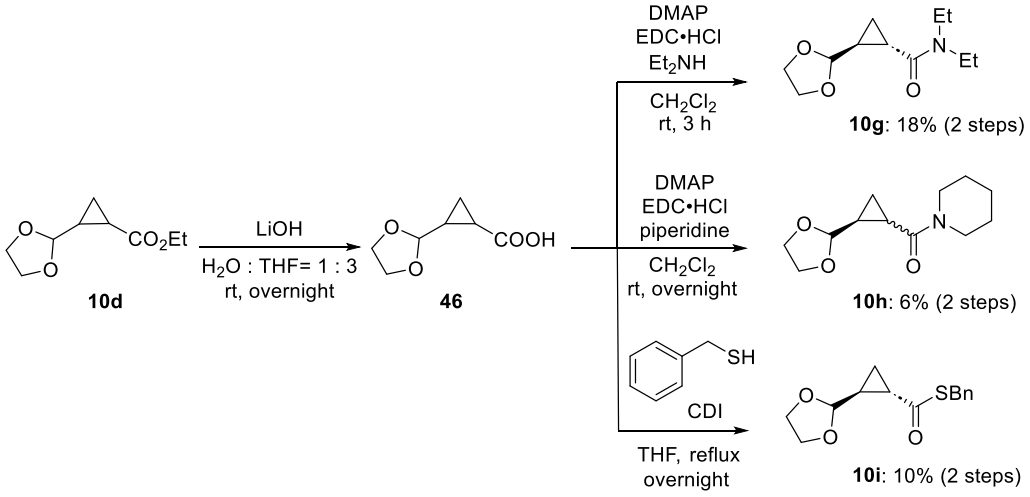
Scheme 26. Preparation of cyclopropyl α,β-unsaturated ester **10e**.

次に、三置換シクロプロピルアセタール **10f** を合成した (Scheme 27)。*trans*-クロチルアルコール **44** をジクロロメタン還流中、スルホニウムイリドと二酸化マンガンで処理することで Corey-Chaykovsky 反応が進行し、シクロプロピルアルデヒド **45** を合成した。続いて **45** をベンゼン還流中、エチレングリコールと *p*-トルエンスルホン酸で処理することでシクロプロピルアセタール **10f** を合成した。



Scheme 27. Preparation of trisubstituted cyclopropyl acetal **10f**.

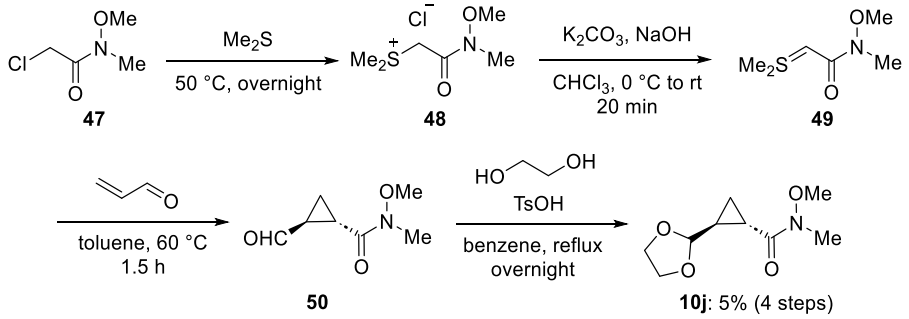
次に、アミドを有するシクロプロピルアセタール **10g, 10h** とチオエステルを有する **10i** を合成した (Scheme 28)。まずエステル **10d** を水酸化リチウムで処理することで、加水分解が進行し、カルボン酸 **46** を得た。続いてジクロロメタン中、カルボン酸 **46** とジエチルアミンを EDC 存在下で縮合することでアミド **10g** を合成した。次にジクロロメタン中、カルボン酸 **46** とピペリジンを EDC 存在下で縮合することでアミド **10h** を合成した。さらにカルボン酸 **46** とベンジルメルカプタンを THF 還流中、CDI 存在下で縮合することでチオエステル **10i** を合成した。



Scheme 28. Preparation of amides **10g, 10h** and thioester **10i**.

最後に文献[27]の手法を参考に Weinreb アミドを有するシクロプロピルアセタール **10j** の合成を行った (Scheme 29)。2-クロロ-*N*-メトキシ-*N*-メチルアセトアミド **47** をジメチルスルフィド中で加熱攪拌することでジメチルスルホニウムクロリド **48** を合成した。その後、水

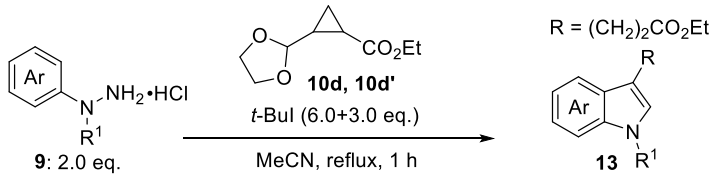
酸化ナトリウムと炭酸カリウムを用いてアミドα位を脱プロトン化し、スルホニウムイリド **49** を合成した。続いて **49** をトルエン中 60 ℃でアクロレインと反応させることで、Corey-Chaykovsky 反応が進行し、シクロプロピルアルデヒド **50** が得られた。最後に、エチレングリコールを用いてアセタール保護することでシクロプロピルアセタール **10j** を合成した。

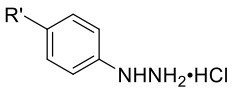
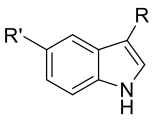
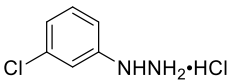
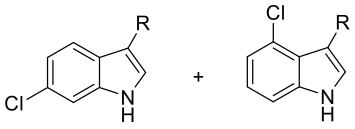
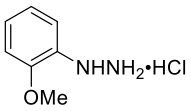
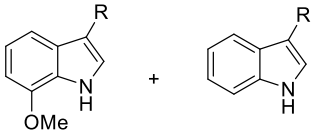
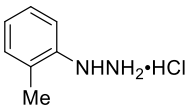
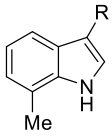
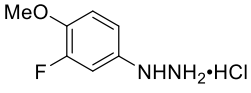
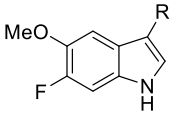


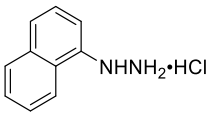
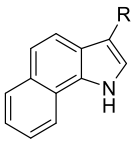
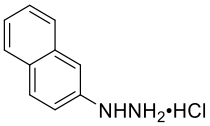
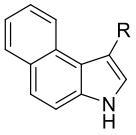
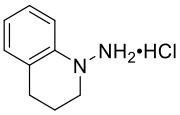
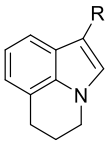
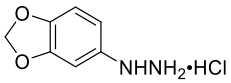
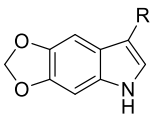
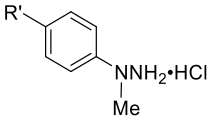
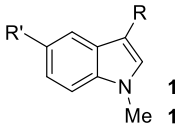
Scheme 29. Preparation of cyclopropyl Weinreb amide **10j**.

第 2 項　アリールヒドラジンの基質適用範囲に関する検討

第 3 節第 1 項で合成したヒドラジンと市販のヒドラジンを用いて還元的インドール合成の基質一般性を検討した (Scheme 30)。まず、4 位に置換基を有するフェニルヒドラジン **9b-l** を検討したところ、電子供与性をもつもので収率が高い傾向にあることが分かった。また、ニトロ基を有するヒドラジン **9m** からはインドールは得られなかった。従って、一般的な Fischer インドール合成と類似した傾向であることが確認された。[28] 次に 2 位または 3 位に置換基を有するフェニルヒドラジンを検討した。3 位にクロロ基をもつフェニルヒドラジン **9n** からはインドール **13na**、**13na'**の混合物が 26%で得られた。2 位にメトキシ基をもつフェニルヒドラジン **9o** からはインドール **13oa** のほかにメトキシ基が脱離した **13ja** が生成した。また、2 位にメチル基をもつフェニルヒドラジン **9p** からは **13pa** のみが得られた。3 位にフルオロ基、4 位にメトキシ基をもつフェニルヒドラジン **9q** からはインドール **13qa** が 67%で得られた。1-ナフチルヒドラジン **9r** からは **13ra** が 56%の収率で得られた一方で、2-ナフチルヒドラジン **9s** からは **13sa** が 36%の収率で得られた。3,4-ジヒドロキノニル (2*H*)-アミン **9t** からは三環性の **13ta** が 37%で得られ、3,4-メチレンジオキシフェニルヒドラジン **9u** からは **13ua** が 53%の収率で得られた。最後に置換基 R^1 にメチル基をもつフェニルヒドラジンを検討したところ、4 位にメトキシ基をもつヒドラジン **9v** からは **13va** が 69%で得られたが、4 位が水素のものは目的のインドール **13wa** の収率が低下した。



hydrazine hydrochrolide	product
 **9b-m**	 **13ba** (R' = BnO): 54% **13ca** (R' = PhO): 59% **13da** (R' = MeS): 69% **13ea** (R' = AcHN): 62% **13fa** (R' = *t*-Bu): 50% **13ga** (R' = *i*-Pr): 46% **13ha** (R' = Et): 56% **13ia** (R' = Me): 42% **13ja** (R' = H): 33% [a] **13ka** (R' = F): 42% **13la** (R' = Cl): 30% **13ma** (R' = NO_2): N.D.
 **9n**	 **13na** + **13na'** = 26% (**13na** : **13na'** = 1.4 : 1)
 **9o**	 **13oa**, 26% [b] **13ja**, 16% [b]
 **9p**	 **13pa**, 34%
 **9q**	 **13qa**: 67%

hydrazine hydrochrolide	product
 **9r**	 **13ra**: 56%
 **9s**	 **13sa**: 36%
 **9t**	 **13ta**: 37%
 **9u**	 **13ua**: 53%
 **9v, 9w**	 **13va** (R' = MeO): 69% **13wa** (R' = H): 29% [a]

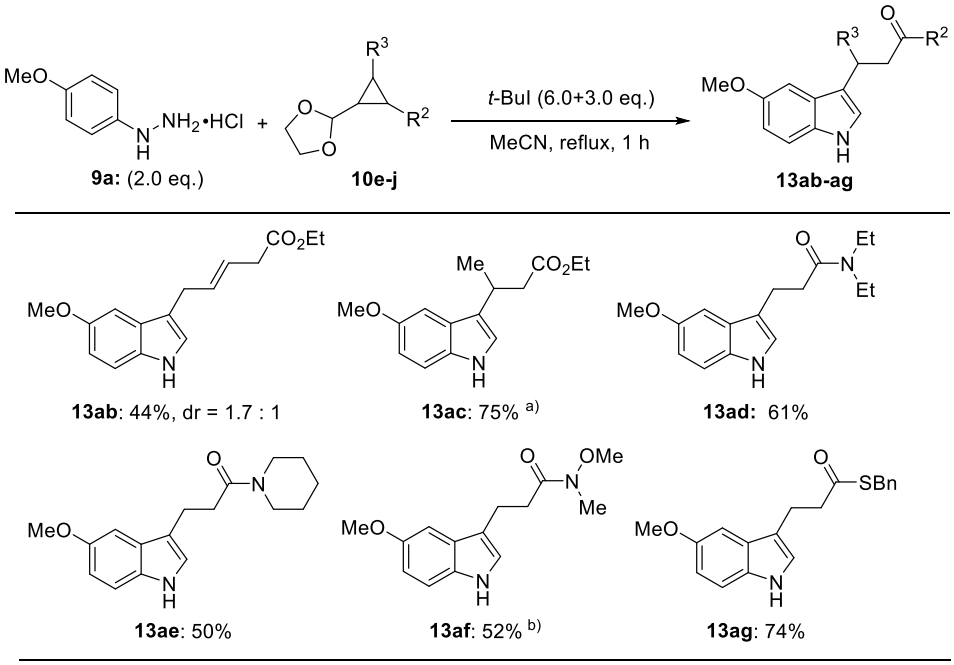
a) Hydrazine was used instead of hydrazine hydrochloride. b) *t*-BuI (12 eq.) was used.

Scheme 30. Scope of arylhydrazines.

以上のように、アリールヒドラジンの基質適用範囲について検討したところ、ベンゼン環上に電子供与性の置換基を有する基質の方が電子求引性の置換基を有する基質よりも効率的に反応が進行することが明らかになった。

第 3 項　シクロプロピルアセタールの基質適用範囲に関する検討

第 3 節第 1 項で合成したシクロプロピルアセタールを用いて還元的インドール合成のシクロプロパン上の置換基に関する一般性を検討した（Scheme 31）。α,β-不飽和エステルをもつシクロプロピルアセタール **10e** からは、β,γ-不飽和エステルを有するインドール **13ab** が得られた。R^3 にメチル基をもつ 3 置換シクロプロピルアセタール **10f** からは良好に反応が進行し、インドール **13ac** が 75%で得られた。続いて R^2 にアミドや Weinreb アミド、チオエステルを有する **10g-j** からも反応が良好に進行した。

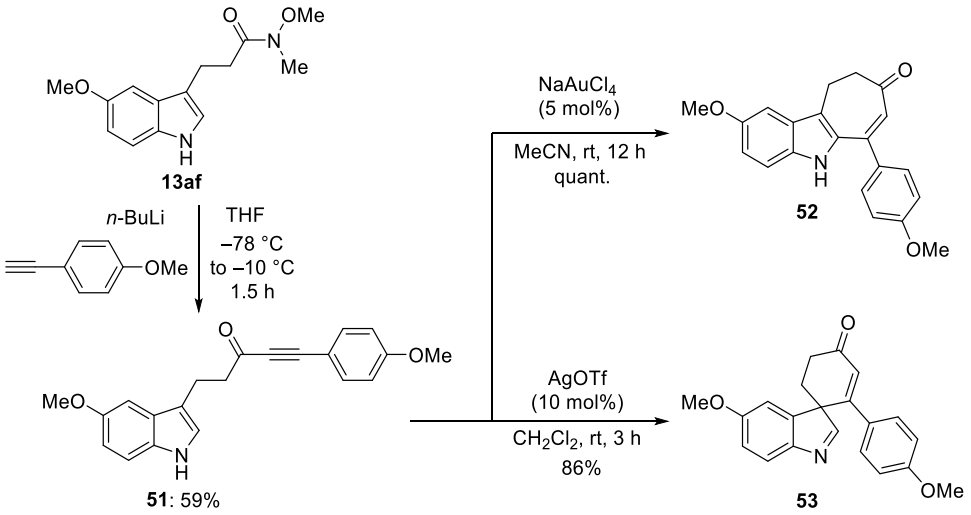


a) *t*-BuI (12 eq.) was used. b) On a 1.0 mmol scale.

Scheme 31. Scope of cyclopropyl acetals.

以上のように、シクロプロピルアセタール上の置換基として、エステルだけでなく、共役エステルやアミド、チオエステルも適用できることが分かり、カルボン酸誘体に関する一般性が実証された。さらに三置換シクロプロピルアセタールも良好に反応が進行することが分かった。

最後に今回合成したインドールの有用性を確認するために、Weinreb アミドを有するインドール **13af** の官能基変換を行った (Scheme 32)。**13af** を 1-エチニル 4-メトキシベンゼンと *n*-ブチルリチウムで処理することで求核置換反応が進行し、イノン **51** が得られた。文献 [29] の手法を参考にイノン **51** をアセトニトリル中で 5 mol%の $NaAuCl_4$ で処理すると、三環性のインドール **52** が得られた。一方、文献 [30] の手法を参考にイノン **51** をジクロロメタン中、10 mol%の AgOTf で処理するとスピロインドレニン **53** が得られた。

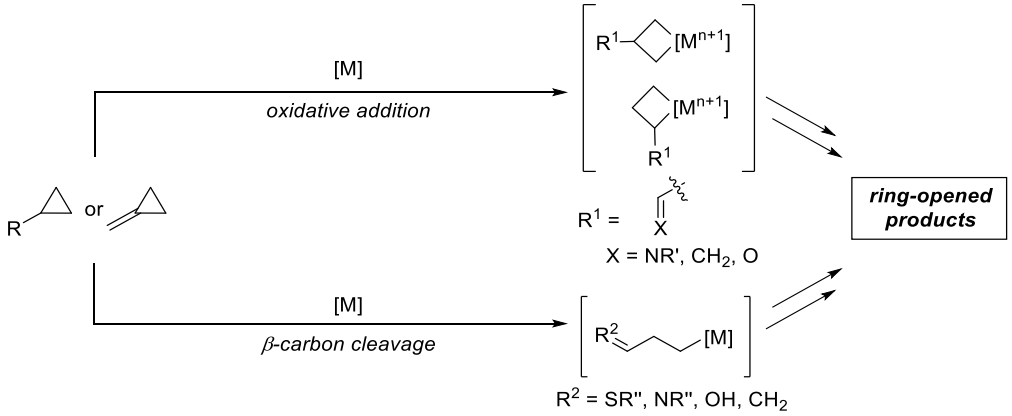


Scheme 32. Transformations of **13af**.

以上のように、著者はヨウ化 *tert*-ブチルから生成する無水ヨウ化水素を利用することで、*N*-アリール-*C*-シクロプロピルヒドラゾンの還元的インドール合成法を確立した。本反応は *N*-アリール-*C*-シクロプロピルヒドラゾンのエンヒドラジンへの異性化を介した Fischer インドール化により生成するスピロシクロプロピルインドレニンの開環反応が進行している。本反応においてヒドラゾンはシクロプロパンの活性化だけでなく、インドール環に取り込まれている反応であることが特徴である。また、ヨウ化 *tert*-ブチルが含水条件下で不安定な中間体を経由する反応に適用できる有用な試薬であることを示すことができた。さらに今回開発した 3-アルキルインドール誘導体は多環性の化合物へ誘導できる有用な原料であることも示せた。

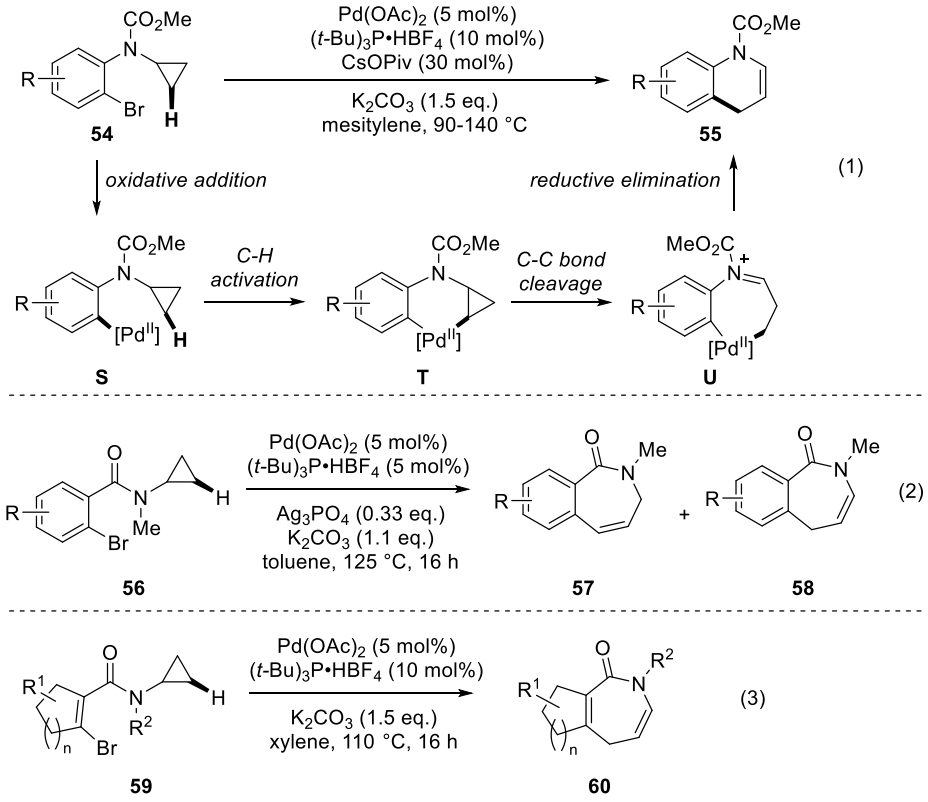
第 2 章　*N*-シクロプロピルアシルヒドラゾンの開環反応を利用したピラゾール合成法の開発

第 1 章で述べたようにドナー・アクセプター型シクロプロパンは電子的に活性化されていることから、シクロプロパン環の開環反応が容易に進行する。一方で置換基をもたないものやアルキル基が置換しただけの単純なシクロプロパンは反応性に乏しく、開環しにくい。[3] このような電子的に活性化されていないシクロプロパンの活性化として遷移金属を用いる手法がある。一般的に遷移金属を用いてシクロプロパンを活性化すると、酸化的付加や β-炭素脱離を介して、開環反応が進行することが知られている (Scheme 33)。[31-33]



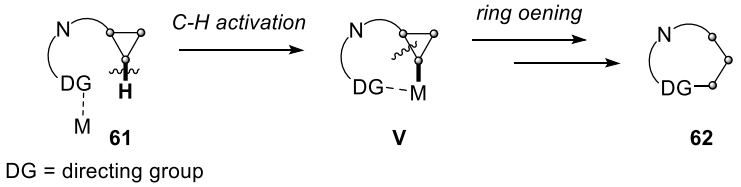
Scheme 33. C-C bond activation of cyclopropane with transition metals.

また、シクロプロパンの C-H 活性化により段階的にシクロプロパンが開環する例も数例報告されている。例えば Fagnou らはオルト位にブロモ基をもつ *N*-シクロプロピルアニリン **54** のパラジウム触媒を用いた C(sp^3)-H 活性化と、続く開環反応により、ジヒドロキノリン **55** が生成することを報告している (Scheme 34、式 1)。[34] 本反応では炭素-臭素結合への酸化的付加により生成する C-Pd 共有結合によりシクロプロパン環の近傍にパラジウム種が接近することで、シクロプロパン環の C-H 活性化が進行し、メタラサイクル **T** が生成する。その後、メタラサイクル中のシクロプロパンの開環、還元的脱離が連続的に進行することでジヒドロキノリン **55** が生成する。さらに類似の反応として、2013 年に Charette らは、シクロプロピルベンズアミド **56** からベンゾ[c]アゼピン **57** の合成を報告している (式 2)。[35] さらに Charette らは 2022 年にシクロプロピルアミド **59** からヘキサヒドロアゼピノン誘導体 **60** の合成に成功している (式 3)。[36]



Scheme 34. Ring opening reaction via C-H activation of cyclopropane.

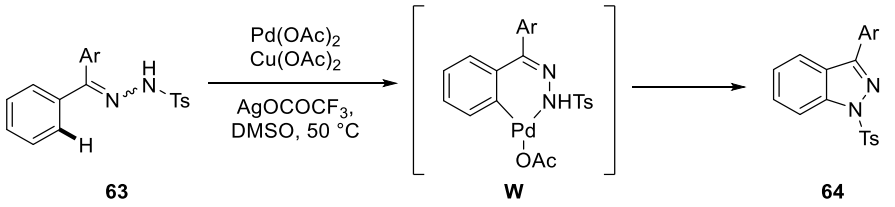
これらの反応ではシクロプロパンの C-H 活性化によりシクロプロパンの開環に続く連続反応が進行することで、含窒素ヘテロ環の効率的な合成に成功している。しかし、目的のシクロプロパンの C-H 活性化を実現するためにあらかじめベンゼン環やシクロアルケン上に合成上不要なハロゲン化物イオンを導入する必要があり、原子効率の観点から課題があった。一方でシクロプロパンの C-H 活性化の別法として配向基を用いる手法が報告されている。[37] 配向基とは配位結合によって目的の基質と金属触媒を近づける官能基である。[38] そこで今回著者は配向基を用いてシクロプロパンの C-H 活性化が進行した後、開環反応に続く連続反応が進行し、配向基を含窒素ヘテロ環の一部として取り込むことができれば、さらに原子効率に優れた合成法が実現できると考えた (Scheme 35)。このようなシクロプロパンの C-H 活性化に続く連続反応の進行が期待できる配向基として、ヒドラゾンに着目した。



Scheme 35. Synthesis of nitrogen containing heterocycle via C-H activation with directing group.

ヒドラゾンはそれぞれの窒素原子に含まれる孤立電子対が遷移金属と相互作用するルイス塩基として働くことで、C-H 活性化の配向基として機能することが知られている。例え

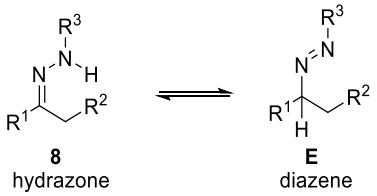
ば 2006 年に稲本らは *N*-トシルヒドラゾン **63** を DMSO 中 50 ℃で酢酸パラジウムおよび酢酸銅で処理することでインダゾール **64** の合成に成功している (Scheme 36)。[39] 本反応ではヒドラゾンアミン窒素がパラジウム触媒のルイス塩基として働き、ヒドラゾンイミン炭素上のアリール基の C-H 活性化をしたのちに還元的脱離が進行することで C-N 結合が形成されることでインダゾール **64** が生成している。この稲本らの例に始まりヒドラゾンを配向基として用いた C-H 活性化が多く開発されている。[40]



63 **W** **64**

Scheme 36. C-H activation with hydrazone directing group.

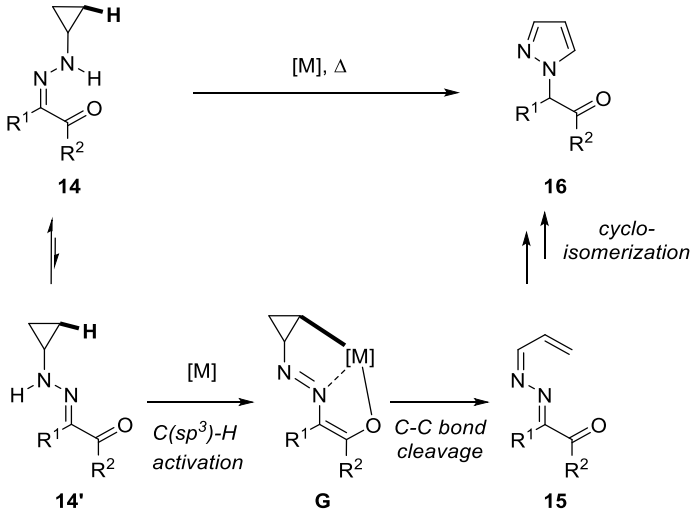
ヒドラゾンは金属に対して配位性を示す一方で、アミノ窒素の孤立電子対が C=N 結合と共鳴することで、アゾ化合物 **E** へ互変異性化する性質をもつ (Scheme 37)。[14] そのため、ヒドラゾンの C=N 結合は、一般的なイミンの C=N 結合よりも単結合に近い性質を有している。



8 hydrazone　　**E** diazene

Scheme 37. Tautomer of hydrazones.

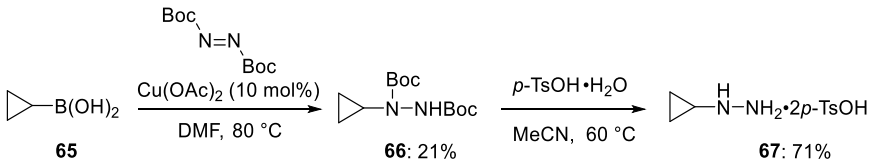
以上のようなヒドラゾンの性質を利用することで、シクロプロパンの C-H 活性化に続く連続反応が進行し、ヒドラゾンが取り込まれるような含窒素ヘテロ環の合成が期待できると考えた。そこで、イミン炭素上にアシル基をもつ *N*-シクロプロピルヒドラゾン **14** を加熱条件下、遷移金属触媒と反応させることでピラゾール **16** の合成を計画した (Scheme 38)。ヒドラゾンのイミン炭素上にアシル基を導入することで、アゾーヒドラゾン互変異性を介した C=N 二重結合の異性化の促進と、イミン窒素との二座配向基としての機能を期待した。すなわちヒドラゾン **14** が **14'**へ異性化したのちに、遷移金属触媒によるシクロプロパンの C(sp^3)-H 活性化が進行し、メタラサイクル **G** が生成する。さらに、メタラサイクルと縮環することで増大したシクロプロパン環のひずみエネルギーの解消を駆動力とすることで、シクロプロパンの開環に続く連続反応が進行し、アジン **15** が生成する。最後に、加熱による環化異性化反応が進行して、ピラゾール **16** が生成すると期待した。本反応はアシルヒドラゾンがシクロプロパンの C-H 活性化を促進するだけでなく、環化異性化反応の促進にも寄与する。さらにヒドラゾンが目的のピラゾールに取り込まれるため、原子効率の観点から優れた含窒素ヘテロ環合成法を実現する。



Scheme 38. Pyrazole synthesis via C-H activation of *N*-cyclopropyl acylhydrazone.

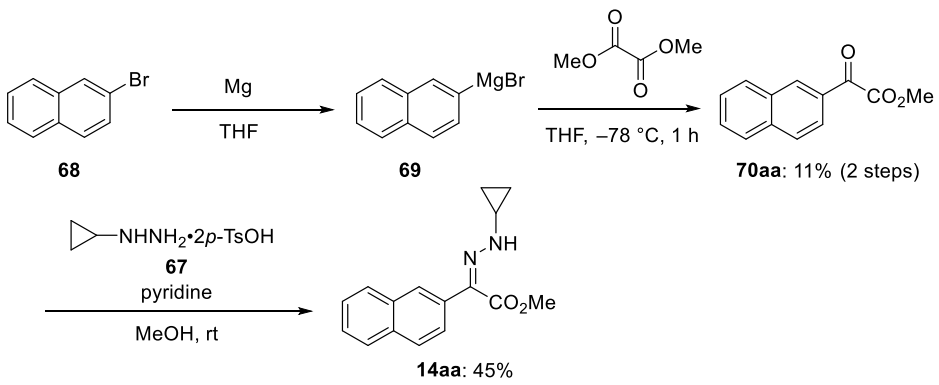
第１節　反応条件最適化の検討

はじめに、基質となる *N*-シクロプロピルヒドラゾン **14aa** の合成を行った。文献[41]を参考に、シクロプロピルボロン酸 **65** をアゾジカルボン酸ジ-*tert*-ブチルと 10 mol%の酢酸銅で処理すると、シクロプロピルボロン酸のアゾ基への触媒的付加反応が進行し、Boc 基をもつヒドラジン **66** が得られた。その後、アセトニトリル中 60 ℃で *p*-トルエンスルホン酸一水和物を添加することで、脱 Boc 化が進行し、シクロプロピルヒドラジン-*p*-トルエンスルホン酸塩 **67** を合成した (Scheme 39)。次に 2-ブロモナフタレン **68** をマグネシウムで処理することで 2-ナフチルマグネシウムブロミド **69** へ誘導する。続いてシュウ酸ジメチルと反応させることで付加脱離反応が進行し、α-ケトエステル **70aa** を合成した (Scheme 40)。合成したケトエステル **70aa** をピリジン存在下でシクロプロピルヒドラジン **67** と縮合することで、シクロプロピルヒドラゾン **14aa** を合成した。



65　　**66**: 21%　　**67**: 71%

Scheme 39. Preparation of cyclopropylhydrazine **67**.



68　　**69**　　**70aa**: 11% (2 steps)

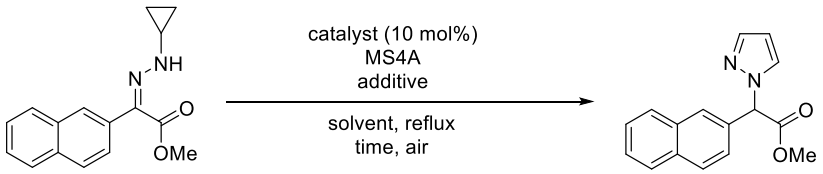
14aa: 45%

Scheme 40. Preparation of *N*-cyclopropylhydrazone **14aa**.

次に合成したシクロプロピルヒドラゾン **14aa** を用いてシクロプロパンの C-H 活性化と開環反応の連続反応を検討した (Table 3)。まずシクロプロピルヒドラゾン **14aa** をキシレン中モレキュラーシーブ 4A 存在下、C-H 活性化の進行を期待して、10 mol%のロジウム触媒やニッケル触媒を用いて検討したところ、ピラゾール **16aa** は効率よく生成しなかった (Table 3, entries 1 and 2)。[42, 43] 一方で 10 mol%の酢酸パラジウムを添加した際にピラゾール **16aa** が 49%の収率で得られた (entry 3)。更なる反応効率の向上を期待し、トリフルオロ酢酸パラジウム 10 mol%を添加したが、収率は向上しなかった (entry 4)。次に 0 価パラジウ

ムから 2 価の酢酸パラジウムへの再生を促進することが期待できる添加剤として 2.0 当量の酢酸銀を添加したところ、収率は向上しなかった (entry 5)。[44] 一方で C-H 活性化を促進することが期待できる添加剤として、2.0 当量の HFIP を添加したところ、収率は 69%に向上した (entry 6)。[45] また HFIP を溶媒として用いたが、ピラゾール **16aa** は得られなかった (entry 7)。次に HFIP と類似の効果を期待して、*tert*-アミルアルコールを溶媒として用いたところ、**16aa** の収率は 80%に向上した (entry 8)。[46] 以上の結果から、*tert*-アミルアルコール還流中、酢酸パラジウム 10 mol%とモレキュラーシーブ 4A を添加する条件でピラゾールが高収率で得られることが明らかになった。

Table 3. Optimization of C(sp^3)-H activation of *N*-cyclopropyl acylhydrazone.



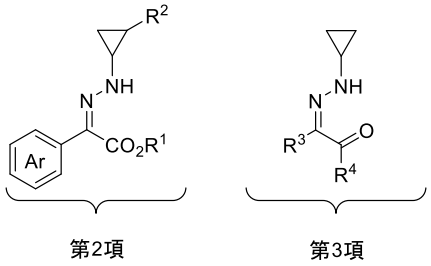
14aa **16aa**

entry	catalyst	additive (eq.)	solvent	time (h)	yield (%)
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (1.0) K_2CO_3 (1.0)	xylene	16	13 [a]
2	$Ni(OTf)_2$	PivOH (1.0)	xylene	16	N.D.
3	$Pd(OAc)_2$	–	xylene	14	49 [a]
4	$Pd(OTFA)_2$	–	xylene	16	42 [a]
5	$Pd(OAc)_2$	AgOAc (2.0)	xylene	16	39 [a]
6	$Pd(OAc)_2$	HFIP (2.0)	xylene	15	69
7	$Pd(OAc)_2$	–	HFIP	21	N.D.
8	$Pd(OAc)_2$	–	*t*-AmylOH	4	80

a) Yields were determined by ^1H NMR using triphenylmethane as an internal standard.

第 2 節　基質適用範囲に関する検討

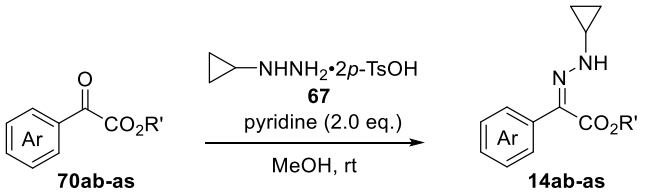
次に *N*-シクロプロピルアシルヒドラゾンのパラジウム触媒を用いたシクロプロパンの開環反応の基質適用範囲を検討した。第 2 章第 2 節第 1 項では原料であるヒドラゾンの合成を行った。第 2 章第 2 節第 2 項ではイミノ炭素上のアリール基とシクロプロパン上の (R^2)、第 2 章第 2 節第 3 項ではイミノ炭素上の置換基 (R^3) およびカルボニル上の置換基 (R^4) について検討した。



第 1 項　*N*-シクロプロピルヒドラゾンの合成

第 2 章第 2 節第 2 項で用いるシクロプロピルヒドラゾンの合成を行った。まず、メタノール中室温で、α-ケトエステルとシクロプロピルヒドラジンをピリジン存在下で縮合させることでヒドラゾン **14ab-as** を合成した (Table 4)。

Table 4. Preparation of *N*-cyclopropylhydrazones.



70ab-as **14ab-as**

entry	α-keto ester	R	R'	time (h)	hydrazone	yield
1	**70ab**	Ph	Me	overnight	**14ab**	49%
2	**70ac**	Ph	Et	overnight	**14ac**	7%, 3%[a)]
3	**70ad**	4-$MeOC_6H_4$	Et	4	**14ad**	12%
4	**70ae**	4-MeC_6H_4	Et	2	**14ae**	49%
5	**70af**	4-FC_6H_4	Et	2	**14af**	50%
6	**70ag**	4-ClC_6H_4	Et	5	**14ag**	46%
7	**70ah**	4-BrC_6H_4	Et	5	**14ah**	54%
8	**70ai**	4-$MeO_2CC_6H_4$	Me	3	**14ai**	41%
9	**70aj**	4-NCC_6H_4	Et	5	**14aj**	51%
10	**70ak**	2-MeC_6H_4	Me	8	**14ak**	14%
11	**70al**	2-$MeOC_6H_4$	Me	17	**14al**	8%
12	**70am**	3-MeC_6H_4	Me	22	**14am**	65%
13	**70an**	3-$MeOC_6H_4$	Me	21	**14an**	25%
14	**70ao**	3-NCC_6H_4	Me	24	**14ao**	45%
15	**70ap**	3,4-$(OCH_2O)C_6H_3$	Me	17	**14ap**	27%
16	**70aq**	2-thiophenyl	Me	22	**14aq**	22%
17	**70ar**	3-benzofuranyl	Et	3	**14ar**	31%
18	**70as**	1-naphthyl	Me	22	**14as**	28%

a) *E*-isomer

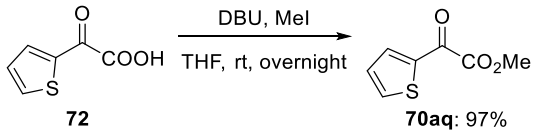
上記のヒドラゾン合成の原料となるα-ケトエステル **70ab-ah, 70aj** は市販であるが、α-ケトエステル **70ai, 70ak-as** は以下のように合成した。まず文献[47)]を参考に、ケトン **71ai, 71ak-ap, 71as** を二酸化セレンで酸化し、α-ケトカルボン酸へと誘導する。続いて塩化チオニルとメタノールによりメチルエステルとした。この際、α-ケトエステルのほかにα,α-ジメトキシエステルが生成している。最後に過塩素酸を用いて、α,α-ジメトキシエステルを加水分解することでα-ケトエステル **70ai, 70ak-ap, 70as** を合成した (Table 5)。

Table 5. Preparation of α-keto esters **70ai, 70ak-ap, 70as**.

71ai, 71ak-ap, 71as → **70ai, 70ak-ap, 70as**

entry	ketone	R	α-keto ester	yield
1	**71ai**	4-CO_2Me	**70ai**	11%
2	**71ak**	2-Me	**70ak**	56%
3	**71al**	2-OMe	**70al**	16%
4	**71am**	3-Me	**70am**	76%
5	**71an**	3-OMe	**70an**	9%
6	**71ao**	3-CN	**70ao**	21%
7	**71ap**	3,4-(OCH_2O)	**70ap**	52%
8	**71as**	1-naphthyl	**70as**	69%

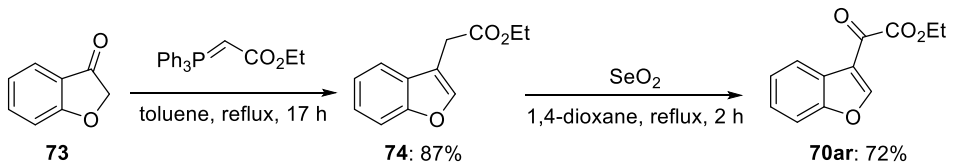
α-ケトエステル **70aq** は 2-チオフェングリオキシル酸 **72** を DBU とヨウ化メチルを用いてメチル化することで合成した (Scheme 41)。



72 → **70aq**: 97%

Scheme 41. Preparation of α-keto ester **70aq**.

α-ケトエステル **70ar** については文献 [48, 49] を参考にクマラノン **73** をトルエン還流中、トリフェニルホスホラニリデン酢酸エチルとの Wittig 反応により、ベンゾフラン-3-酢酸エチル **74** を合成し、さらに二酸化セレンで酸化することで合成した (Scheme 42)。

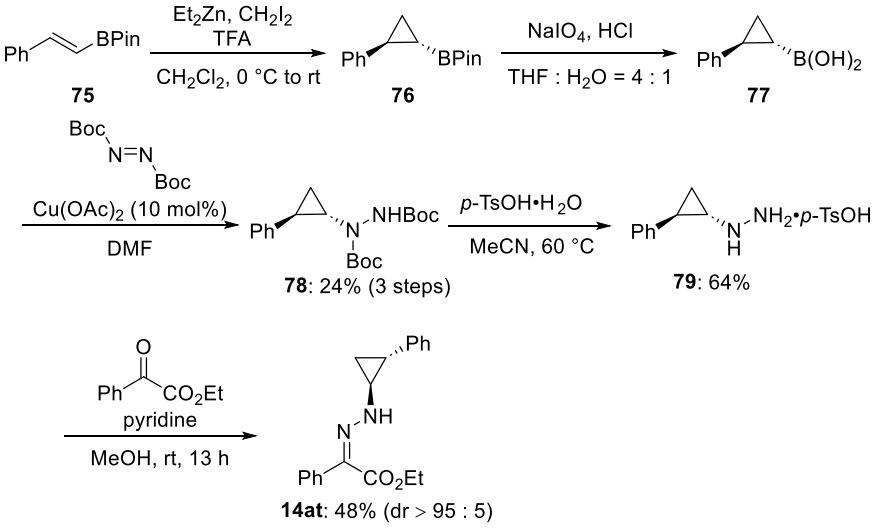


73 → **74**: 87% → **70ar**: 72%

Scheme 42. Preparation of α-keto ester **70ar.**

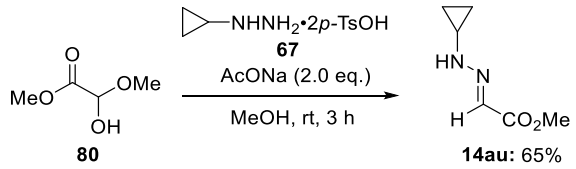
次にシクロプロパン上にフェニル基を有するシクロプロピルヒドラゾン **14at** の合成を行った (Scheme 43)。文献 [50] を参考にトランス-2-フェニルビニルボロン酸ピナコールエステル **75** をジエチル亜鉛とジヨードメタン、TFA で処理することで Simmons-Smith 反応が進行し、シクロプロピルボロン酸ピナコールエステル **76** が生成した。続いて **76** を過ヨウ素酸

ナトリウムと塩化水素で処理することで、ピナコールエステルを脱保護し、シクロプロピルボロン酸 **77** を得た。次に得られたシクロプロピルボロン酸 **77** をアゾジカルボン酸ジ-*tert*-ブチルと 10 mol%の酢酸銅で処理すると、シクロプロピルボロン酸のアゾ基への触媒的付加反応が進行し、Boc 基をもつヒドラジン **78** が得られた。その後アセトニトリル中 60 ℃で *p*-トルエンスルホン酸一水和物を添加することで、脱 Boc 化が進行し、シクロプロピルヒドラジン-*p*-トルエンスルホン酸塩 **79** を合成した。最後にメタノール中室温でシクロプロピルヒドラジン **79** とベンゾイルギ酸エチルをピリジン存在下で縮合させることでヒドラゾン **14at** を合成した。



Scheme 43. Preparation of cyclopropylhydrazone **14at**.

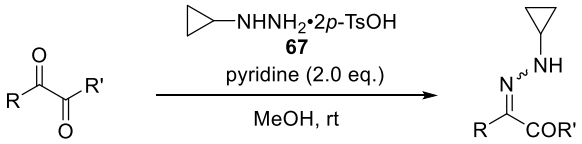
次に、第 2 章第 2 節第 3 項で用いるシクロプロピルヒドラゾン **14au-az, 14ba-bc, 14ca** の合成を行った。まず、イミノ炭素上に水素を有するシクロプロピルヒドラゾン **14au** の合成を行った。メタノール中室温で市販の 2-ヒドロキシ-2-メトキシ酢酸メチル **80** とシクロプロピルヒドラジン **67** を酢酸ナトリウム存在下で縮合することで合成した (Scheme 44)。



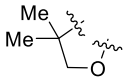
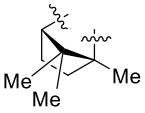
Scheme 44. Preparation of cyclopropylhydrazone **14au**.

次に、前述と同じくメタノール中室温でシクロプロピルヒドラジン **67** と α-ケトカルボニル化合物 **81av-az, 81ba-bc, 81ca** をピリジン存在下で縮合させることで合成した (Table 6)。

Table 6. Preparation of cyclopropylhydrazones **14av-az, 14ba-bc, 14ca**.

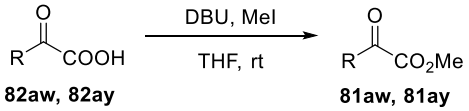


81av-az, 81ba-bc, 81ca **14av-az, 14ba-bc, 14ca**

entry	α-keto carbonyl compound	R	R'	time (h)	hydrazone	yield
1	**81av**	Me	OEt	9	**14av**	88% (*E*-isomer)
2	**81aw**	benzyl	OMe	4	**14aw**	40% (*E*-isomer)
3	**81ax**	cyclopentyl	OEt	7	**14ax**	49% (*Z*-isomer)
4	**81ay**	*t*-Bu	OMe	4	**14ay**	53% (*Z*-isomer)
5	**81az**			2	**14az**	67% (*E*-isomer)
6	**81ba**	Ph	Ph	4	**14ba**	24% (*E/Z* mixture)
7	**81bb**	Me	Ph	7	**14bb**	69% (*E*-isomer)
8	**81bc**			9	**14bc**	18% (*E/Z* mixture)
9	**81ca**	4-nitrophenyl		overnight	**14ca**	34% (*E*-isomer)

α-ケトカルボニル化合物 **81av, 81az, 81ba-bc** は市販であるが、α-ケトカルボニル化合物 **81aw, 81ax, 81ay**, **81ca** は以下のように合成した。まずイミン炭素上にベンジル基をもつ α-ケトエステル **81aw** と *tert*-ブチル基をもつ α-ケトエステル **81ay** の合成については、α-ケトカルボン酸 **82aw**, **82ay** を DBU とヨウ化メチルを用いてメチル化することで合成した (Table 7)。

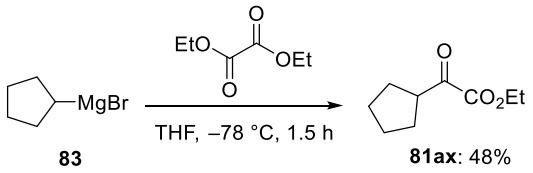
Table 7. Preparation of α-keto esters **81aw, 81ay**.



82aw, 82ay → **81aw, 81ay**

entry	α-keto carboxylic acid	R	time	α-keto ester	yield
1	**82aw**	benzyl	22 h	**81aw**	48%
2	**82ay**	*t*-Bu	4 h	**81ay**	quant.

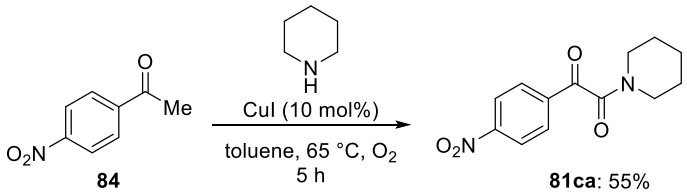
続いてシクロペンチルマグネシウムブロミド **83** を用い、シュウ酸ジエチルへ付加脱離反応を進行させることで、シクロペンチル基をもつ α-ケトエステル **81ax** を合成した (Scheme 45)。



83 → **81ax**: 48%

Scheme 45. Preparation of α-keto ester **81ax**.

次に α-ケトアミド **81ca** は文献[51]を参考にケトン **84** をトルエン中 65 ℃で酸素雰囲気下、ピペリジンと 10 mol%のヨウ化銅で処理することで合成した (Scheme 46)。

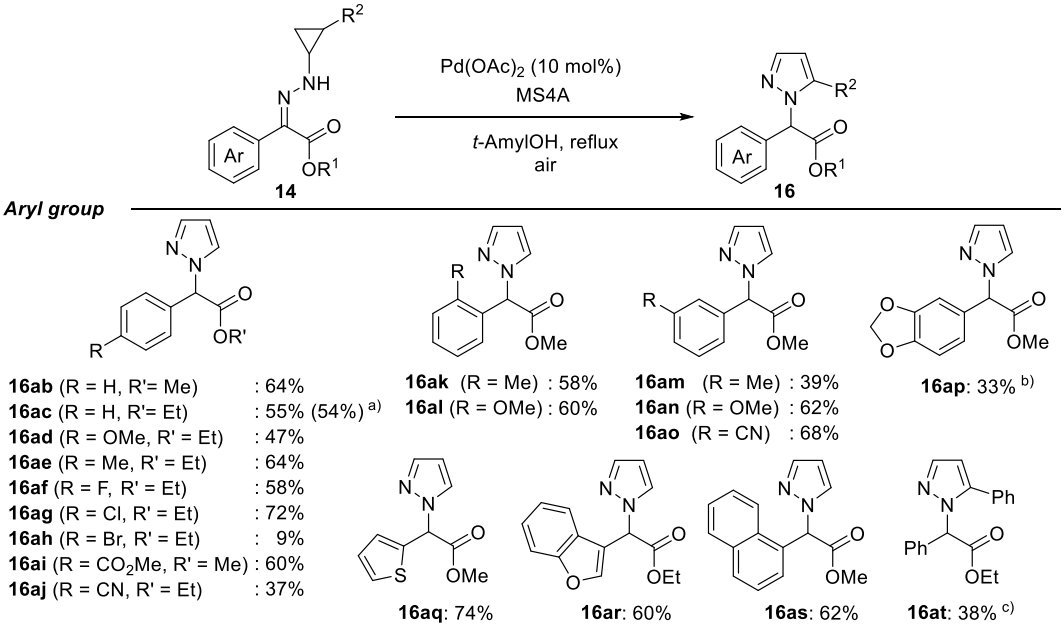


84 → **81ca**: 55%

Scheme 46. Preparation of α-keto amide **81ca**.

第 2 項　イミノ炭素上にアリール基を有するシクロプロピルヒドラゾンの基質適用範囲に関する検討

第 2 節第 1 項で合成したシクロプロピルヒドラゾン **14ab-at** を用いて、パラジウム触媒を用いたシクロプロパンの開環反応を検討した (Scheme 47)。まず、ヒドラゾンイミン炭素上のアリール基の置換基効果について検討した。**14ab**, **14ac** のようにフェニル基をもつヒドラゾンからはピラゾール **16ab** (64%), **16ac** (55%) が得られた。また、**14ac** の幾何異性体を用いた場合も目的のピラゾール **16ac** が 54%の収率で得られた。そのため、本反応では原料のヒドラゾンの幾何異性が反応に影響しないことが示唆された。**14ad-aj** のように 4 位に置換基をもつアリール基でも反応が進行したが、ブロモ基をもつ **14ah** からは収率が大幅に低下し、ピラゾール **16ah** が 9%で得られた。ブロモ基を有する **16ah** の収率が大幅に低下した原因について、反応途中で生成する 0 価パラジウムが炭素-臭素結合に酸化的付加することで副反応が進行したと考えている。また、2 位や 3 位に置換基をもつ **14ak-ao** からはピラゾール **16ak-ao** が得られたが、3,4-メチレンジオキシ基を有する **14ap** は反応速度が遅かったため、反応開始 19 時間後に 150 °C まで昇温しさらに 9 時間攪拌したところ、原料は消失し、ピラゾール **16ap** が 33%の収率で得られた。アリール基としてチオフェンを有する **14aq** やベンゾフランを有する **14ar**、1-ナフチルを有する **14as** からはピラゾール **16aq** (74%), **16ar** (60%), **16as** (62%) がそれぞれ得られた。最後にシクロプロパン上の置換基 R^2 にフェニル基を有する基質 **14at** も適応できたが、シールドチューブを用いて 140 °C に昇温して 21 時間攪拌した後、さらに 10 mol%の酢酸パラジウムを追加し、4 時間攪拌することでピラゾール **16at** を 38%の収率で得ることができた。

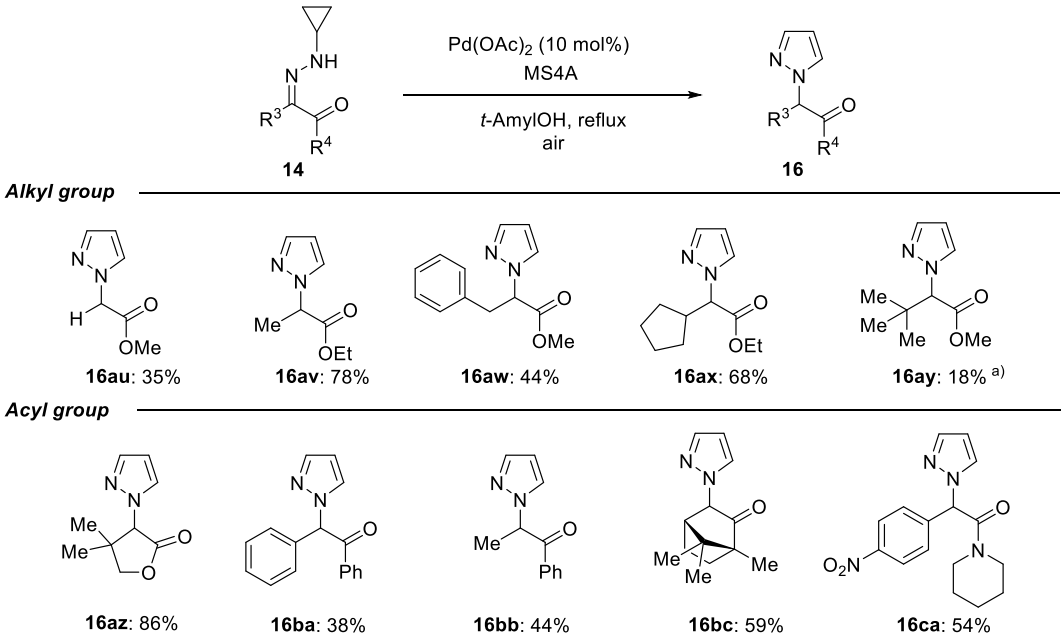


a) (*E*)-isomer was used. b) After 19 h, stirred at 150 °C in a sealed tube for 9 h. c) After stirred at 140 °C in a sealed tube for 21 h, $Pd(OAc)_2$ (10 mol%) was added and stirred for 4 h.

Scheme 47. Screening of aryl groups and substituent on cyclopropane.

第 3 項　イミノ炭素上にアルキル基や様々なアシル基を有するシクロプロピルヒドラゾンの基質適用範囲に関する検討

第 2 節第 1 項で合成したシクロプロピルヒドラゾンを用いてイミノ炭素上の置換基とカルボニル基上の置換基について基質適用範囲を検討した (Scheme 48)。置換基 R^3 が水素、メチル、ベンジル、シクロペンチルをもつ **14au-ax** で反応は進行したが、*tert*-ブチル基をもつ **14ay** は 20 mol%の酢酸パラジウムと高い反応温度が必要であった。次にカルボニル上の置換基について検討した。環状ラクトンをもつヒドラゾン **14az** を用いると 86%の収率でピラゾール **16az** が得られた。また、ケトンをもつヒドラゾン **14ba** や **14bb** を用いて検討したところ、ピラゾール **16ba** (38%) および **16bb** (44%) が得られた。環状ケトンをもつヒドラゾン **14bc** からはピラゾール **16bc** が 59%の収率で得られた。最後にアミドを有するヒドラゾン **14ca** を用いると、ピラゾール **16ca** が 54%の収率で得られた。

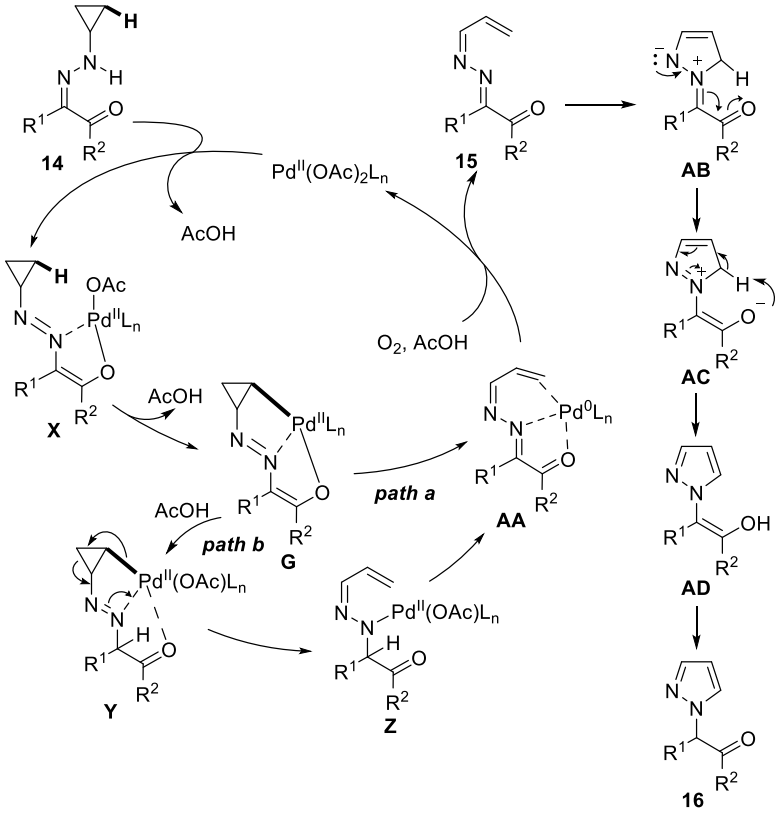


a) After stirred at 130 °C in a sealed tube for 13 h, $Pd(OAc)_2$ (10 mol%) was added and stirred for 11 h.

Scheme 48. Screening of alkyl groups and acyl groups.

第 3 節　反応経路の考察

本反応の推定反応経路を Scheme 49 に示す。まず、ヒドラゾン **14** の C=N 二重結合が異性化した後に、酢酸パラジウムが配位して中間体 **X** が生成する。次に、協奏的なメタル化ー脱プロトン化、すなわち CMD (Concerted Metallation-Deprotonation) 機構により、シクロプロパンの C-H 結合が切断されてパラダサイクル **G** が生成する。次に酢酸によりプロトン化されて **Y** となり、続いてシクロプロパンの開環により **Z** が生成する。その後、β-ヒドリド脱離が進行して、0 価パラジウムが配位した共役アジン **AA** となる (path b)。一方で、パラダサイクル **G** からシクロプロパンの開環とパラジウム触媒の還元を伴う脱離反応が協奏的に進行し、0 価パラジウムが配位したアジン **AA** となる経路も考えられる (path a)。その後、**AA** の 0 価パラジウムが酸素と酢酸により酢酸パラジウム種へと変換され、遊離のアジン **15** が生成する。最後に、**15** の環化異性化反応により中間体 **AB** と **AC** と **AD** を経由して、ピラゾール **16** が生成する。



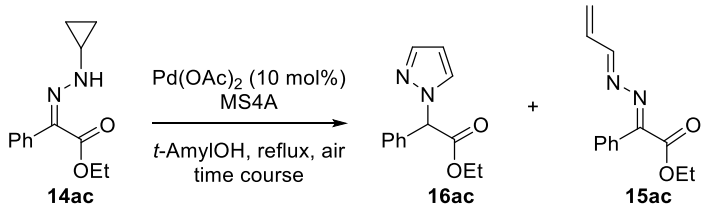
Scheme 49. Proposed reaction pathway.

そこで、本反応を以下の段階に分けて詳しく考察した。

1. ヒドラゾンから共役アジンの生成経路 **(14 → 15)**
2. 0 価パラジウムから酢酸パラジウムが再生する反応経路について
3. 共役アジンからピラゾールが生成する経路 **(15 → 16)**

1. ヒドラゾンから共役アジンの生成経路

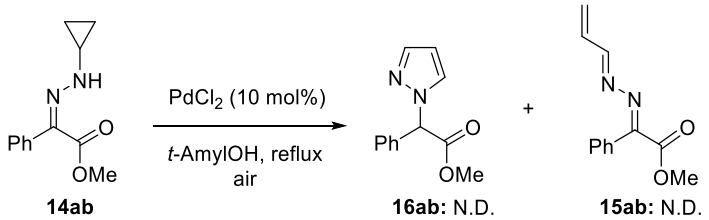
本反応を最適条件下で反応開始後、30 分、1 時間、2 時間で反応を停止させ NMR 測定を行ったところ、それぞれの時間でピラゾール **16ac** の生成とともにアジン **15ac** が低収率で生成していることが確認された (Scheme 50)。さらに、17 時間後ではアジン **15ac** が消失し、目的のピラゾール **16ac** のみが確認された。このことから共役アジンが中間体であることが推定された。



Time	**14ac**	**16ac**	**15ac** (NMR yield)
30 min	43%	4%	22%
1 h	17%	19%	26%
2 h	2%	42%	15%
17 h	0%	44%	0%

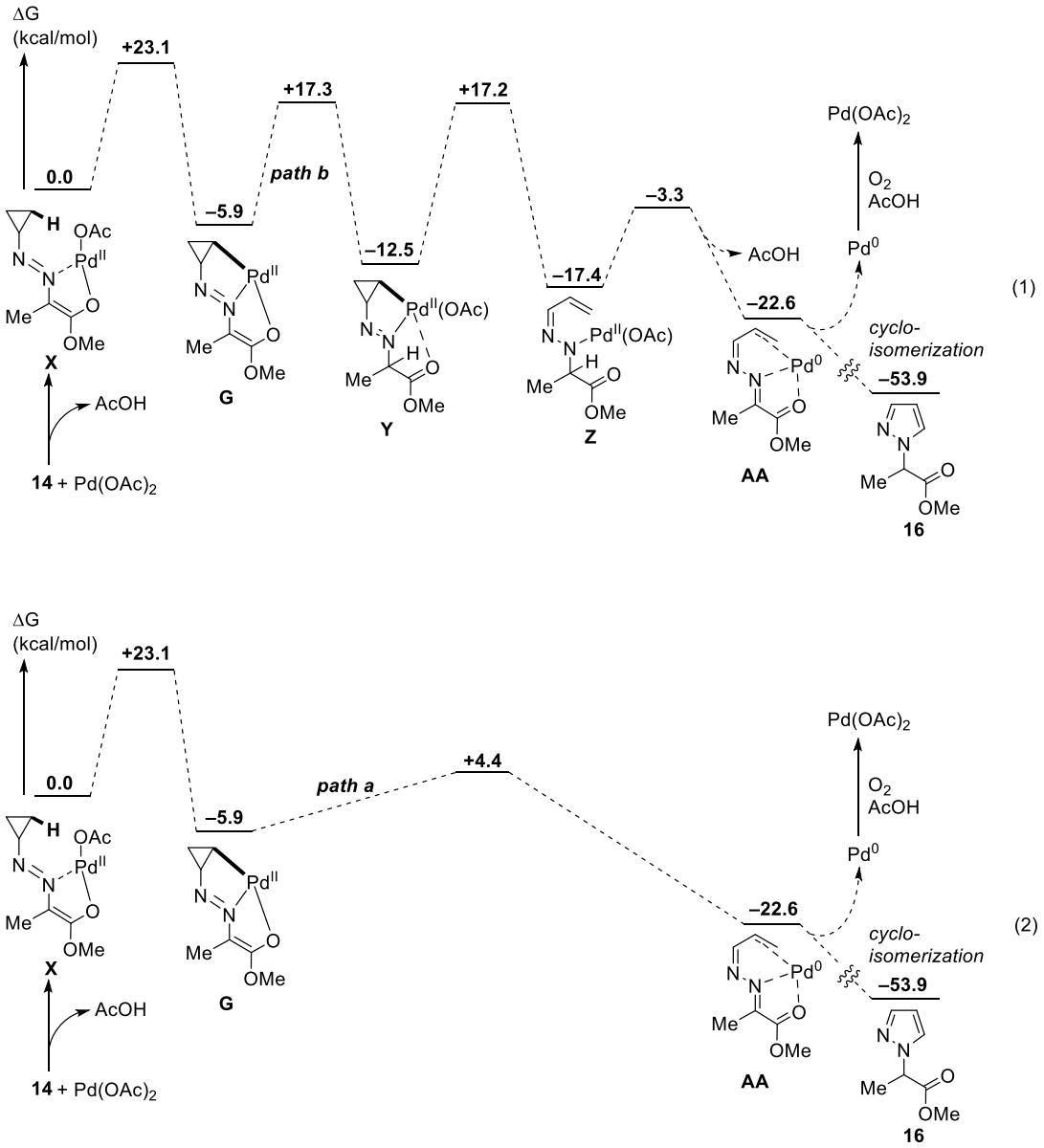
Scheme 50. Synthesis of conjugated azine and control experiments.

次に *N*-シクロプロピルヒドラゾンから共役アジンの生成経路について考察した。本反応は前述のようにパラジウム触媒によるシクロプロパンの C-H 活性化が進行し、シクロプロパンの開環反応に続く連続反応が進行してアジンが生成したと推定した。そこで C-H 活性化が進行していることを実験的に示すためにシクロプロピルヒドラゾン **14ab** を *tert*-アミルアルコール還流中、10 mol%の塩化パラジウムで処理したところ、目的のピラゾール **16ab** とアジン **15ab** は全く得られなかった (Scheme 51)。これは本反応において、パラジウム触媒の配位子として酢酸アニオンが重要であることを示しており、CMD 機構にて C-H 活性化が進行していることが示唆された。



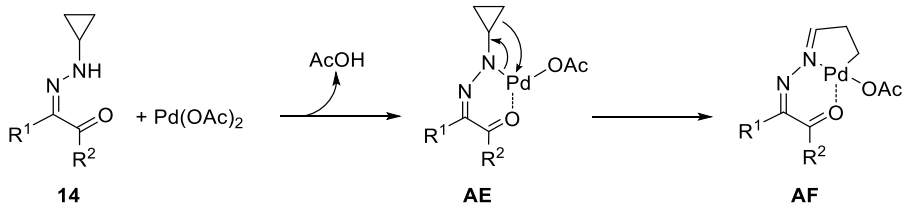
Scheme 51. Control experiment of C-H activation.

続いて DFT 計算を用いて、C-H 活性化を経由する反応経路について考察した (Scheme 52)。汎関数には M06 を適用し、基底関数としてパラジウムに対し Lanl2DZ、その他の原子に対しては 6-31G+(d, p)を用いた。まず、酢酸パラジウムの配位子交換が進行し、酢酸の脱離を伴ってヒドラゾンにパラジウムが配位した中間体 **X** が生成する。その後、中間体 X から CMD 機構による C-H 活性化が進行してパラダサイクル **G** が生成する反応の活性化エネルギーを計算したところ 23.1 kcal/mol であることが分かった。続いて、path b のように 23.2 kcal/mol の活性化エネルギーを伴い、酢酸の配位とともにヒドラゾンがプロトン化され、パラダサイクル **Y** になる (Scheme 52、式 1)。次に 29.7 kcal/mol の活性化エネルギーを伴いシクロプロパンが開環、14.1 kcal/mol の活性化エネルギーを伴い β-ヒドリド脱離が進行してアジン **AA** が生成すると計算した。一方で path a のようにパラダサイクル **G** からシクロプロパンの開環とパラジウムの還元が協奏的に進行してアジン **AA** が生成する経路では活性化エネルギーが 10.3 kcal/mol と計算された (Scheme 52、式 2)。この値はシクロプロパンの開環と β-ヒドリド脱離が段階的に進行する path b と比較して 12.8 kcal/mol 低いので、シクロプロパンの開環とパラジウムの還元が協奏的に進行する path a が主経路であると考えた。



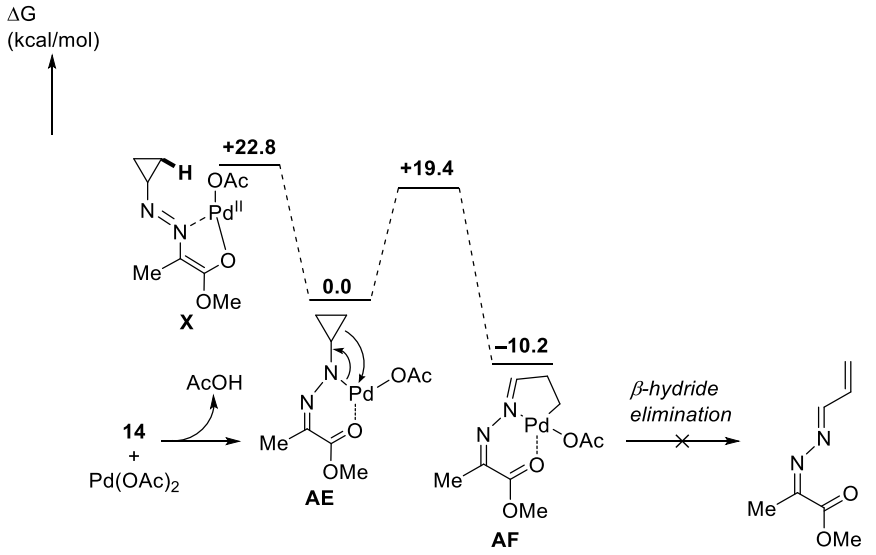
Scheme 52. Gibbs free energy profile of C-H activation pathway. (R^1 = Me, R^2 = OMe)

ここまでで C-H 活性化の経路について検討した。一方で本反応のシクロプロパンの開環反応の別経路も考えられる。すなわち、酢酸パラジウムの配位子交換が進行し、酢酸の脱離を伴ってパラジウムが配位し、6 員環のパラジウム錯体 **AE** が生成する (Scheme 53)。その後、β-炭素脱離が進行し、シクロプロパンの C-C 結合が直接切断される反応経路である。そこで、本反応経路についても汎関数として M06 を適用し、基底関数としてパラジウムに対し Lanl2DZ、その他の原子に対しては 6-31G+(d, p)を用いた DFT 計算を行った。



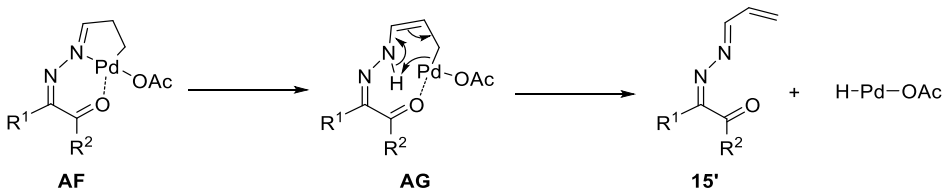
Scheme 53. Reaction mechanism of β-carbon elimination.

まず 6 員環の錯体 **AE** は C-H 活性化の前駆体である 5 員環のパラジウム錯体 **X** よりも 22.8 kcal/mol 安定であることが計算された (Scheme 54)。続いて **AE** から 19.4 kcal/mol の活性化エネルギーを伴い、β-炭素脱離が進行し、5 員環のパラダサイクル **AF** が生成する。次に **AF** からβ-ヒドリド脱離が進行して共役アジンが生成する経路について計算を行ったが、パラダサイクル **AF** は非常に安定な錯体であり、β-ヒドリド脱離が進行するような遷移状態を見つけることはできなかった。このことからパラダサイクル **AF** からはβ-ヒドリド脱離が進行しないと考えている。

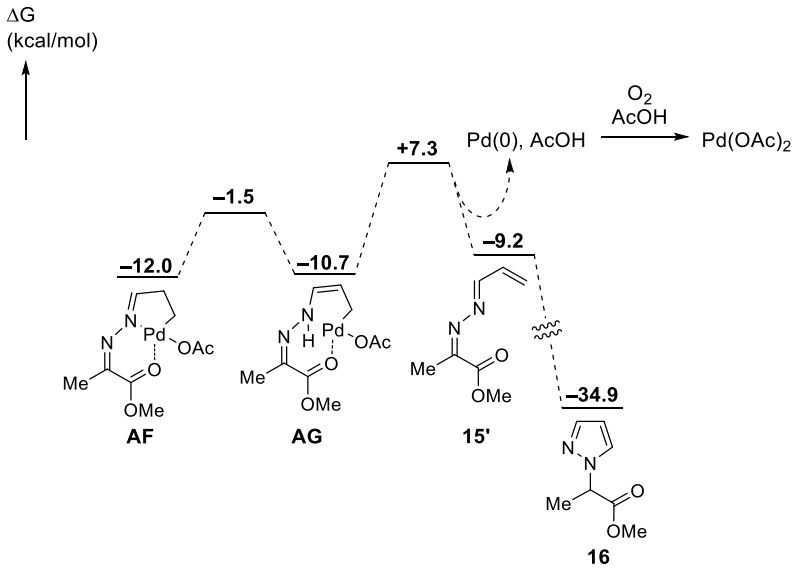


Scheme 54. Gibbs free energy profile of β-carbon elimination pathway. (R^1 = Me, R^2 = OMe)

そこで、パラダサイクル **AF** から互変異性化が進行し、エナミン構造を有する **AG** となる。続いてアミン窒素上の水素脱離が進行し、共役アジン **15'** とパラジウムヒドリドが生成する経路を考案した (Scheme 55)。本経路について種々検討した結果、汎関数として分散力補正が行われた B97D、基底関数としてパラジウムに対し Lanl2DZ、その他の原子に対して 6-31G+(d, p)-def2TZV を用いた DFT 計算を行った場合、中間体 **AF** から 10.5 kcal/mol の活性化エネルギーを伴い、エナミン中間体 **AG** が生成する (Scheme 56)。続いて 18 kcal/mol の活性化エネルギーを伴い共役アジン **15'** が生成することが計算された。

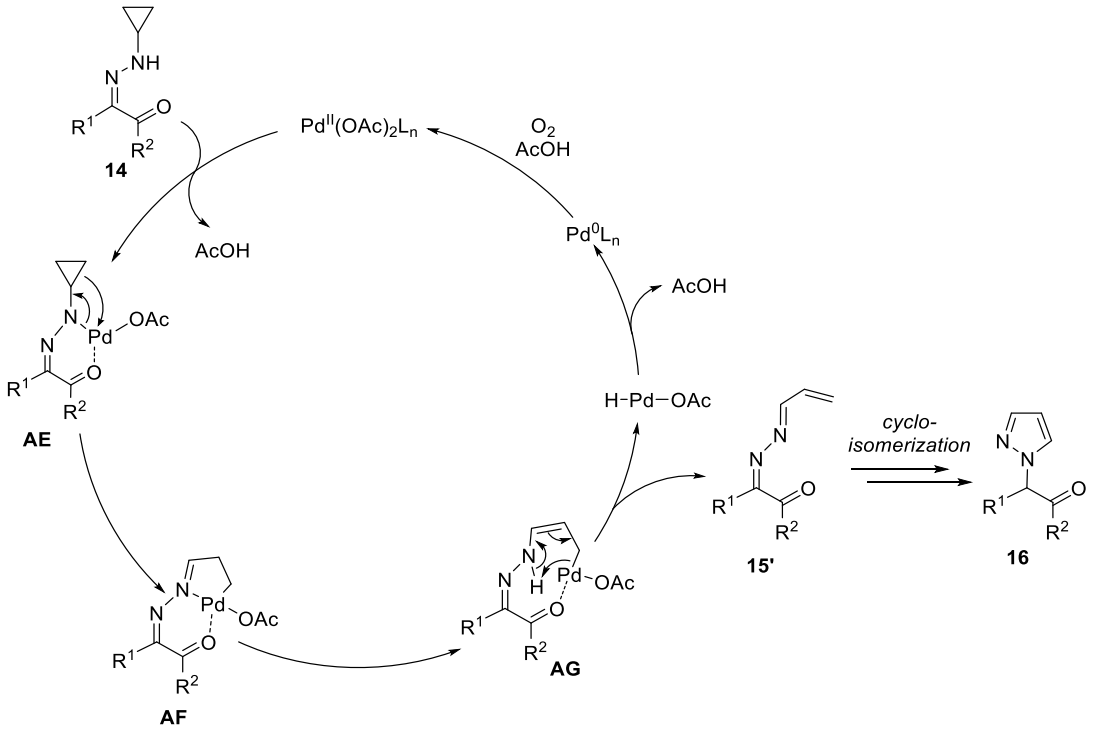


Scheme 55. Another pathway of generating conjugated azine from 5-membered palladacycle **AF**.



Scheme 56. Gibbs free energy profile of generating conjugated azine from 5-membered palladacycle **AF**. (R^1 = Me, R^2 = OMe)

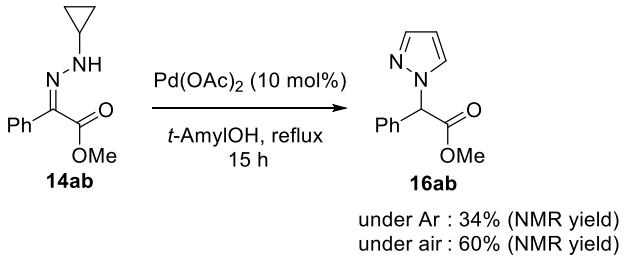
以上のように、β-炭素脱離を介したシクロプロパンの開環反応は C-H 活性化を経由する開環反応よりも活性化エネルギーが低いことが分かり、本反応は β-炭素脱離を介したシクロプロパンの開環反応が主経路であると考えた。すなわち、ヒドラゾン **14** に酢酸パラジウムが配位して 6 員環パラダサイクル **AE** が生成した後、β-炭素脱離を介したシクロプロパンの開環反応が進行し、5 員環パラダサイクル **AF** が生成する (Scheme 57)。**AF** から互変異性化が進行し、エナミン構造を有する中間体 **AG** となる。続いてアミン窒素上の水素脱離が進行し、共役アジン **15'** とパラジウムヒドリドが生成する。パラジウムヒドリドは還元的脱離により 0 価のパラジウム種となり、その後酸素と酢酸により酢酸パラジウム種へと変換される。最後に共役アジン **15'** の環化異性化反応によりピラゾール **16** が生成する。



Scheme 57. Main reaction pathway.

2. 0 価パラジウムから酢酸パラジウムが再生する反応経路について

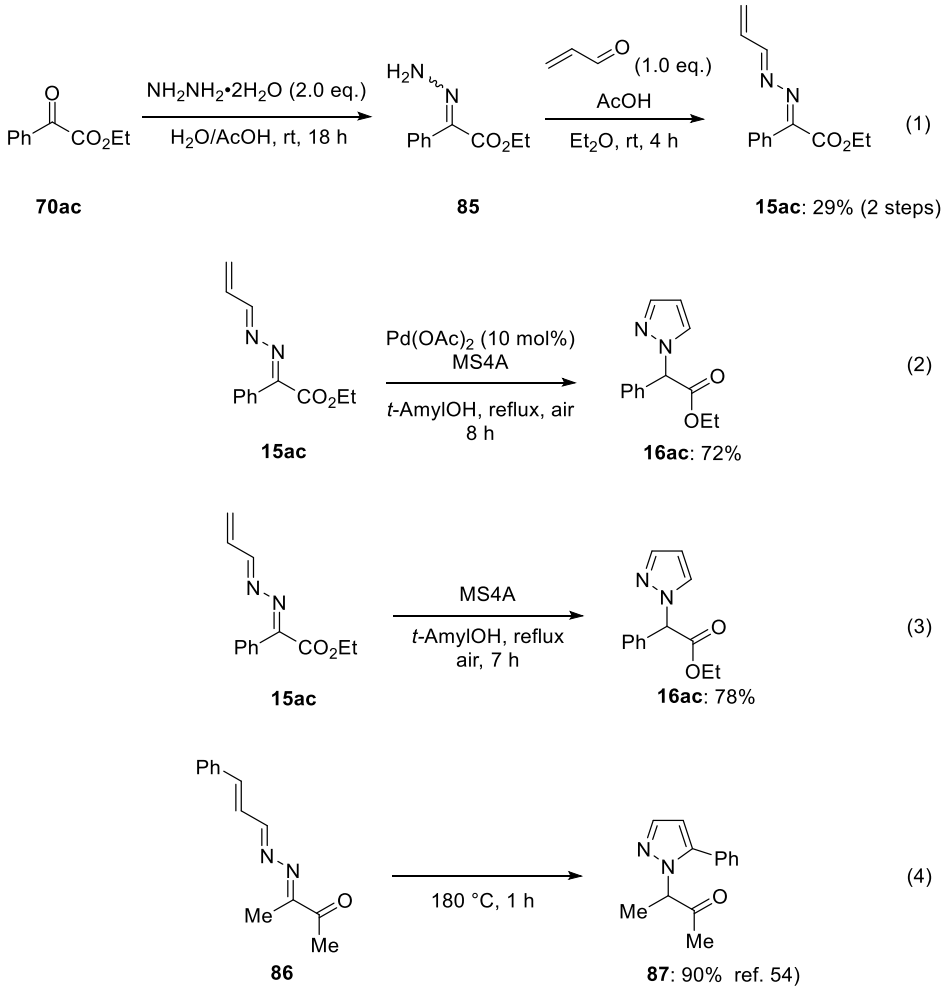
本反応を最適条件の空気存在下ではなく、アルゴン雰囲気化で検討したところ、ピラゾール **16ab** の収率は 34%に低下した (Scheme 58)。ここから本反応に酸素が必要であることが示唆された。この理由について、0 価パラジウムが酸化され 2 価の酢酸パラジウムが再生する際に空気中の酸素が必要であることが考えられる。[52, 53)]



Scheme 58. The reaction mechanism of regenerating $Pd(OAc)_2$.

3. 共役アジンからピラゾールが生成する経路

本反応途中で共役アジン **15ac** が生成することを確認したが、低収率であった (Scheme 50)。そこで、アジン **15ac** を別途合成した後に対照実験を検討することとした。まず α-ケトエステル **70ac** をヒドラジン水和物と縮合することでヒドラゾン **85** を合成した (Scheme 59、式 1)。得られたヒドラゾン **85** をアクロレインと縮合することで、アジン **15ac** を 29%の収率で合成した。次に、合成したアジン **15ac** を最適条件に付すと、ピラゾール **16ac** が 72%の収率で得られた (式 2)。以上のことから共役アジンが本反応の中間体であることが示唆された。共役アジン **15ac** をパラジウム触媒非存在下で加熱すると、ピラゾール **16ac** が 78%の収率で得られ、パラジウム触媒存在下よりもわずかに高い収率となった (式 3)。そのため、共役アジンの環化異性化反応によりピラゾールが生成する過程においてパラジウム触媒は関与せず、わずかに反応を阻害していることが示唆された。なお、報告されている類似の環化異性化反応でも加熱のみで反応が進行しており、本検討でも同様の結果が確認された (式 4)。[54)]

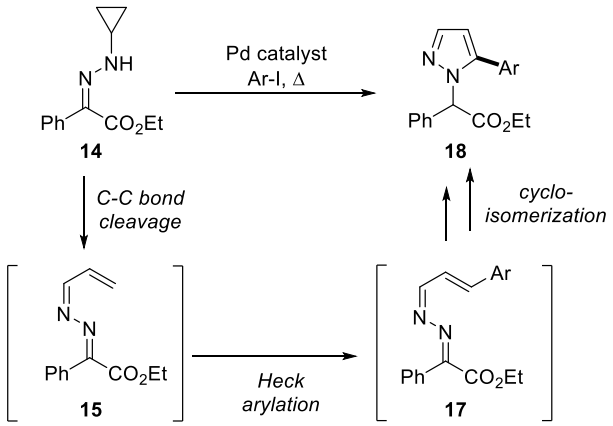


Scheme 59. Cycloisomerization of conjugated azine without Pd catalyst.

以上のように著者は*N*-シクロプロピルアシルヒドラゾンのパラジウム触媒によるシクロプロパンの C-C 結合切断に続く連続反応によりピラゾールの合成に成功した。本反応において、アシルヒドラゾンはシクロプロパン活性化の配向基としての役割だけでなく、その後の環化異性化反応の促進にも関与し、目的のピラゾールに取り込まれているため、原子効率の観点から優れた合成法が実現できる配向基である。

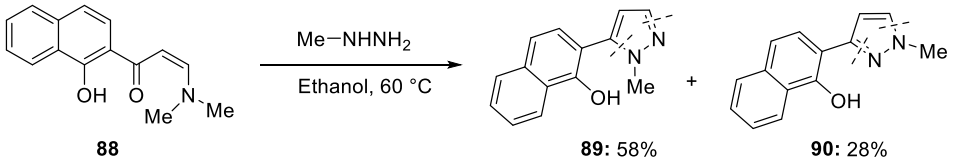
第 3 章　*N*-シクロプロピルアシルヒドラゾンの開環反応と Heck 反応の連続反応による 1-アルキル-5-アリールピラゾール合成法の開発

第 2 章で *N*-シクロプロピルアシルヒドラゾンをパラジウム触媒で処理することでアミノ基上のシクロプロパンの C-C 結合切断を起点とする連続反応の開発に成功した。しかし、合成できるピラゾールのほとんどが一置換ピラゾールに限られており、二置換ピラゾールの合成は、原料である二置換シクロプロパンの合成に多くの工程を要することから実用的でなかった。この問題の解決案として、著者は本反応の共役アジン中間体に Heck 反応で置換基導入ができれば、二置換ピラゾールを簡便に合成できると考えた。すなわち、加熱条件下で *N*-シクロプロピルヒドラゾン **14** とヨードアレーンをパラジウム触媒と反応させることで 1-アルキル-5-アリールピラゾール **18** が合成できると考えた (Scheme 60)。本反応は第 2 章の反応と同様にパラジウム触媒によるシクロプロパンの開環反応が進行し、共役アジン **15** が生成する。続いて Heck 反応が進行し、アリール化されたアジン **17** が生成し、最後に加熱による環化異性化が進行することで、1-アルキル-5-アリールピラゾール **18** が生成する。



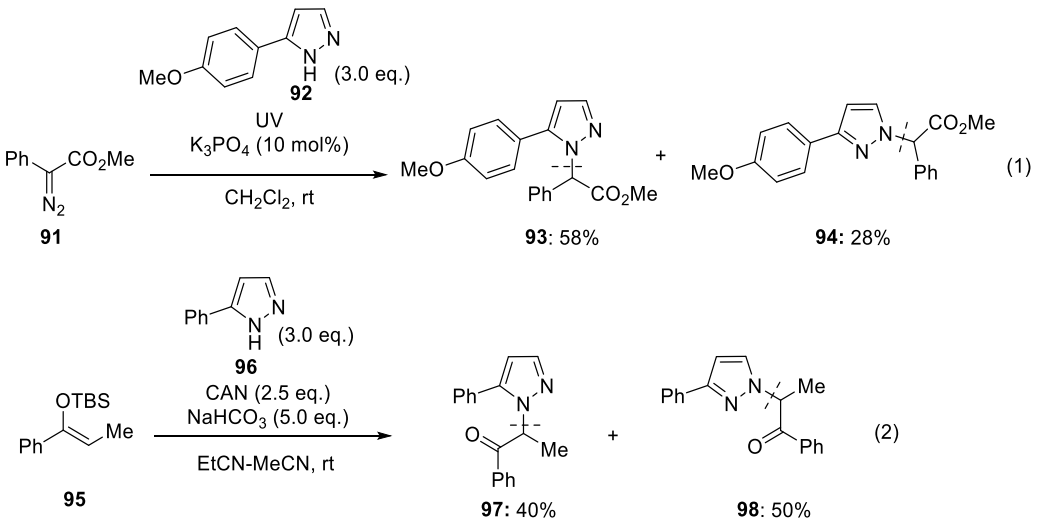
Scheme 60.　1-Alkyl-5-aryl pyrazole synthesis via C-C bond cleavage of cyclopropane, Heck arylation and cycloisomerization.

今回合成する 1-アルキル-5-アリールピラゾールはこれまでに様々な手法が報告されているが、効率的な合成法は未だ報告されていない。1-アルキル-5-アリールピラゾール合成の最も単純な例として、1,3-ジカルボニル化合物等価体とヒドラジンを用いた縮合反応がある。Reedjik らはビニロガスアミド **88** とメチルヒドラジンを縮合させることで 1-アルキル-5-アリールピラゾール **89** を合成できることを報告している (Scheme 61)。[55] しかし、同時に 1-アルキル-3-アリールピラゾール **90** が副生することから、位置選択性に課題があった。



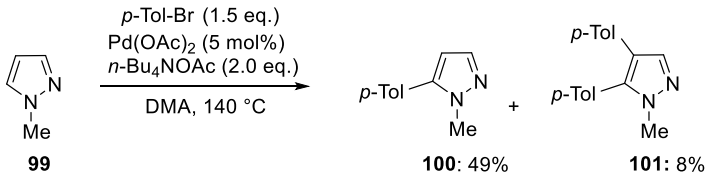
Scheme 61. Pyrazole synthesis via condensation of hydrazine and 1,3-dicarbonyl isostere.

また、一置換ピラゾールを用いてN1位にアルキル基を導入する手法が報告されている。Jurbergらはアリールジアゾアセテート**91**をUV照射下、3.0当量の3-アリールピラゾール**92**と10 mol%のリン酸カリウムで処理することで、N-H挿入反応が進行し、1-アルキル-5-アリールピラゾール**93**の合成に成功している (Scheme 62、式1)。[56] また、Thomsonらはシリルエノールエーテル**95**をCAN存在下で3.0当量の3-アリールピラゾール**96**と5.0当量の炭酸水素ナトリウムで処理することで、酸化的カップリングが進行し、1-アルキル-5-アリールピラゾール**97**の合成に成功している (式2)。[57] しかし、これら2つのN1位アルキル化反応でも同様に、1-アルキル-3-アリールピラゾール**94**や**98**が副生するために、位置選択性に課題があった。



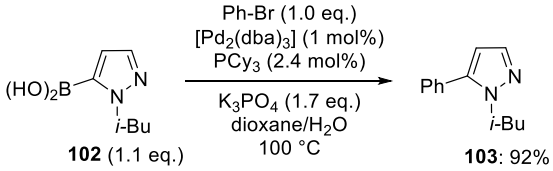
Scheme 62. N-H insertion of pyrazoles.

さらにN1位一置換ピラゾールを用い、5位にアリール基を導入する手法も報告されている。Manziniらは*N*-メチルピラゾール**99**を5 mol%の酢酸パラジウム触媒存在下、4-ブロモトルエンと*n*-Bu_4NOAcで処理することで、5-アリールピラゾール**100**の合成に成功している (Scheme 63)。[58] しかし、アリール化がさらに進行した三置換ピラゾール**101**も同時に生成しているため、本手法は化学選択性に課題があった。



Scheme 63. C-H arylation of pyrazoles.

以上のような位置選択性または化学選択性の課題を解決する合成法として、カップリング反応を利用する手法がある。例えば Fu らは 1-アルキルピラゾールボロン酸 **102** とフェニルブロミドを鈴木クロスカップリングの条件に付すことで、位置選択的に 1-アルキル-5-アリールピラゾール **103** の合成に成功している (Scheme 64)。[59] しかし、原料の 1-アルキルピラゾールボロン酸 **102** の合成において、強塩基である *n*-BuLi を用いた条件を利用しているため、合成できる 1-アルキルピラゾールボロン酸が制限されている。

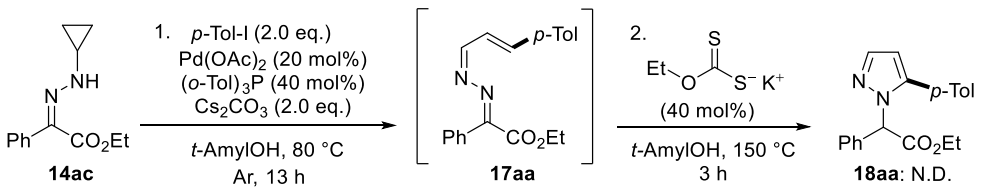


Scheme 64. Cross coupling reaction of pyrazoleboronic acid with arylbromide.

以上のように 1-アルキル-5-アリールピラゾールはこれまでに様々な手法が報告されているが、主に位置選択性や化学選択性に課題があった。著者が開発する *N*-シクロプロピルヒドラゾンの C-C 結合切断、Heck 反応、環化異性化の連続反応は 1-アルキル-5-アリールピラゾールを単一生成物として提供することができ、位置選択性や化学選択性の課題を解決する合成法になることが期待できる。

第 1 節　反応条件最適化の検討

シクロプロピルヒドラゾン **14ac** を用いて *N*-シクロプロピルアシルヒドラゾンのシクロプロパンの C-C 結合切断と Heck 反応による 1-アルキル-5-アリールピラゾールの合成を検討した (Scheme 65)。まずシクロプロパンの開環により共役アジンが生成した後、Heck 反応が進行することで、5-アリール共役アジン **17aa** が生成する反応の条件を探索した。前章で、共役アジンは 100 ℃の条件下において速やかに環化異性化が進行し、一置換ピラゾールへ変換されることが分かっているため、反応温度を下げることで共役アジンの環化異性化を抑制し、Heck 反応を優先して進行させることで、5-アリール共役アジンが選択的に得られると考えた。そこで、Heck 反応の条件を参考にし、*tert*-アミルアルコール中、80 ℃でシクロプロピルヒドラゾン **14ac** と 2.0 当量の *p*-ヨードトルエンを 20 mol%の酢酸パラジウムと 40 mol%の(o-Tol)$_3$P、および塩基として 2.0 当量の炭酸セシウムを用いて 13 時間攪拌すると、期待通り、5-アリール共役アジン **17aa** が生成した。[60,61] 5-アリール共役アジン **17aa** は 80 °C の条件において環化異性化反応が進行しないため、続いて昇温することとした。また、第 2 章第 3 節での対照実験の結果から、パラジウム触媒は環化異性化を阻害することが分かっていた。そこで、パラジウム捕捉剤としての機能を期待して、系中に 40 mol%のエチルキサントゲン酸カリウムを加えて 150 ℃で加熱攪拌したところ、ピラゾール **18aa** は全く得られなかった。これは *tert*-アミルアルコール中 150 °C の条件では、5-アリール共役アジン **17aa** またはピラゾール **18aa** が分解したためだと考えている。

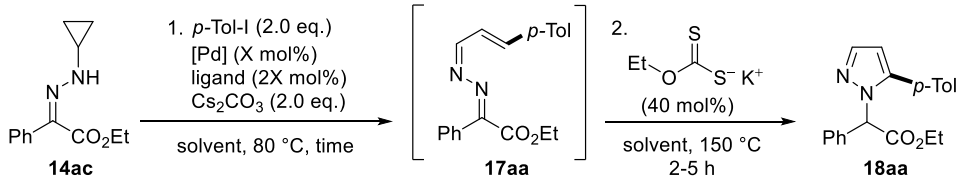


Scheme 65. Heck reaction of *N*-cyclopropyl acylhydrazone.

そこでシクロプロパンの開環、Heck 反応、および環化異性化反応に最適な溶媒について種々検討した (Table 8、entries 1-4)。アセトニトリルまたは DMF を溶媒に用いた場合、ピラゾール **18aa** は全く得られなかったが、キシレンを溶媒として用いると、ピラゾール **18aa** が 35%の収率で得られた。続いてベンゾニトリルを溶媒に用いた際にピラゾール **18aa** の収率が 56%に向上し、ベンゾニトリルが本反応を効率よく進行させる溶媒であることが分かった (entry 4)。次に、環化異性化反応の際にエチルキサントゲン酸カリウムを添加しなかったところ、ピラゾール **18aa** の収率は 46%に低下した (entry 5)。これによりエチルキサントゲン酸カリウムがパラジウム捕捉剤として有用であることが明らかになった。続いて更なる収率の向上を目指し、様々な配位子について検討した (entries 6-8)。その結果、(o-Tol)$_3$P が最も良い結果を与えることが分かった。次に Heck 反応の促進が期待できるパラジウム触

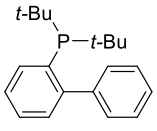
媒として Herrmann 触媒を 10 mol%用いたところ、同様の収率でピラゾール **18aa** が得られた (entry 9)。[62] さらに、反応系中で生成するパラジウムヒドリドの還元的脱離を促進する添加剤を検討した (entries 10-12)。塩化リチウムを 20 mol%添加した場合、収率は向上しなかったが、*n*-Bu_4NOAc または *n*-Bu_4NI を 20 mol%添加したところ、いずれの場合も収率は 61%に向上した (entries 11 and 12)。[63] 最後に、塩基の検討を行った (entries 13-15)。有機塩基としてトリエチルアミン、無機塩基として水酸化カリウムや炭酸カリウムも検討したが、それぞれ収率の向上は見られなかった。以上の検討の結果、シクロプロピルヒドラゾンをベンゾニトリル中 80 °C で 2.0 当量のヨードアレーンと 10 mol%の Herrmann 触媒、塩基として 2.0 当量の炭酸セシウム、添加剤として 20 mol%の *n*-Bu_4NOAc または *n*-Bu_4NI で処理し、5-アリール共役アジンへと誘導する。その後、40 mol%のエチルキサントゲン酸カリウムを添加し、150 °C で加熱攪拌する条件が最適であることが明らかになった。

Table 8. Reaction optimization for synthesis of 1-alkyl-5-arylpyrazole.

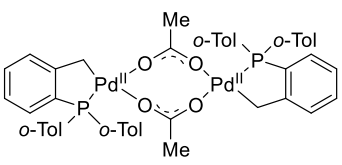


entry	[Pd] (mol%) / ligand	base	solvent	additive (mol%)	time (h)	yield (%)
1	$Pd(OAc)_2$ (20) / $(o\text{-Tol})_3P$	Cs_2CO_3	MeCN	–	14	N.D.
2	$Pd(OAc)_2$ (20) / $(o\text{-Tol})_3P$	Cs_2CO_3	DMF	–	2	N.D.
3	$Pd(OAc)_2$ (20) / $(o\text{-Tol})_3P$	Cs_2CO_3	Xylene	–	17	35
4	$Pd(OAc)_2$ (20) / $(o\text{-Tol})_3P$	Cs_2CO_3	PhCN	–	5	56
5 [b]	$Pd(OAc)_2$ (20) / $(o\text{-Tol})_3P$	Cs_2CO_3	PhCN	–	12	46
6	$Pd(OAc)_2$ (20) / Ph_3P	Cs_2CO_3	PhCN	–	2	36 [a]
7	$Pd(OAc)_2$ (20) / $(t\text{-Bu})_3P$	Cs_2CO_3	PhCN	–	17	10 [a]
8	$Pd(OAc)_2$ (20) / JohnPhos	Cs_2CO_3	PhCN	–	17	5 [a]
9	Herrmann cat. (10)	Cs_2CO_3	PhCN	–	12	57
10	Herrmann cat. (10)	Cs_2CO_3	PhCN	LiCl (20)	21	54
11	Herrmann cat. (10)	Cs_2CO_3	PhCN	*n*-Bu_4NOAc (20)	19	61
12	Herrmann cat. (10)	Cs_2CO_3	PhCN	*n*-Bu_4NI (20)	7	61
13	Herrmann cat. (10)	Et_3N	PhCN	*n*-Bu_4NOAc (20)	36	4 [a]
14	Herrmann cat. (10)	KOH	PhCN	*n*-Bu_4NOAc (20)	65	51
15	Herrmann cat. (10)	K_2CO_3	PhCN	*n*-Bu_4NOAc (20)	67	58

a) Yields were determined by ^1H NMR using triphenyl methane as an internal standard.
b) Without potassium ethyl xanthate.



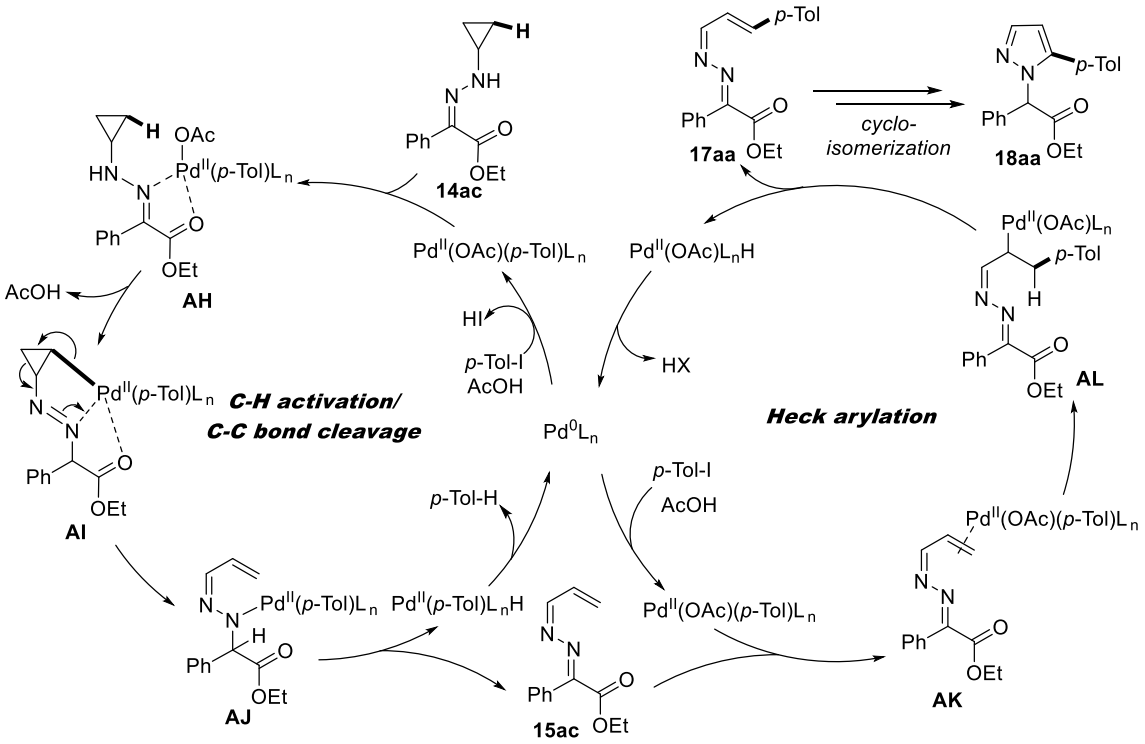
JohnPhos



Herrmann cat.

第 2 節　反応経路の考察

本反応の推定反応経路を Scheme 66 に示す。Herrmann 触媒から生じる 0 価のパラジウム種について、ヨードアレーンへの酸化的付加と酢酸の配位子交換が進行し、アリール基の結合したパラジウムアセテート種が生成する。その後ヒドラゾン **14ac** へパラジウムアセテート種が配位し中間体 **AH** になる。次に、パラジウムが近傍のシクロプロパン C-H 結合を切断し、パラダサイクル **AI** が生成する。続いて、パラダサイクル **AI** におけるシクロプロパンの開環反応が進行し、**AJ** になる。その後、β-ヒドリド脱離が進行して、アジン **15ac** とパラジウムヒドリドが生成する。パラジウムヒドリドは還元的脱離の進行により 0 価パラジウムへと変換される。その後、0 価パラジウムのヨードアレーンへの酸化的付加から生じたアリールパラジウム種がオレフィンへ挿入することで **AL** となり、β-ヒドリド脱離の進行により 5-アリール共役アジン **17aa** が生成する。**17aa** は加熱による環化異性化反応が進行して目的のピラゾールへ **18aa** と変換されたと考えている。また、パラジウムアセテート種がヒドラゾンに配位して中間体 **AH** になる反応において、第 2 章ではヒドラゾンの脱プロトン化を伴う酢酸アニオンとの配位子置換が進行したが、本反応ではパラジウムアセテート種のトリル基のシグマ供与性が高いので、ヒドラゾンのパラジウムへの配位が弱くなっていると考えられる。そのため、パラジウム上の酢酸アニオンの脱離が起こりにくく、塩基存在下でもヒドラゾンの脱プロトン化を伴う配位子置換は進行しにくいと考えている。[64] また、Scheme 66 のシクロプロピルヒドラゾン **14ac** から開環反応が進行し、共役アジン **15ac** が生成する過程では β-炭素脱離が進行する経路も考えられるが、パラジウム種が異なるため、暫定的な反応機構を提唱している。



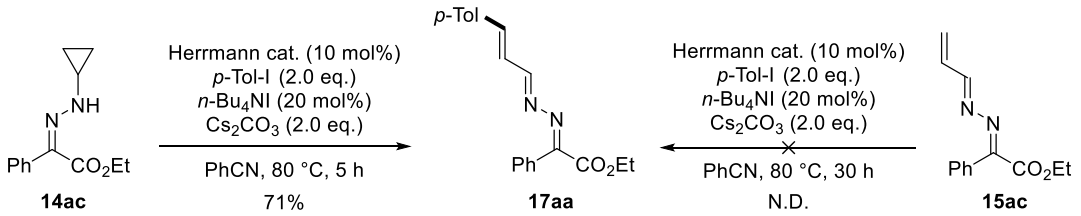
Scheme 66. Proposed reaction mechanism.

次に、本反応の詳細について以下の段階に分けて詳しく説明する。

1. シクロプロピルヒドラゾンから 5-アリール共役アジンの生成経路 (**14ac → 17aa**)
2. 5-アリール共役アジンからピラゾールの生成経路 (**17aa → 18aa**)

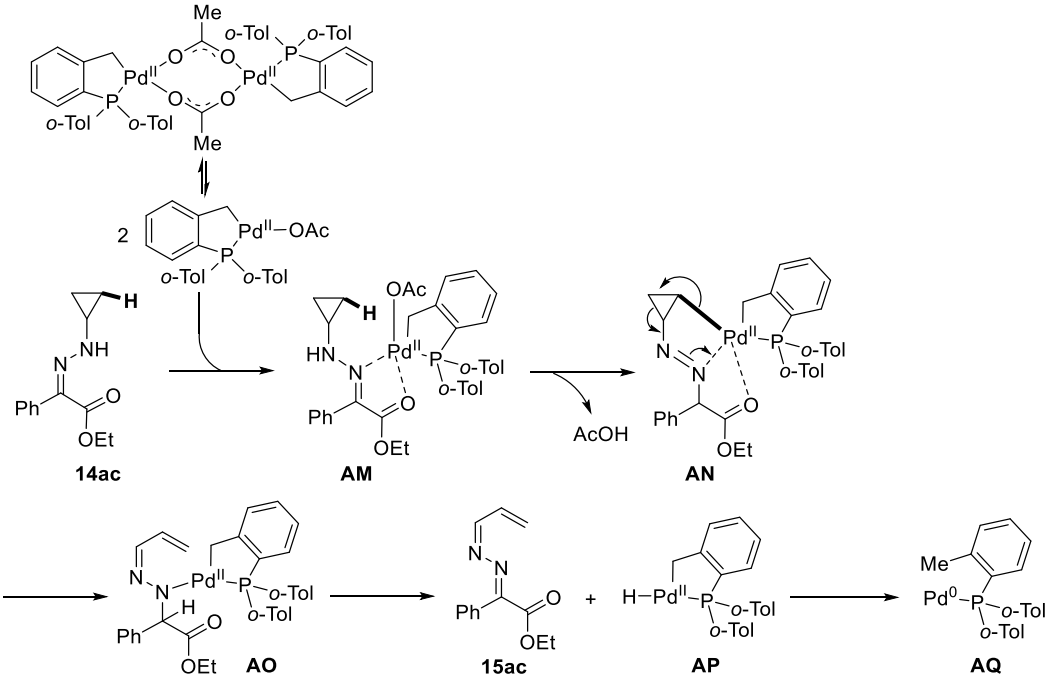
1. <u>シクロプロピルヒドラゾンから 5-アリール共役アジンの生成経路</u>

本反応をエチルキサントゲン酸カリウムの添加前に反応を停止させると、5-アリール共役アジン **17aa** が 71%の収率で得られた (Scheme 67)。次に共役アジン **15ac** を最適条件下に付したところ、5-アリール共役アジン **17aa** は全く得られなかった。この理由について、Herrmann 触媒は 2 価のパラジウム触媒であるためにヨードアレーンへの酸化的付加が進行しないため、Heck 反応が進行しなかったことが考えられる。



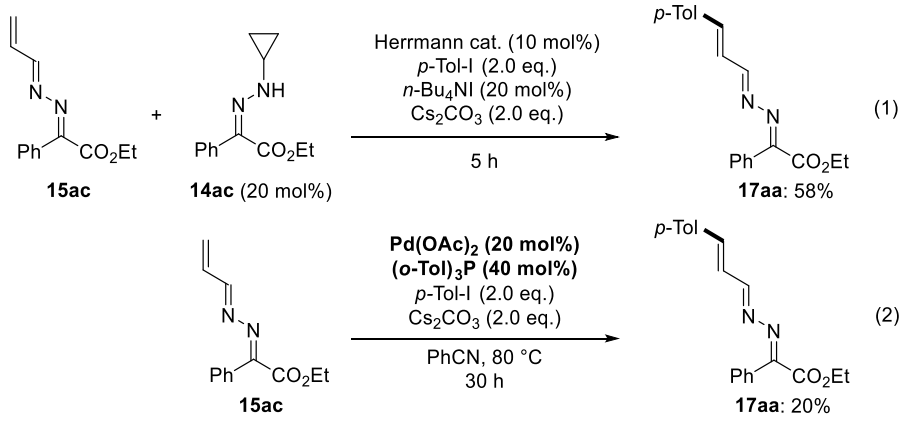
Scheme 67. Generation of 5-aryl conjugated azine.

そこで、第 2 章で得た知見から、Herrmann 触媒が出発原料によって 0 価のパラジウム種に還元されれば、反応は進行すると考えた。すなわち、シクロプロピルヒドラゾン **14ac** を触媒量添加することで、二核錯体と平衡状態にある Herrmann 触媒の単核錯体がシクロピルヒドラゾン **14ac** に配位して、中間体 **AM** が生成する。その後、シクロプロパンの C-H 活性化と開環反応が進行し、**AO** となる。続いて β-ヒドリド脱離が進行して、アジン **15ac** とパラジウムヒドリド **AP** が生成する。次に、還元的脱離の進行により、**AP** から 0 価の (*o*-Tol)$_3$PPd **AQ** が生成することで、反応が触媒的に進行すると期待した (Scheme 68)。



Scheme 68. Reduction of Herrmann catalyst.

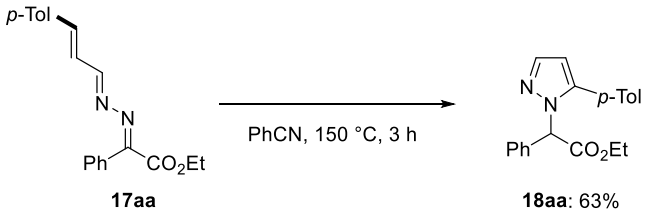
そこで、共役アジン **15ac** を基質として用い、最適条件に対してシクロプロピルヒドラゾン **14ac** を 22 mol%添加した条件に付すと、5-アリール共役アジン **17aa** が 58%の収率で得られた (Scheme 69、式 1)。また、反応系中で生成する 0 価パラジウムを利用することで、共役アジンへの Heck 反応が進行し、5-アリール共役アジンが生成すると期待した。そこで、アジン **15ac** と 2.0 当量の *p*-ヨードトルエンをベンゾニトリル中、80 ℃で 20 mol%の酢酸パラジウムと 40 mol%の (*o*-Tol)$_3$P、および塩基として 2.0 当量の炭酸セシウムを用いた場合、5-アリール共役アジン **17aa** が 20%の収率で生成した (式 2)。これらの検討で共役アジン **15ac** の Heck 反応が進行したことから、本反応でも同様に、共役アジンから 5-アリール共役アジンが生成することが明らかになった。



Scheme 69. Heck reaction of conjugated azine.

2 5-アリール共役アジンからピラゾールの生成経路

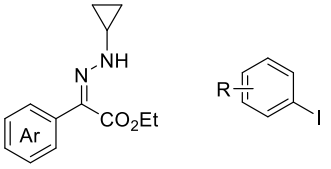
5-アリール共役アジン **17aa** をベンゾニトリル中、150 °C で加熱攪拌すると、ピラゾール **18aa** が 63%の収率で得られた (Scheme 70)。このことから 5-アリール共役アジンから環化異性化反応が進行してピラゾールが生成する経路では、パラジウム触媒が不要であることが示唆された。



Scheme 70. Cycloisomerization of 5-aryl conjugated azine.

第 3 節　基質適用範囲に関する検討

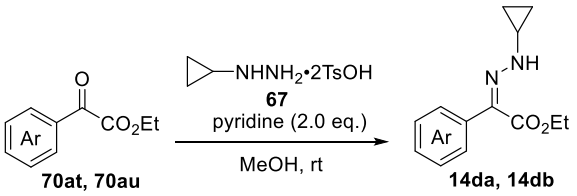
次に、著者は *N*-シクロプロピルアシルヒドラゾンのシクロプロパンの C-C 結合切断と Heck 反応による 1-アルキル-5-アリールピラゾール合成の基質適用範囲に関して検討した。第 3 節第 1 項では原料合成について説明する。第 3 節第 2 項ではヨードアレーンやシクロプロピルヒドラゾンの基質適用範囲について検討した。



第 1 項　シクロプロピルヒドラゾンとヨードアレーンの合成

まず、基質となるヨードアレーンとシクロプロピルヒドラゾンの合成を行った。メタノール中室温で、ケトエステル **70at, 70au** とシクロプロピルヒドラジン **67** をピリジン存在下で縮合させることでヒドラゾン **14da, 14db** を合成した (Table 9)。

Table 9. Preparation of cyclopropylhydrazones.

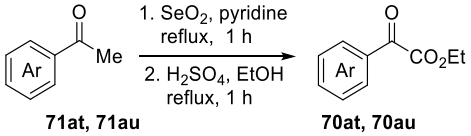


70at, 70au　　**14da, 14db**

entry	α-keto ester	Ar	time (h)	hydrazone	yield
1	**70at**	2-naphthyl	16 h	**14da**	53%
2	**70au**	4-$EtO_2CC_6H_4$	13 h	**14db**	62%

また、上記のヒドラゾン合成の原料となる α-ケトエステル **70at**, **70au** は以下のように合成した (Table 10)。すなわちケトン **71at**, **71au** をピリジン還流中、二酸化セレンで α-ケトカルボン酸に酸化した後、硫酸存在下でエタノールと縮合することで合成した。

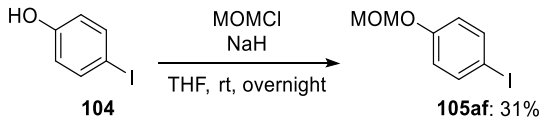
Table 10. Preparation of α-keto ester **70at, 70au**.



71at, 71au　　**70at, 70au**

entry	R	α-keto ester	yield
1	2-naphthyl	**70at**	89%
2	4-$EtO_2CC_6H_4$	**70au**	33%

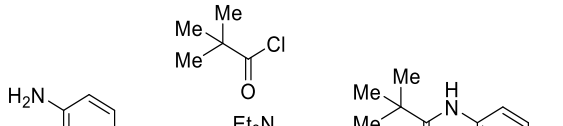
次に市販されていないヨードアレーン **105af, 105ag** の合成を行った。
4-ヨードフェノール **104** を水素化ナトリウム存在下でクロロメチルメチルエーテルを用い、ヒドロキシ基を MOM 保護することで、**105af** を合成した (Scheme 71)。



104 **105af**: 31%

Scheme 71. Preparation of iodoarene **105af**.

次に 4-ヨードアニリン **106** をトリエチルアミン存在下で塩化ピバロイルを用い、アミノ基を保護することで、アミド **105ag** を合成した (Scheme 72)。



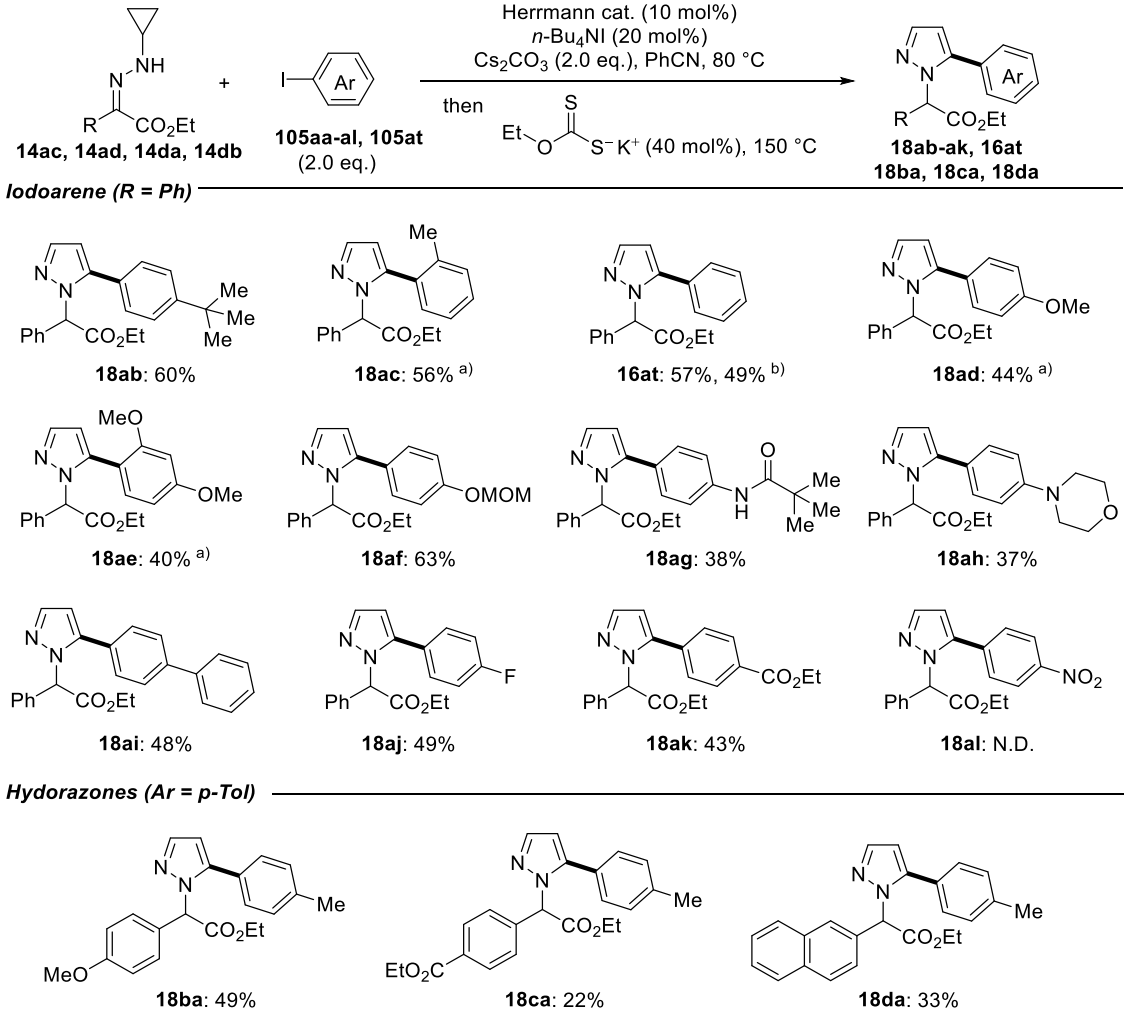
106 **105ag:** 96%

Scheme 72. Preparation of iodoarene **105ag.**

第 2 項　シクロプロピルヒドラゾンとヨードアレーンの基質適用範囲に関する検討

合成したヨードアレーン **105af, 105ag** と市販のヨードアレーン **105ab-ae**, **105ah-ak, 105at** を用いて、*N*-シクロプロピルアシルヒドラゾンのシクロプロパンの C-C 結合切断と Heck 反応による 1-アルキル-5-アリールピラゾールの合成を検討した (Scheme 73)。**105ab, 105ac** のようにアルキル基を有するアレーンを用いた場合、良好に反応が進行し、ピラゾール **18ab** (60%), **18ac** (56%) が得られた。オルト位にメチル基をもつヨードアレーン **105ac** がパラ位にメチル基をもつヨードアレーンの収率とほぼ同程度であることから、本反応ではヨードアレーンの立体障害が反応に影響しないことが示唆された。また、ヨードベンゼン **105at** からは **16at** が 57%の収率で得られた。フェニル基や電子供与基のメトキシ基、2,4-ジメトキシ基を有するアレーン **105ad, 105ae** からも反応が進行し、さらに MOM 基で保護されたフェノール **105af** からは 63%の収率でピラゾール **18af** が得られた。アミドを有するアレーン **105ag** や、モルホリンを有するアレーン **105ah** からは収率は低下したもののピラゾール **18ag** (38%), **18ah** (37%) が得られた。また、ジフェニルを有するアレーン **105ai**、電子求引基のフッ素やエステルを有するアレーン **105aj, 105ak** も適用できたが、ニトロ基を有するアレーン **105al** からはピラゾールは得られなかった。

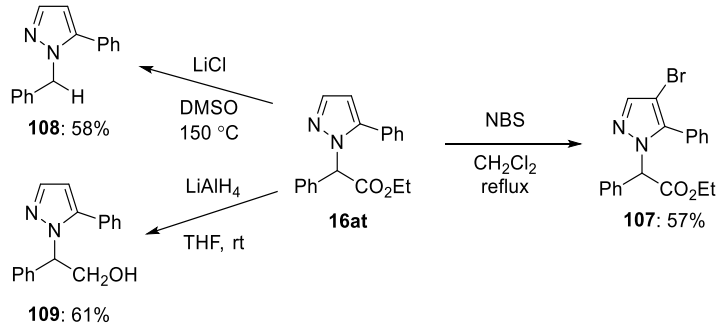
続いて 4-ヨードトルエン **105aa** をアリール化剤として用い、シクロプロピルヒドラゾンのイミン炭素上の置換基について検討した。置換基 R に 4-メトキシフェニル基をもつヒドラゾン **14ad** からは 49%の収率でピラゾール **18ba** が得られたが、R に 4-エトキシカルボニルフェニル基を有するヒドラゾン **14db** からはピラゾール **18ca** の収率が低下した。また、R にナフチル基を有するヒドラゾン **14da** からも反応が進行し、目的のピラゾール **18da** が 33％の収率で得られた。



a) n-Bu_4NOAc was used instead of n-Bu_4NI. b) 2.0 mmol scale.

Scheme 73. Scope of iodoarenes and cyclopropylhydrazones.

次に合成したピラゾール **16at** の官能基変換を試みた (Scheme 74)。まず、**16at** をジクロロメタン還流中、NBS で処理すると、4 位がブロモ化されたピラゾール **107** が 57%の収率で得られた。次に **16at** を DMSO 中、塩化リチウムを用いて 150 ℃で処理すると、Krapcho 脱炭酸が進行し、ピラゾール **108** が 58%の収率で得られた。また、ピラゾール **16at** を THF 中、室温で $LiAlH_4$ によってエステルの還元反応が進行し、ピラゾール **109** が 61%の収率で得られた。



Scheme 74. Transformations of **16at**.

以上のように著者は *N*-シクロプロピルヒドラゾンのシクロプロパンの C-C 結合切断、Heck 反応、環化異性化反応の連続反応の開発に成功し、1-アルキル-5-アリールピラゾールの合成に成功した。本反応は 1 つの触媒が 2 つの反応サイクルを回転させるオートタンデム型の反応であることが特徴である。また、1-アルキル-5-アリールピラゾールの合成はこれまで様々な手法が報告されているにもかかわらず、それらの合成法では位置選択性や化学選択性に課題があった。一方、本研究では 1-アルキル-5-アリールピラゾールを単一の生成物として合成することに成功しており、位置選択性や化学選択性の課題を解決した。さらに、今回合成した 1-アルキル-5-アリールピラゾールを官能基変換することができ、本手法は様々なピラゾール誘導体の合成にも有用であることが示された。また、第 2 章、3 章で合成したピラゾール誘導体は α-ピラゾールカルボニル骨格を有しており、生物活性物質として有用であることが期待される (Figure 1)。例えば、JAK 阻害能や殺虫作用を示す α-ピラゾールケトン化合物がこれまでに報告されている。[65, 66] また、α-ピラゾールカルボニル骨格はカルボニル α 位にアミノ基を有しており今後、不斉合成を達成することができれば、新規アミノ酸誘導体の開発が期待できる。

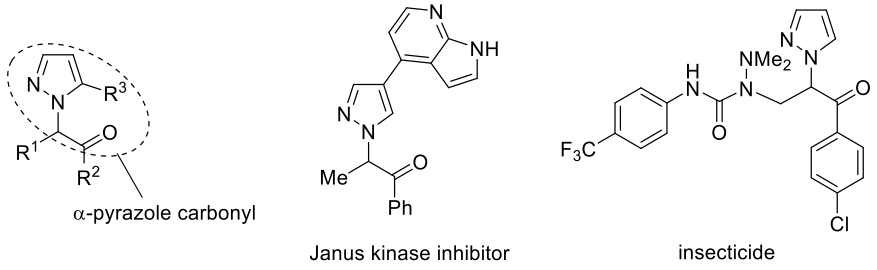
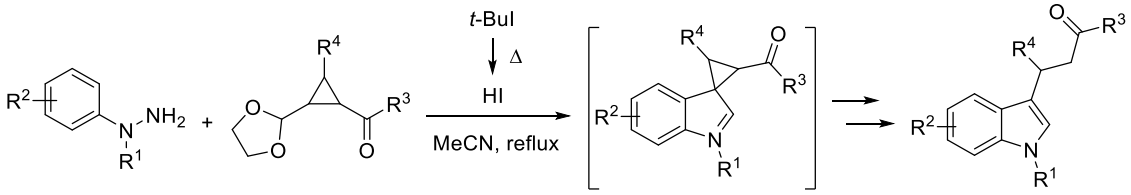


Figure 1. Examples of bioactive molecules containing α-pyrazole carbonyl unit.

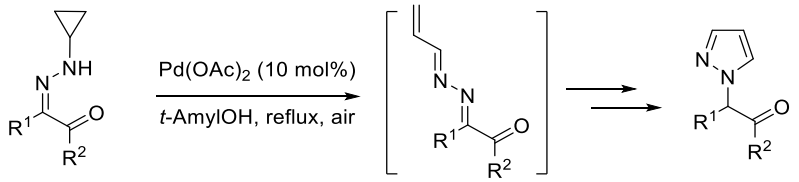
結論

ヒドラゾンによるシクロプロパンの活性化に続く連続反応が進行することで、ヒドラゾンの窒素原子が含窒素ヘテロ環に取り込まれるような合成法の開発研究を行った結果、以下のようにインドールやピラゾールの新規合成法を見出した。

① アリールヒドラジンとシクロプロピルアセタールをヨウ化水素発生源としてヨウ化*tert*-ブチルと反応させることで、Fischer インドール化反応によりスピロシクロプロピルインドレニンが生成する。続いてヨウ化水素による還元反応が進行し、3-アルキルインドールが生成することを見出した。本反応はヒドラゾンがシクロプロパンの活性化だけでなく、インドール環に取り込まれる反応であることが特徴である。

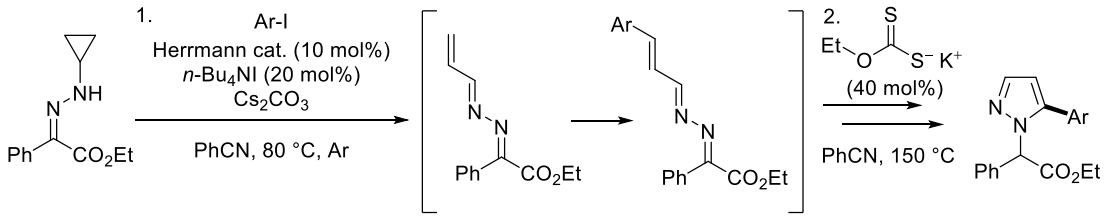


② *N*-シクロプロピルアシルヒドラゾンを触媒として酢酸パラジウムで処理することで、シクロプロパンの開環反応により共役アジンが生成する。続いて環化異性化反応が進行し、ピラゾールが生成することを見出した。本反応において、アシルヒドラゾンはシクロプロパン活性化の配向基としての役割だけでなく、その後の環化異性化反応の促進にも関与し、目的のピラゾールに取り込まれている。このことから本反応は原子効率に優れた反応であるといえる。



③ *N*-シクロプロピルアシルヒドラゾンを Herrmann 触媒存在下、ヨードアレーンと反応させるとシクロプロパンの開環反応により共役アジンが生成した後に Heck 反応が進行し、5-アリール共役アジンが生成する。続いて環化異性化反応が進行することで、1-アルキル-5-アリールピラゾールが生成することを見出した。本反応は 1 つの触媒が 2 つの反応サイクルを回転させるオートタンデム型の反応であることが特徴である。また、1-アルキル-5-アリールピラゾールの合成はこれまで様々な手法が報告されているにもかか

わらず、それらの合成法では位置選択性や化学選択性に課題があった。一方、本研究では 1-アルキル-5-アリールピラゾールを単一の生成物として合成することに成功しており、位置選択性や化学選択性の課題を解決した。



以上をまとめると、著者はヒドラゾンの互変異性化を利用することで、シクロプロパンの開環に続く連続反応に成功し、ヒドラゾンが含窒素ヘテロ環の一部に取り込まれる合成法を開発した。エンヒドラジンを介した反応では N-N 結合の開裂を伴う連続反応が進行することで、1 つの窒素原子が取り込まれた 3-アルキルインドールの合成に成功した。また、ジアゼンへの互変異性化を利用する連続反応では 2 つの連続する窒素原子が取り込まれたピラゾールの合成に成功した。

謝辞

本研究に際して終始ご懇篤な御指導、御鞭撻を賜りました恩師、上田昌史教授に衷心より感謝致します。また，種々有益な御助言と御指導を直接頂きました安井基博助教に厚く深謝致します。実験に際し種々の御協力を頂きました武田紀彦准教授に厚く深謝致します。

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計算化学に関し、多大な御協力を頂きました京都薬科大学、浜田翔平助教、小林祐輔准教授、古田巧教授に感謝いたします。

末筆ながら、博士課程において経済的援助を賜りました日本薬学会長井記念薬学研究奨励金に感謝致します。

第 4 章 実験の部

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz, 400 MHz JNM-ECZ400S, a Varian VNS AS 500 MHz or a Bruker AVANCE III HD 600 MHz operating at 300 MHz/75 MHz, 400 MHz/100 MHz, 500 MHz/125 MHz, or 600 MHz/150 MHz for ^{1}H and ^{13}C acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance or TMS as the internal standard. ^{19}F NMR spectra were recorded on a 376 MHz JNM-ECZ400S. Chemical shifts are reported in ppm with $CFCl_3$ as the standard in machine setting. Multiplicities are indicated by (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, td = triplet of doublets, qd = quartet of doublets, qt = quartet of triplets, qq = quartet of quartets, septd = septet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet, br = broad). Infrared (IR) spectra were recorded on a Perkin-Elmer SpectrumOne A spectrometer. High-resolution mass spectra (HRMS) were obtained by ESI method on Thermo Fisher Scientific Exactive Instrument. Melting points (uncorrected) were determined on BÜCHI M-565 apparatus. Flash column chromatography were performed using Silicycle silica gel (SiliaFlash® F60, 40-63 μm) or performed on Yamazen Automated Liquid Chromatography System Smart Flash EPCLC-AI-580S using ULTRAPACK SI-40B or Biotage Automated Liquid Chromatography System Isolera One using Santai Science Inc. SepaFlash iLOK-SL 10g or 20g flash cartridges. Preparative thin-layer chromatography (preparative TLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60 F_{254}).

第 1 節　第 1 章第 1 節の実験

(Ethoxycarbonylmethyl)dimethylsulfonium bromide (27) [Scheme 13]. To a solution of methyl 2-bromoacetate (6.6 mL, 59.9 mmol) in acetone (10 mL) was added dimethyl sulfide (5.3 mL, 71.8 mmol). The mixture was stirred at room temperature overnight. Then the mixture was filtered with Kiriyama funnel and dried under vaccum. (Ethoxycarbonylmethyl)dimethylsulfonium bromide (9.77 g) was obtained as a white solid without purification. The spectral data were identical with those reported in the literature. [67)]

Dimethylsulfonium ethoxycarbonylmethylide (28) [Scheme 13]. To a solution of (Ethoxycarbonylmethyl)dimethylsulfonium bromide **27** (9.77 g, 42.7 mmol) in $CHCl_3$ (42.6 mL) were added saturated K_2CO_3 aq. (21 mL) and 12.5 M NaOH aq. (4.4 mL). The mixture was stirred for 15 min, then stirred at room temperature for 1 h. The top of organic layer was decanted, dried over K_2CO_3, filtered and evaporated to afford dimethylsulfonium ethoxycarbonylmethylide (5.51 g) **28** as yellow oil without purification. The spectral data were identical with those reported in the literature. [68)]

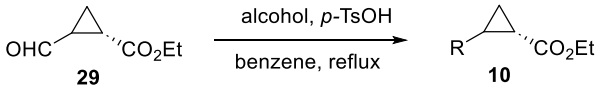
2-Formylcyclopropane carboxylic acid ethyl ester (29) [Scheme 13]. To a solution of allyl alcohol (1.62 g, 27.8 mmol) in dichloromethane (100 mL) were added powdered 4 Å molecular sieves (28 g), (ethoxycarbonylmethylene) dimethylsulfarane (6.19 g, 41.8 mmol) and manganese dioxide (24.2 g, 278 mmol). The mixture was heated at reflux for overnight, and then cooled to room temperature. The crude mixture was then filtered through Celite® and the residue was washed with dichloromethane to give a pale yellow solution. After removal of the solvent in vacuo, the residue was purified by flash column chromatography (hexane/EtOAc = 5 : 1) to give cyclopropyl aldehyde **29** (307 mg, 8%, trans/cis = 6 : 1) as a colorless oil. The spectral data were identical with those reported in the literature. [23)]

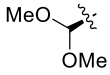
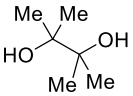
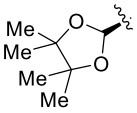
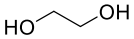
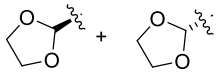
One pot reaction of reductive indolization from cyclopropyl aldehyde and arylhydrazine.

Ethyl 3-(5-methoxy-1*H*-indol-3-yl)propanoate (13aa) [Scheme 15]. To a solution of cyclopropyl aldehyde **29** (25.4 mg, 0.178 mmol) in MeCN (5 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (31.2 mg, 0.178 mmol) and *t*-BuI (63.7 μL, 0.534 mmol). The mixture was stirred at reflux for 5 h. Then *t*-BuI (63.7 μL, 0.534 mmol) was added and stirred for 2 h. The resulting mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative TLC (toluene : EtOAc = 19 : 1) to afford the indole **13aa** (15.2 mg, 32%) as a brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.25

(d, J = 11.2 Hz, 1H), 7.01 (d, J = 16.0 Hz, 2H), 6.86 (dd, J = 8.8, 2.8 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.07 (t, J = 7.8 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 154.0, 131.4, 127.6, 122.1, 114.8, 112.3, 111.8, 100.5, 60.4, 55.9, 34.8, 20.6, 14.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_3N$ $[M+H]^+$ 248.1281, found 248.1283.

Table S1. Synthesis of cyclopropyl acetals.



entry	alcohol	R	cyclopropyl acetal	time	yield
1	MeOH (6.0 eq.)		**10a**	9 h	2%
2	 (1.5 eq.)		**10b**	4 h	41%
3	 (1.7 eq.)		**10c**	4 h	42%
4	 (2.4 eq.)		**10d** + **10d'**	1 h	47%

Ethyl (1*S*,2*S*)-2-(dimethoxymethyl)cyclopropane-1-carboxylate (10a) [Table S1, entry 1]. To a solution of cyclopropyl aldehyde **29** (1.61 g, 11.3 mmol) in benzene (20 mL) were added methanol (1.01 g, 33.9 mmol) and *p*-toluenesulfonic acid (133 mg, 0.700 mmol). The mixture was heated at reflux with Dean-Stark trap for 2 h. Then methanol (1.01 g, 33.9 mmol) was added to the mixture, stirred at reflux for 8 h and then cooled to room temperature. The resulting mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 7 : 3) to afford cyclopropyl acetal **10a** (40.6 mg, 2%) as a yellow oil. The spectral data were identical with those reported in the literature. [69)]

Ethyl (1*S*,2*S*)-2-(1,3-dioxan-2-yl)cyclopropane-1-carboxylate (10b) [Table S1, entry 2] To a solution of aldehyde **29** (3.00 g, 21.0 mmol) in benzene (20 mL) were added 1,3-propanediol (2.17 mL, 30.0 mmol) and *p*-toluenesulfonic acid (238 mg, 1.25 mmol). The mixture was heated at reflux with Dean-Stark trap for 3 h and then cooled to room temperature. The resulting mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography

(hexane/EtOAc = 3 : 1) to afford cyclopropyl acetal **10b** (1.71 g, 41%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (d, *J* = 4.0 Hz, 1H), 4.21-4.05 (m, 4H), 3.86-3.63 (m, 2H), 2.14-1.98 (m, 1H), 1.81-1.66 (m, 2H), 1.39-1.29 (m, 1H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.17-1.10 (m, 1H), 1.10-0.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 100.3, 66.9, 60.5, 25.6, 24.8, 16.3, 14.2, 10.6; HRMS (ESI) *m/z* calcd for $C_{10}H_{17}O_4$ $[M+H]^+$ 201.1121, found 201.1123.

Ethyl (1*S*,2*S*)-2-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)cyclopropane-1-carboxylate (10c) [Table S1, entry 3] To a solution of aldehyde **29** (3.00 g, 21.0 mmol) in benzene (20 mL) were added pinacol (3.54 g, 30.0 mmol) and *p*-toluenesulfonic acid (238 mg, 1.25 mmol). The mixture was heated at reflux with Dean-Stark trap for overnight and then cooled to room temperature. The resulting mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5 : 1) to afford mixture of cyclopropyl acetals **10c** (2.15 g, 42%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (d, *J* = 6.0 Hz, 1H), 4.18-4.05 (m, 2H), 1.73-1.65 (m, 2H), 1.27-1.19 (m, 16H), 1.0-0.91 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 101.8, 82.2, 82.1, 60.6, 25.6, 24.1, 23.9, 21.9, 17.0, 14.2, 11.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{23}O_4$ $[M+H]^+$ 243.1591, found 243.1592.

[Table S1, entry 4] To a solution of aldehyde **29** (5.39 g, 37.9 mmol) in benzene (50 mL) were added ethyleneglycol (5.72 g, 92.2 mmol) and *p*-toluenesulfonic acid (730 mg, 3.84 mmol). The mixture was heated at reflux with Dean-Stark trap for 1.5 h and then cooled to room temperature. The resulting mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/acetone = 5 : 1) to afford mixture of cyclopropyl acetals **10d** and **10d'** (3.35 g, 47%).

Ethyl (1*S*,2*S*)-2-(1,3-dioxolan-2-yl)cyclopropane-1-carboxylate (10d)

Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (d, *J* = 4.6 Hz, 1H), 4.19-4.06 (m, 2H), 4.03-3.92 (m, 2H), 3.92-3.80 (m, 2H), 1.81-1.70 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.23-1.15 (m, 1H), 1.07-0.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 103.8, 65.1, 65.1, 60.7, 23.8, 16.5, 14.2, 10.8; HRMS (ESI) *m/z* calcd for $C_9H_{15}O_4$ $[M+H]^+$ 187.0965, found 187.0963.

Ethyl (1*R*,2*S*)-2-(1,3-dioxolan-2-yl)cyclopropane-1-carboxylate (10d')

Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (d, *J* = 7.8 Hz, 1H), 4.17 (dd, *J* = 14.4, 5.6 Hz, 2H), 4.07-3.95 (m, 2H), 3.92-3.79 (m, 2H), 1.94-1.82 (m, 1H), 1.53-1.39 (m, 1H), 1.34-1.24 (m, 4H), 1.21-1.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 103.6, 65.1, 65.0, 60.8, 22.9, 17.1, 14.2, 10.8; HRMS (ESI) *m/z* calcd for $C_9H_{15}O_4$ $[M+H]^+$ 187.0965, found 187.0965.

[Table 1, entry 1]. To a solution of cyclopropyl acetal **10a** (27.1 mg, 0.14 mmol) in MeCN (5.0 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (25.2 mg, 0.14 mmol) and *t*-BuI (100 μL, 0.84 mmol) at room temparature. Then, the mixture was stirred at reflux for 0.5 h. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative TLC (toluene/EtOAc = 19 : 1) to afford the indole **13aa** (8.1 mg, 23%).

[Table 1, entry 2]. To a solution of cyclopropyl acetal **10b** (31.6 mg, 0.16 mmol) in MeCN (5.0 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (27.6 mg, 0.16 mmol) and *t*-BuI (113 μL, 0.95 mmol) at room temperature. Then the mixture was stirred at reflux for 0.5 h. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative TLC (toluene/EtOAc = 19 : 1) to afford the indole **13aa** (7.7 mg, 20%).

[Table 1, entry 3]. To a solution of cyclopropyl acetal **10c** (33.5 mg, 0.138 mmol) in MeCN (5.0 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (24.1 mg, 0.138 mmol) and *t*-BuI (98.7 μL, 0.828 mmol) at room temperature. Then the mixture was stirred at reflux for 1 h. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative TLC (toluene/EtOAc = 19 : 1) to afford the 4-methoxyaniline (7.0 mg, 37%) and cyclopropyl acetal **10c** (18.7 mg, 56%).

[Table 1, entry 4]. To a solution of cyclopropyl acetal **10d** (30.3 mg, 0.16 mmol) in MeCN (5.0 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (28.4 mg, 0.16 mmol) and *t*-BuI (114 μL, 0.96 mmol) at room temperature. Then the mixture was stirred at reflux for 30 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative TLC (toluene/EtOAc = 19 : 1) to afford the indole **13aa** (21.4 mg, 54%).

[Table 1, entry 6]. To a solution of cyclopropyl acetal **10d** (37.0 mg, 0.20 mmol) in MeCN (12 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (34.9 mg, 0.20 mmol), NaI (180 mg, 1.20 mmol) and TMSCl (151 μL, 1.20 mmol) at room temperature. Then the mixture was stirred at reflux for 1.5 h. Then the mixture was cooled to room temperature, quenched with saturated aqueous

$Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative TLC (hexane/EtOAc = 7 : 3) to afford the indole **13aa** (10.0 mg, 20%).

[Table 1, entry 7]. To a solution of cyclopropyl acetal **10d** (27.7 mg, 0.15 mmol) in EtOH (5.0 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (25.8 mg, 0.15 mmol) and *t*-BuI (106 μL, 0.89 mmol) at room temperature. Then the mixture was stirred at reflux for 1 h. Then *t*-BuI (53 μL, 0.45 mmol) was added to the mixture and stirred for 2 h. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated at room temperature. The crude product was purified by preparative TLC (toluene/EtOAc = 19 : 1) to afford the indole **13aa** (5.6 mg, 15%).

[Table 1, entry 11]. To a solution of cyclopropyl acetal **10d** (36.9 mg, 0.20 mmol) in MeCN (12 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (69.1 mg, 0.40 mmol) and *t*-BuI (142 μL, 1.19 mmol) at room temperature. After being stirred for 15 min, *t*-BuI (61 μL, 0.59 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated at room temperature. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford the indole **13aa** (43.3 mg, 89%).

[Table 1, entry 12]. To a solution of 4-methoxyphenylhydrazine hydrochloride **9a** (114 mg, 0.65 mmol) and *t*-BuI (233 μL, 1.96 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d'** (60.7 mg, 0.33 mmol) in MeCN (2.0 mL) at reflux. After being stirred for 15 min, *t*-BuI (117 μL, 0.98 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 50 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated at room temperature. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford the indole **13aa** (66.7 mg, 83%).

第 2 節　第 1 章第 2 節の実験

Ethyl 3-iodo-2-(5-methoxy-1*H*-indol-3-yl)propanoate (31a) and Ethyl α-iodo-5-methoxy-1*H*-indole-3-propanoate (12a) [Scheme 18, eq 1] To a solution of cyclopropylacetal **10d** (142 mg, 0.76 mmol) in MeCN (20 mL) were added 4-methoxyphenylhydrazine hydrochloride (133 mg, 0.76 mmol) and *t*-BuI (420 mg, 2.28 mmol). The mixture was stirred at reflux for 5 min followed by cooled to room temperature and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative thin-layer chromatography (toluene/EtOAc = 19 : 1) to afford the mixture of iodinated indoles **31a** and **12a** (151 mg, 53%, **31a** : **12a** = 5 : 1) as a yellow oil.

Ethyl 3-iodo-2-(5-methoxy-1*H*-indol-3-yl)propanoate (31a)

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (s, br, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.16 (d, *J* = 2.6 Hz, 1H), 7.10 (d, *J* = 2.2 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.28-4.22 (m, 2H), 4.20-4.13 (m, 1H), 3.87 (s, 3H), 3.77 (t, *J* = 10.1 Hz, 1H), 3.45-3.43 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 154.6, 131.3, 126.2, 123.0, 113.3, 113.2, 112.3, 100.7, 61.5, 56.1, 47.0, 14.5, 5.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}O_3NI$ $[M+H]^+$ 374.0250, found 374.0248.

Ethyl 2-iodo-3-(5-methoxy-1*H*-indol-3-yl)propanoate (12a)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91-8.01 (s, br, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 2.6 Hz, 1H), 7.01 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 8.6, 2.0 Hz, 1H), 4.57 (dd, *J* = 9.9, 5.9 Hz, 1H), 4.22-4.09 (m, 2H), 3.88 (s, 3H), 3.62 (dd, *J* = 15.0, 9.9 Hz, 1H), 3.40 (dd, *J* = 15.0, 5.9 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 154.3, 131.1, 127.2, 123.8, 113.3, 112.5, 112.0, 100.4, 61.8, 56.0, 32.6, 20.6, 13.7; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}O_3NI$ $[M+H]^+$ 374.0250, found 374.0248.

Ethyl 3-(5-methoxy-1*H*-indol-3-yl)propanoate (13aa) [Scheme 18, eq 2] To a solution of mixture of iodinated indoles **31a** and **12a** (4.7 mg, 0.0130 mmol) in MeCN (5.0 mL) was added *t*-BuI (46.8 mg, 0.0570 mmol). The mixture was stirred at reflux for 30 min followed by cooled to room temperature and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative thin-layer chromatography (toluene/EtOAc = 19 : 1) to afford indole **13aa** (1.1 mg, 35%)

Ethyl (1*R*,2*R*)-5'-methoxyspiro[cyclopropane-1,3'-indole]-2-carboxylate (11a') and Ethyl (1*R*,2*S*)-5'-methoxyspiro[cyclopropane-1,3'-indole]-2-carboxylate (11a") [Scheme 20, eq 2]. To a solution of mixture of iodinated indoles **31a** and **12a** (59.6 mg, 0.160 mmol) in MeCN (5.0 mL) was added Ag_2CO_3 (46.8 mg, 0.170 mmol). The mixture was stirred in the absence of light at room temperature for 3 h. Then the resulting mixture was concentrated in vacuo and diluted with toluene. The mixture was filtered through Celite® followed by washed with toluene. After removal of the solvent in vacuo, the residue was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford spiroindolenines **11a'** (7.4 mg, 19%) and **11a"** (18.8 mg, 48%).

Ethyl (1*R*,2*R*)-5'-methoxyspiro[cyclopropane-1,3'-indole]-2-carboxylate (11a'). Physical state: brown solid; m.p.: 79 °C (decomposed); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.58 (m, 2H), 7.06 (d, *J* = 2.8 Hz, 1H), 6.91 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.27-4.01 (m, 2H), 3.82 (s, 3H), 3.01 (t, *J* = 8.0 Hz, 1H), 2.34-2.31 (m, 1H), 2.25-2.21 (m, 1H), 1.19 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 168.3, 158.2, 150.4, 136.2, 121.7, 113.5, 107.7, 61.5, 55.7, 42.4, 28.0, 17.5, 14.1; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_3N$ $[M+H]^+$ 246.1125, found 246.1125.

Ethyl (1*R*,2*S*)-5'-methoxyspiro[cyclopropane-1,3'-indole]-2-carboxylate (11a"). Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.54 (d, *J* = 2.8 Hz, 1H), 4.31-4.16 (m, 2H), 3.82 (s, 3H), 2.82-2.78 (m, 1H), 2.64-2.61 (m, 1H), 2.00-1.97 (m, 1H), 1.28 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 168.2, 158.5, 149.4, 139.2, 122.0, 112.8, 104.2, 61.6, 55.8, 42.5, 30.6, 20.2, 14.1; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_3N$ $[M+H]^+$ 246.1125, found 246.1124

Ethyl 3-(5-methoxy-1*H*-indol-3-yl)propanoate (13aa) [Scheme 20, eq 3]. To a solution of mixture of indolenines **11a'** and **11a"** (13.1 mg, 0.053 mmol) in MeCN (2.0 mL) was added *t*-BuI (29.5 mg, 0.16 mmol). The mixture was stirred at reflux. The reaction mixture was stirred at reflux for 30 min followed by cooled to room temperature and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative thin-layer chromatography (toluene/EtOAc = 19 : 1) to afford indole **13aa** (4.7 mg, 36%).

Methyl 2-iodo-3-phenylpropanoate (33) [Scheme 21, eq 1]. To a stirred solution of cinnamaldehyde **32** (131 mg, 0.990 mmol) in THF (5.0 mL) at 0 °C were added trimethylsilyl cyanide (188 μL, 1.49 mmol) and DBU (30.0 μL, 0.198 mmol). After stirring for 20 min at 0 °C, was added iodide (380 mg, 2.97 mmol) to the reaction mixture. After stirring for 10 min, was added methanol (410 μL, 9.90 mmol) to the reaction mixture and stirred for 20 min at 0 °C. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The organic phase was collected and the

aqueous phase was extracted with EtOAc two times. The combined organic extract was washed with brine and dried over Na_2SO_4, filtered and concentrated. Iodoester **33** (211 mg, 74%) was obtained after purification with flash column chromatography (hexane/EtOAc = 7 : 3). The spectral data were identical with those reported in the literature. [70)]

Methyl 3-phenylpropanoate (34) [Scheme 21, eq 2]. To a solution of iodoester **33** (63.6 mg, 0.22 mmol) in MeCN (10 mL) was added *t*-BuI (121 mg, 0.66 mmol). The mixture was stirred at reflux for 10 min. Then *t*-BuI (121 mg, 0.66 mmol) was added to the solution. The reaction mixture was stirred at reflux for additional 30 min followed by cooled to room temperature and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford methyl 3-phenylpropanoate **34** (22.4 mg, 62%). The spectral data were identical with those reported in the literature. [71)]

第 3 節　第 1 章第 3 節の実験

4-Phenoxyphenylhydrazine hydrochloride (9c) [Table 2. Entry 1]. To a solution of 4-phenoxyaniline **35c** (741 mg, 4.00 mmol) in EtOH (14 mL) was added $NaNO_2$ (290 mg, 42.0 mmol) solution in H_2O (3.0 mL) at 0 °C. Then conc. HCl (14 mL) was dropwised for 10 min and stirred at 0 °C for 1 h. The resulting mixture was added $SnCl_2 \cdot H_2O$ in conc. HCl (4 mL) and stirred for additional 30 min. Then precipitates were filtered, and washed with H_2O. Then 1M NaOH aq. was added to precipitates. The mixture was extracted with EtOAc three times. The organic layers were dried over Na_2SO_4, filtered and concentrated. Then the oil was dissolved in HCl in dioxane and the precipitates were filtered, washed with Et_2O. 4-Phenoxyphenylhydrazine hydrochloride **9c** (439 mg, 46%) was obtained as a brown solid after and dried in desiccator in vacuo. The spectral data were identical with those reported in the literature. [72)]

3,4-Methylenedioxyphenylhydrazine hydrochloride (9u) [Table 2. Entry 2]. To a solution of 3,4-methylenedioxyaniline **35u** (686 mg, 5.00 mmol) in H_2O (3.0 mL) were added $NaNO_2$ (414 mg, 6.00 mmol) solution in H_2O (2.0 mL) and conc. HCl (5.2 mL) at 0 °C. Then the mixture was stirred at 0 °C for 1 h. The resulting mixture was added $SnCl_2 \cdot H_2O$ in conc. HCl (6.4 mL) and stirred for additional 30 min. Then precipitates were filtered and washed with H_2O. 3,4-Methylenedioxyphenylhydrazine hydrochloride **9u** (118 mg, 13%) was obtained as a brown solid after and dried in desiccator in vacuo. The spectral data were identical with those reported in the literature. [73)]

3-Fluoro-4-methoxyphenylhydrazine hydrochloride (9q) [Table 2. Entry 3]. To a solution of 3-fluoro-4-methoxyaniline **35q** (565 mg, 4.00 mmol) in EtOH (14 mL) was added $NaNO_2$ (290 mg, 42.0 mmol) solution in H_2O (3.0 mL) at 0 °C. Then conc. HCl (14 mL) was dropwised for 10 min and stirred at 0 °C for 1 h. The resulting mixture was added $SnCl_2 \cdot H_2O$ in conc. HCl (4.0 mL) and stirred for additional 30 min. Then precipitates were filtered and washed with H_2O. Then 1 M NaOH aq. was added to precipitates. The mixture was extracted with EtOAc three times. The organic layers were dried over Na_2SO_4, filtered and concentrated. Then the oil was dissolved in HCl in dioxane and the precipitates were filtered, washed with Et_2O. 3-Fluoro-4-methoxyphenylhydrazine hydrochloride **9q** (493 mg, 64%) was obtained as a purple solid after drying in desiccator in vacuo. The spectral data were identical with those reported in the literature. [74)]

1,2,3,4-Tetrahydro-1-nitrosoquinoline (37) [Scheme 23]. To a solution of 1,2,3,4-tetrahydroquinoline **36** (628 μL, 5.00 mmol) in H_2O (3.0 mL) were added $NaNO_2$ (414 mg, 6.0 mmol) solution in H_2O (2.0 mL) and conc. HCl (5.2 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. Then the resulting mixture was diluted with water and extracted with toluene three times. The

combined organic layer was washed with water, dried over Na_2SO_4 and concentrated. 1,2,3,4-Tetrahydro-1-nitrosoquinoline **37** was obtained as a crude mixture. The spectral data were identical with those reported in the literature. [75)]

3,4-Dihydroquinonyl (2*H*)-amine hydrochloride (9t) [Scheme 23]. To a solution of 1,2,3,4-tetrahydro-1-nitrosoquinoline (810 mg, 5.00 mmol) in THF (5.00 mL) was added $LiAlH_4$ (380 mg, 10.0 mmol) at 0 °C. The mixture was stirred at rt for 30 min. Then the resulting mixture was quenched with water at 0 °C and filtered through Celite® and the residue was washed with water, dried over Na_2SO_4 and concentrated to afford 3,4-dihydroquinonyl (2*H*)-amine. To a solution of 3,4-dihydroquinonyl (2*H*)-amine (433 mg, 2.90 mmol) in CH_2Cl_2 was added HCl (4M in dioxane, 3.60 mL) and stirred at rt for 1 h. The precipitates were filtered and washed with Et_2O. The residue was dried in desiccator in vacuo to obtain 3,4-dihydroquinonyl (2*H*)-amine hydrochloride **9t** (491 mg, 53%, 3 steps from **36**) as a white solid; Mp: 179 °C (decomp.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 2H), 7.19-7.07 (m, 3H), 6.91 (t, J = 6.8 Hz, 1H), 2.73 (t, J = 6.4 Hz, 2H), 2.01-1.98 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 144.1, 129.5, 126.7, 125.7, 122.1, 115.1, 50.6, 25.8, 21.0; HRMS (ESI) *m/z* calcd for $C_9H_{13}N_2$ $[M+H]^+$149.1073, found 149.1074.

4-Methoxy-*N*-nitroso-*N*-methylaniline (39) [Scheme 24]. To a solution of 4-methoxy-*N*-methylaniline **38** (1.95 g, 14.2 mmol) in MeCN/H_2O = 1 : 2 solution (42.6 mL) were added $NaNO_2$ (1.96 g, 68.3 mmol) solution in H_2O (14.2 mL) and conc. HCl (5.70 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min. Then the resulting mixture was diluted with EtOAc and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. 4-methoxy-*N*-nitroso-*N*-methylaniline **39** (1.83 g, 79%) was obtained after purification with flash column chromatography (hexane/EtOAc = 7 : 3). The spectral data were identical with those reported in the literature. [75)]

1-(4-Methoxyphenyl)-1-methylhydrazine hydrochloride (9v) [Scheme 24]. To a solution of 4-methoxy-*N*-nitroso-N-methylaniline **39** (1.83 g, 11.0 mmol) in MeOH/H_2O = 1 : 1 solution (50 mL) were added NH_4Cl (707 mg, 13.2 mmol) and Zn (1.44 g, 22.0 mmol). The mixture was stirred at 45 °C for 5 h. Then the resulting mixture was diluted with $CHCl_3$ and extracted with $CHCl_3$ three times. The combined organic layer was dried over $MgSO_4$ and concentrated. 1-(4-methoxypheny)-1-methylhydrazine was obtained after purification with flash column chromatography (hexane/EtOAc = 3 : 1). Then 1-(4-methoxypheny)-1-methylhydrazine was dissolved in HCl (4 M in dioxane) and the precipitates were filtered and washed with Et_2O. 1-(4-Methoxypheny)-1-methylhydrazine hydrochloride **9v** (603 mg, 29%) was obtained as a white solid after drying in desiccator in vacuo; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.72 (s, 3H), 3.03 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 156.4, 141.7, 120.4, 114.4, 55.4, 43.9;

HRMS (ESI) *m/z* calcd for $C_8H_{13}ON_2$ $[M+H]^+$153.1022, found 153.1023.

1,1-Dimethylethyl 1-[4-(acetylamino)phenyl]hydrazinecarboxylate (41) [Scheme 25] To a solution of *N*-(4-iodophenyl)acetamide **40** (1.50 g, 5.75 mmol) in DMSO (6 mL) were added *tert*-butyl carbazate (900 mg, 6.90 mmol), CuI (55.0 mg, 0.290 mmol) and Cs_2CO_3 (2.80 g, 8.65 mmol). After being stirred at 50 °C for 22 h, the reaction mixture was diluted with H_2O and extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered and concentrated. Hydrazine **41** (740 mg, 49%) was obtained after purification with flash column chromatography (hexane/EtOAc = 7 : 3). The spectral data were identical with those reported in the literature. [22)]

***N*-(4-Hydrazinylphenyl)acetamide hydrochloride (9e) [Scheme 25]** To a solution of 1,1-dimethylethyl 1-[4-(acetylamino)phenyl]hydrazinecarboxylate **41** (740 mg, 2.74 mmol) in CH_2Cl_2 (14 mL) was added HCl (4 M in dioxane, 12 mL) at 0 °C. After being stirred at room temperature for 15 h, the resulting pale brown solid was filtered and washed with Et_2O to give *N*-(4-hydrazinylphenyl)acetamide hydrochloride **9e** (690 mg, quant.). The spectral data were identical with those reported in the literature. [22)]

((1*S*,2*S*)-2-(1,3-Dioxolan-2-yl)cyclopropyl)methanol (42) [Scheme 26] To a solution of cyclopropyl acetal **10d** (214 mg, 1.15 mmol) in THF (6.2 mL) was added $LiAlH_4$ (87.0 mg, 2.30 mmol) slowly and stirred at room temperature for 1 h. Then the mixture was cooled to 0 °C and quenched with 1 M HCl aq. and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford crude cyclopropanemethanol **42**; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.51 (d, *J* = 6.4 Hz, 1H), 4.04-3.95 (m, 2H), 3.90-3.81 (m, 2H), 3.56 (dd, *J* = 11.2, 6.8 Hz, 1H), 3.45 (dd, *J* = 11.2, 7.6 Hz, 1H), 1.28-1.18 (m, 1H), 1.05-1.01 (m, 1H), 0.72-0.70 (m, 1H), 0.58-0.55 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 106.1, 65.8, 64.9, 19.2, 17.5, 6.3; HRMS (ESI) *m/z* calcd for $C_7H_{12}O_3Na$ $[M+Na]^+$ 167.0679, found 167.0680.

(1*S*,2*S*)-2-(1,3-Dioxolan-2-yl)cyclopropane-1-carbaldehyde (43) [Scheme 26] To a solution of Dess-Martin periodinane (537 mg, 1.27 mmol) in CH_2Cl_2 (6.0 mL) was added crude cyclopropyl methanol **42**. The mixture was stirred at room temperature for 30 min. Then saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ were added to the mixture and extracted with CH_2Cl_2 three times. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to afford cyclopropanecarboxaldehyde **43** as a colorless oil without purification. The spectral data were identical with those reported in the literature. [76)]

Ethyl (*E*)-3-((1*R*,2*S*)-2-(1,3-dioxolan-2-yl)cyclopropyl)acrylate (10e) [Scheme 26] To a solution of ethyl(triphenylphosphoranylidene)acetate (998 mg, 2.87 mmol) in toluene (11 mL) was added

crude cyclopropanecarboxaldehyde **43** (81.5 mg, 0.573 mmmol). The mixture was stirred at 100 °C overnight. Then the mixture was cooled to room temperature and washed with water and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford cyclopropyl α,β-saturated ester **10e** (59.6 mg, 23%, 3 steps from **10d**) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 15.2, 9.6 Hz, 1H), 5.90 (d, *J* = 15.2 Hz, 1H), 4.68 (d, *J* = 4.8 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.05-3.93 (m, 2H), 3.92-3.82 (m, 2H), 1.75-1.65 (m, 1H), 1.43-1.35 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.12-1.04 (m, 1H), 0.94-0.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 151.0, 119.4, 104.7, 65.1, 60.1, 24.3, 17.9, 14.3, 11.2; HRMS (ESI) *m/z* calcd for $C_{11}H_{17}O_4$ $[M+H]^+$ 213.1121, found 213.1120

Ethyl 2-formyl-3-methylcyclopropane-1-carboxylate (45) [Scheme 27] To a solution of (*E*)-but-2-en-1-ol (472 mg, 6.55 mmol) in CH_2Cl_2 (65 mL) were added powdered 4Å molecular sieves (5.00 g), (ethoxycarbonylmethylene)dimethylsulfarane **44** (1.33 g, 13.1 mmol) and manganese dioxide (5.67 g, 65.5 mmol). The mixture was heated at reflux for 4 h, and then cooled to room temperature. The crude mixture was then filtered through Celite® and the residue was washed with CH_2Cl_2. After removal of the solvent in vacuo, the residue was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford crude cyclopropyl aldehyde **45**. The spectral data were identical with those reported in the literature. [77)]

Ethyl 2-(1,3-dioxolan-2-yl)-3-methylcyclopropane-1-carboxylate (10f) [Scheme 27] To a solution of cyclopropyl aldehyde **45** in benzene (5.0 mL) were added ethylene glycol (52.5 mg, 0.845 mmol) and *p*-toluenesulfonic acid (6.60 mg, 0.0347 mmol). The mixture was heated at reflux with Dean-Stark trap overnight and then cooled to room temperature. The resulting mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford cyclopropyl acetal **10f** (52.7 mg, 4%, from **44**) as a diastereomeric mixture (dr = ca. 50 : 35 : 15, 52.7 mg). The cyclopropyl acetal **10f** was colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (d, *J* = 8.0 Hz, 0.15H), 4.71 (d, *J* = 4.8 Hz, 0.50H), 4.68 (d, *J* = 7.2 Hz, 0.35H), 4.22-4.07 (m, 2H), 4.06-3.93 (m, 2H), 3.92-3.78 (m, 2H), 1.80 (dd, *J* = 9.2, 4.8 Hz, 0.50H), 1.75-1.53 (m, 1.5H), 1.49-1.38 (m, 0.5H), 1.35-1.20 (m, 6H), 1.17 (d, *J* = 6.0 Hz, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.0, 171.5, 104.0, 103.4, 103.3, 65.0, 64.9, 64.9, 60.7, 60.6, 60.4, 31.2, 29.7, 28.7, 25.1, 25.0, 22.0, 19.8, 19.8, 18.6, 17.1, 14.2, 14.2, 12.4, 11.3; One carbon peak of diastereomers could not be detected probably due to overlapping; HRMS (ESI) *m/z* calcd for $C_{10}H_{17}O_4$ $[M+H]^+$ 201.1121, found 201.1123.

2-(1,3-Dioxolan-2-yl)cyclopropane-1-carboxylic acid (46) [Scheme 28] To a solution of

cyclopropyl acetal **10d** (303 mg, 1.63 mmol) in H_2O-THF (1:3, 6.07 mL) was added LiOH (54.6 mg, 2.28 mmol).The mixture was stirred at room temperature overnight and then cooled to 0 °C, diluted with $CHCl_3$, and quenched with 1 M HCl. The mixture was extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$, filtered, and concentrated to afford cyclopropane carboxylic acid **46** without purification.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.78 (d, *J* = 4.4 Hz, 1H), 4.01-3.93 (m, 2H), 3.91-3.83 (m, 2H), 1.85-1.80 (m, 1H), 1.76-1.72 (m, 1H), 1.28-1.23 (m, 1H), 1.13-1.08 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 179.3, 103.3, 65.1, 65.1, 24.7, 16.2, 11.5; HRMS (ESI) *m/z* calcd for $C_7H_{11}O_4$ $[M+H]^+$ 159.0652, found 159.0654.

(1*S*,2*S*)-2-(1,3-Dioxolan-2-yl)-*N*,*N*-diethylcyclopropane-1-carboxamide (10g) [Scheme 28] To a solution of crude cyclopropane carboxylic acid **46** (80.5 mg, 0.509 mmol) and EDC·HCl (117 mg, 0.611 mmol) in CH_2Cl_2 (2.0 mL) were added diethylamine (64 μL, 0.611 mmol) and DMAP (12.4 mg, 0.102 mmol). The mixture was stirred at room temperature for 3 h. Then the mixture was quenched with 10% citric acid and extracted with $CHCl_3$ three times. The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 1 : 2) to afford cyclopropyl amide **10g** (63.5 mg, 18%, 2 steps from **10d**) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (d, *J* = 5.0 Hz, 1H), 4.04-3.92 (m, 2H), 3.92-3.81 (m, 2H), 3.58-3.32 (m, 4H), 1.87-1.78 (m, 1H), 1.75-1.66 (m, 1H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.27-1.22 (m, 1H), 1.11 (t, *J* = 7.6 Hz, 3H), 0.97-0.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 104.5, 65.0, 65.0, 42.1, 40.9, 23.1, 15.1, 14.7, 13.2, 9.9; HRMS (ESI) *m/z* calcd for $C_{11}H_{20}O_3N$ $[M+H]^+$ 214.1437, found 214.1438.

(2-(1,3-Dioxolan-2-yl)cyclopropyl)-(piperidine-1-yl)methanone (10h) [Scheme 28] To a solution of crude cyclopropane carboxylic acid **46** (73.8 mg, 0.467 mmol) and EDC·HCl (108 mg, 0.564 mmol) in CH_2Cl_2 (2.0 mL) were added piperidine (56 μL, 0.564 mmol) and DMAP (11.4 mg, 0.0930 mmol). The mixture was stirred at room temperature overnight. Then the mixture was quenched with 10% citric acid and extracted with $CHCl_3$ three times. The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford cyclopropyl amide **10h** (37.7 mg, 6%, 2 steps from **10d**) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (d, *J* = 4.4 Hz, 0.1H), 4.75 (d, *J* = 4.4 Hz, 0.9H), 4.06-3.92 (m, 2H), 3.92-3.79 (m, 2H), 3.71-3.47 (m, 4H), 1.93-1.84 (m, 1H), 1.84-1.47 (m, 7H), 1.33-1.19 (m, 1H), 1.12-1.04 (m, 0.1H), 0.96-0.86 (m, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$, trans isomer) δ 170.1, 104.6, 65.2, 65.1, 46.8, 43.4, 26.6, 25.6, 24.8, 22.8, 15.2, 9.6; HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_3N$ $[M+H]^+$ 226.1438, found 226.1438.

***S*-Benzyl (1*S*,2*S*)-2-(1,3-dioxolan-2-yl)cyclopropane-1-carbothioate (10i) [Scheme 28]** To a solution of cyclopropane carboxylic acid **46** (71.0 mg, 0.448 mmol) in THF (2.0 mL) was added 1,1'-

carbonylimidazole (87.3 mg, 0.539 mmol). The mixture was stirred at reflux for 1 h. After cooling to room temperature, was added benzyl mercaptan (55.6 mg, 0.448 mmol). The mixture was stirred at reflux for 15 h. Then the mixture was diluted with water and extracted with CH_2Cl_2 three times. The mixture was stirred at room temperature overnight. Then the mixture was quenched with 10% citric acid and extracted with $CHCl_3$ three times. The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford cyclopropyl thioester **10i** (71.2 mg, 10%, 2 steps from **10d**) as a pale orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 4.79 (d, *J* = 4.0 Hz, 1H), 4.13 (dd, *J* = 20.8, 14.0 Hz, 2H), 4.00-3.90 (m, 2H), 3.89-3.80 (m, 2H), 2.17-2.09 (m, 1H), 1.99-1.88 (m, 1H), 1.41-1.32 (m, 1H), 1.17-1.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 137.4, 128.8, 128.6, 127.2, 103.1, 65.1, 33.3, 26.0, 25.5, 12.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}O_3S$ $[M+H]^+$ 265.0893, found 265.0893.

(2-(Methoxy(methyl)amino)-2-oxoethyl)dimethylsulfonium chloride (48) [Scheme 29] To 2-chloro-*N*-methoxy-*N*-methylethanamide **47** (2.56 g, 18.8mmol) was added dimethyl sulfide (6.90 mL, 94 mmol). The mixture was heated at 50 °C overnight. The excess dimethyl sulfide was decanted and the remaining clear gel was rinsed with EtOAc to afford sulfonium chloride **48** as a colorless oil without purification. The spectral data were identical with those reported in the literature. [78)]

(2-(Methoxy(methyl)amino)-2-oxoethyl)dimethylsulfonium inner salt (49) [Scheme 29] To a crude mixture of Weinreb amide sulfur ylide chloride salt **48** was added $CHCl_3$ (6.0 mL). After the starting materials had dissolved, the solution was cooled in ice-bath. To the solution were added saturated aqueous K_2CO_3 (3.0 mL) and aqueous NaOH (12.5 M, 0.4 mL). The ice bath was removed, and the mixture was stirred 20 min. The solution was filtered through Celite® and eluted with CH_2Cl_2. The filtrate was dried with K_2CO_3, filtered and concentrated under vacuum to yield ylide **49** as a crude mixture.

2-Formyl-*N*-methoxy-*N*-methylcyclopropanecarboxamide (50) [Scheme 29] To a crude mixture of ylide **49** (1.56 g) were added toluene (10 mL) and acrolein (747 μL, 11.2 mmol). The solution was heated at 60 °C for 90 min and concentrated in vacuo to afford crude cyclopropyl aldehyde **50**. This crude was used next reaction without purification. The spectral data of cyclopropyl aldehyde **50** were identical with those reported in the literature. [78)]

***rel*-(1*R*,2*R*)-2-(1,3-Dioxolan-2-yl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (10j) [Scheme 29]** To the crude mixture of cyclopropyl aldehyde **50** were added benzene (10 mL), ethylene glycol (474 μL, 8.40 mmol) and *p*-toluenesulfonic acid (68.4 mg, 0.360 mmol). The mixture was heated at reflux with Dean-Stark trap overnight. The resulting mixture was cooled to room

temperature, diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 1 : 1) to afford cyclopropyl acetal **10j** (201 mg, 5%, 4 steps from 2-chloro-*N*-methoxy-*N*-methylethanamide) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (d, *J* = 4.6 Hz, 1H), 4.04-3.93 (m, 2H), 3.93-3.82 (m, 2H), 3.77 (s, 3H), 3.21 (s, 3H), 2.28 (s, br, 1H), 1.78-1.69 (m, 1H), 1.30-1.21 (m, 1H), 1.04-0.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 104.4, 65.1, 65.0, 61.6, 32.5, 23.6, 13.6, 10.2; HRMS (ESI) *m/z* calcd for $C_9H_{16}O_4N$ $[M+H]^+$ 202.1074, found 202.1075.

Ethyl 3-(5-benzyloxy-1*H*-indol-3-yl)propanoate (13ba) [Scheme 30] To a solution of 4-benzyloxyphenylhydrazine hydrochloride **9b** (162 mg, 0.646 mmol) and *t*-BuI (231 μL, 1.94 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d** (60.1 mg, 0.323 mmol) in MeCN (2.0 mL) at reflux. After being stirred at reflux for 25 min, *t*-BuI (116 μL, 0.97 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 15 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ba** (55.9 mg, 54%) as a black oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, br, 1H), 7.48 (d, *J* = 6.9 Hz, 2H), 7.42-7.35 (m, 2H), 7.35-7.28 (m, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.13 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.10 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 153.1, 137.6, 131.6, 128.5, 127.8, 127.6, 127.5, 122.2, 114.7, 112.8, 111.8, 102.2, 71.0, 60.3, 34.8, 20.6, 14.2; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}O_3N$ $[M+H]^+$ 324.1594, found 324.1597.

Ethyl 3-(5-phenoxy-1*H*-indol-3-yl)propanoate (13ca) [Scheme 30] To a solution of cyclopropyl acetal **10d** (34.9 mg, 0.188 mmol) in MeCN (10 mL) were added 4-phenoxyphenylhydrazine hydrochloride **9c** (88.8 mg, 0.375 mmol) and *t*-BuI (134 μL, 1.13 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 17 min, *t*-BuI (67 μL, 0.565 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 30 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ca** (34.4 mg, 59%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, br, 1H), 7.33-7.24 (m, 4H), 7.06-6.92 (m, 5H), 4.12 (q, *J* = 6.8 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 159.4, 149.5, 133.2, 129.5, 127.9, 122.7, 121.8, 117.1, 115.9, 115.2, 112.0, 109.6, 60.4, 34.8, 20.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}O_3N$ $[M+H]^+$ 310.1438, found 310.1436.

Ethyl 3-(5-methylthio-1*H*-indol-3-yl)propanoate (13da) [Scheme 30] To a solution of cyclopropyl acetal **10d** (33.3 mg, 0.179 mmol) in MeCN (10 mL) were added 4-(methylthio)phenylhydrazine hydrochloride **9d** (68.1 mg, 0.357 mmol) and *t*-BuI (128 μL, 1.07 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 15 min, *t*-BuI (64 μL, 0.537 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 35 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13da** (32.3 mg, 69%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, br, 1H), 7.61 (s, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.23 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 135.0, 128.0, 127.4, 124.2, 122.2, 119.8, 114.8, 111.7, 60.4, 34.9, 20.5, 19.0, 14.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_2NS$ $[M+H]^+$ 264.1053, found 264.1052.

Ethyl 3-(5-acetylamino-1*H*-indol-3-yl)propanoate (13ea) [Scheme 30] To a solution of *N*-(4-hydrazinylphenyl)acetamide hydrochloride **9e** (114 mg, 0.568 mmol) and *t*-BuI (203 μL, 1.70 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d** (52.9 mg, 0.284 mmol) in MeCN (1.7 mL) at reflux. After being stirred for 15 min, *t*-BuI (102 μL, 0.852 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography ($CHCl_3$/CH_3CN = 3 : 1) to afford indole **13ea** (48.0 mg, 62%) as a gray oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, br, 1H), 7.69 (s, 1H), 7.63 (s, br, 1H), 7.17 (s, 2H), 6.93 (s, 1H), 4.11 (q, *J* = 7.6 Hz, 2H), 3.02 (t, *J* = 8.0 Hz, 2H), 2.65 (t, *J* = 8.0 Hz, 2H), 2.15 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 168.8, 133.8, 129.8, 127.2, 122.5, 116.8, 114.8, 111.3, 111.2, 60.4, 34.8, 24.2, 20.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{19}O_3N_2$ $[M+H]^+$ 275.1390, found 275.1392.

Ethyl 3-(5-(*tert*-butyl)-1*H*-indol-3-yl)propanoate (13fa) [Scheme 30] To a solution of cyclopropyl acetal **10d** (40.2 mg, 0.216 mmol) in MeCN (14 mL) were added 4-(*tert*-butyl)phenylhydrazine hydrochloride **9f** (86.6 mg, 0.431 mmol) and *t*-BuI (155 μL, 1.30 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 12 min, *t*-BuI (78.0 μL, 0.648 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 48 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted

with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13fa** (29.4 mg, 50%) as a white solid; Mp: 67 °C (decomposed); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.57 (s, 1H), 7.28 (d, *J* = 1.4 Hz, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.10 (t, *J* = 7.8 Hz, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 1.40 (s, 9H), 1.25 (t, *J* = 7.2 Hz 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 142.2, 134.4, 126.9, 121.4, 120.4, 115.1, 114.3, 110.6, 60.3, 34.9, 34.6, 32.0, 20.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{17}H_{24}O_2N$ $[M+H]^+$ 274.1802, found 274.1780.

Ethyl 3-(5-(isopropyl)-1*H*-indol-3-yl)propanoate (13ga) [Scheme 30] To a solution of cyclopropyl acetal **10d** (43.8 mg, 0.235 mmol) in MeCN (16 mL) were added 4-(*iso*-propyl)phenylhydrazine hydrochloride **9g** (87.7 mg, 0.470 mmol) and *t*-BuI (168 μL, 1.41 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 20 min, *t*-BuI (84.0 μL, 0.705 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7:3) to afford indole **13ga** (28.2 mg, 46%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.42 (s, 1H), 7.29-7.24 (m, 1H), 7.09 (dd, *J* = 8.6, 1.6 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.09 (t, *J* = 6.8 Hz, 2H), 3.06-2.97 (m, 1H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.31 (d, *J* = 7.2 Hz, 6H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 140.1, 134.8, 127.2, 121.5, 121.2, 115.6, 114.8, 110.9, 60.3, 35.0, 34.3, 24.7, 20.6, 14.2; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_2N$ $[M+H]^+$ 260.1645, found 260.1644.

Ethyl 3-(5-ethyl-1*H*-indol-3-yl)propanoate (13ha) [Scheme 30] To a solution of cyclopropyl acetal **10d** (55.2 mg, 0.296 mmol) in MeCN (16 mL) were added 4-ethylphenylhydrazine hydrochloride **9h** (102 mg, 0.592 mmol) and *t*-BuI (212 μL, 1.78 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 15 min, *t*-BuI (106 μL, 0.890 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ha** (40.8 mg, 56%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.40 (s, 1H), 7.27 (d, *J* = 9.6 Hz, 2H), 7.05 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.98 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.09 (t, *J* = 7.8 Hz, 2H), 2.81-2.67 (m, 4H), 1.33-1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 135.3, 134.7, 127.4, 122.6, 121.5, 117.2, 114.7, 110.9, 60.3, 35.0, 29.1, 20.6, 16.6, 14.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_2N$ $[M+H]^+$ 246.1489, found 246.1490.

Ethyl 3-(5-methyl-1*H*-indol-3-yl)propanoate (13ia) [Scheme 30] To a solution of *p*-tolylhydrazine hydrochloride **9i** (92.9 mg, 0.585 mmol) and *t*-BuI (210 μL, 1.76 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d** (54.5 mg, 0.293 mmol) in MeCN (1.6 mL) at reflux. After being stirred at reflux for 32 min, *t*-BuI (105 μL, 0.879 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 28 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ia** (28.3 mg, 42%) as a black oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, br, 1H), 7.38 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 7.01 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 2.46 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 173.5, 134.6, 128.5, 127.4, 123.6, 121.5, 118.4, 114.5, 110.7, 60.3, 35.0, 21.5, 20.6, 14.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_2N$ $[M+H]^+$ 232.1332, found 232.1332.

Ethyl 3-(1*H*-indol-3-yl)propanoate (13ja) [Scheme 30] To a solution of cyclopropyl acetal **10d** (30.0 mg, 0.161 mmol) in MeCN (10 mL) were added phenylhydrazine **9j** (31.7 μL, 0.322 mmol) and *t*-BuI (115 μL, 0.966 mmol) at room temperature. After being stirred at reflux for 7 min, *t*-BuI (57.5 μL, 0.483 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 53 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ja** (11.4 mg, 33%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.23-7.09 (m, 2H), 7.02 (d, *J* = 2.0 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.11 (t, *J* = 7.8 Hz, 2H), 2.71 (t, *J* = 7.8 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 136.2, 127.2, 122.0, 121.4, 119.3, 118.7, 115.1, 111.1, 60.3, 35.0, 20.6, 14.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_2N$ $[M+H]^+$ 218.1176, found 218.1175.

Ethyl 3-(5-fluoro-1*H*-indol-3-yl)propanoate (13ka) [Scheme 30] To a solution of 4-fluorophenylhydrazine hydrochloride **9k** (101 mg, 0.622 mmol) and *t*-BuI (222 μL, 1.87 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d** (57.9 mg, 0.311 mmol) in MeCN (2.0 mL) at reflux. After being stirred at reflux for 32 min, *t*-BuI (111 μL, 0.933 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 28 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ka** (30.8 mg,

42%) as a brown solid; Mp: 41-46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, br, 1H), 7.28-7.20 (m, 2H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.95-6.90 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 157.7 (d, J_{C-F} = 234.1 Hz), 132.7, 127.5 (d, $J_{C-C-C-F}$ = 9.6 Hz), 123.2, 115.1 (d, $J_{C-C-C-C-F}$ = 4.8 Hz), 111.7 (d, $J_{C-C-C-F}$ = 9.6 Hz), 110.3 (d, J_{C-C-F} = 27.0 Hz), 103.6 (d, J_{C-C-F} = 23.1 Hz), 60.4, 34.8, 20.5, 14.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2NF$ $[M+H]^+$ 236.1081, found 236.1081.

Ethyl 3-(5-chloro-1*H*-indol-3-yl)propanoate (13la) [Scheme 30] To a solution of 4-chlorophenylhydrazine hydrochloride **9l** (117 mg, 0.654 mmol) and *t*-BuI (234 μL, 1.96 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d** (60.9 mg, 0.327 mmol) in MeCN (2.0 mL) at reflux. After being stirred at reflux for 12 min, *t*-BuI (117 μL, 0.981 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13la** (24.7 mg, 30%) as a brown solid; Mp: 63-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 4.4 Hz, 1H), 7.13 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.03 (s, 1H), 4.12 (q, *J* = 6.8 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 134.6, 128.3, 125.1, 122.8, 122.3, 118.3, 114.9, 112.1, 60.4, 34.9, 20.4, 14.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2N^{35}Cl$ $[M+H]^+$ 252.0786, found 252.0787, $C_{13}H_{15}O_2N^{37}Cl$ $[M+H]^+$ 254.0756, found 254.0757.

Ethyl 3-(6-chloro-1*H*-indol-3-yl)propanoate (13na) and Ethyl 3-(4-chloro-1*H*-indol-3-yl)propanoate (13na'), [Scheme 30] To a solution of cyclopropyl acetal **10d**+**10d'** (37.0 mg, 0.199 mmol) in MeCN (12 mL) were added 3-chlorophenylhydrazine hydrochloride **9n** (71.2 mg, 0.398 mmol) and *t*-BuI (142 μL, 1.19 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 10 min, *t*-BuI (71.0 μL, 0.595 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 50 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13na** (7.7 mg, 15%) and indole **13na'** (5.4 mg, 11%)

Ethyl 3-(6-chloro-1*H*-indol-3-yl)propanoate (13na). Physical state: white solid; Mp: 82-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, br, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.08 (dd, *J* = 8.8, 1.8 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.06 (t, *J* = 7.2 Hz, 2H),

2.68 (t, J = 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 136.5, 128.0, 125.8, 122.0, 120.1, 119.6, 115.3, 111.0, 60.4, 34.9, 20.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2N^{35}Cl$ $[M+H]^+$ 252.0786, found 252.0785, $C_{13}H_{15}O_2N^{37}Cl$ $[M+H]^+$ 254.0756, found 254.0755.

Ethyl 3-(4-chloro-1*H*-indol-3-yl)propanoate (13na'). Physical state: white solid; Mp: 78-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, br, 1H), 7.24 (dd, J =4.8, 3.6 Hz, 1H), 7.07-7.04 (m, 3H), 4.13 (q, J = 7.2 Hz, 2H), 3.32 (t, J = 8.0 Hz, 2H), 2.75 (t, J = 8.0 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 137.8, 126.3, 124.1, 123.2, 122.5, 120.4, 115.5, 109.8, 60.2, 36.3, 21.8, 14.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2N^{35}Cl$ $[M+H]^+$ 252.0786, found 252.0786, $C_{13}H_{15}O_2N^{37}Cl$ $[M+H]^+$ 254.0756, found 254.0755.

Ethyl 3-(7-methoxy-1*H*-indol-3-yl)propanoate (13oa) and Ethyl 3-(1*H*-indol-3-yl)propanoate (13ja) [Scheme 30] To a solution of 2-methoxyphenylhydrazine hydrochloride **9o** (104 mg, 0.597 mmol) and *t*-BuI (213 μL, 1.79 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d** (55.6 mg, 0.298 mmol) in MeCN (2.0 mL) at reflux. After being stirred at reflux for 20 min, *t*-BuI (107 μL, 0.894 mmol) was added to the reaction mixture. After being stirred at reflux for 28 min, *t*-BuI (107 μL, 0.894 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 10 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13oa** (18.8 mg, 26%) and indole **13ja** (10.6 mg, 16%).

Ethyl 3-(7-methoxy-1*H*-indol-3-yl)propanoate (13oa). Physical state: Pale orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, br, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.13 (q, J = 6.8 Hz, 2H), 3.94 (s, 3H), 3.08 (t, J = 7.6 Hz, 2H), 2.70 (t, J = 7.6 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 146.2, 128.5, 126.7, 121.0, 119.7, 115.4, 111.5, 101.9, 60.3, 55.3, 35.1, 20.8, 14.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_3N$ $[M+H]^+$ 248.1281, found 248.1280.

Ethyl 3-(7-methyl-1*H*-indol-3-yl)propanoate (13pa) [Scheme 30] To a solution of cyclopropyl acetal **10d** (41.1 mg, 0.221 mmol) in MeCN (16 mL) were added 2-methylphenylhydrazine hydrochloride **9p** (70.1 mg, 0.442 mmol) and *t*-BuI (158 μL, 1.33 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 12 min, *t*-BuI (79.0 μL, 0.663 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 50 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and

concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13pa** (17.6 mg, 34%) as a white solid; Mp: 45 °C (decomposed); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.12-6.91 (m, 3H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.10 (t, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 7.8 Hz, 2H), 2.48 (s, 3H), 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 136.4, 127.2, 123.1, 121.6, 120.8, 120.1, 117.0, 116.1, 60.9, 35.5, 21.3, 17.1, 14.8; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_2N$ $[M+H]^+$ 232.1332, found 232.1322.

Ethyl 3-(6-fluoro-5-methoxy-1*H*-indol-3-yl)propanoate (13qa) [Scheme 30] To a solution of cyclopropyl acetal **10d**+**10d'** (31.5 mg, 0.169 mmol) in MeCN (10 mL) were added 3-fluoro-4-methoxyphenylhydrazine hydrochloride **9q** (65.1 mg, 0.338 mmol) and *t*-BuI (121 μL, 1.01 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 12 min, *t*-BuI (61 μL, 0.505 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 50 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13qa** (30.2 mg, 67%) as a white solid; Mp: 98-103 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.09 (d, *J* = 4.0 Hz, 1H), 7.07 (s, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.94 (s, 3H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 150.8 (d, $J_{C\text{-}F}$ = 239.9 Hz), 142.9, (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 12.5 Hz), 129.5 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 11.6 Hz), 122.7, 121.6 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 3.9 Hz), 114.9, 102.0, 98.6 (d, $J_{C\text{-}C\text{-}F}$ = 23.1 Hz), 60.4, 56.9, 34.8, 20.5, 14.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -140.1; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}O_3NF$ $[M+H]^+$ 266.1187, found 266.1186.

Ethyl 3-(1*H*-benzo[*g*]indol-3-yl)propanoate (13ra) [Scheme 30] To a solution of 1-naphthylhydrazine hydrochloride **9r** (123 mg, 0.630 mmol) and *t*-BuI (225 μL, 1.89 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d** (58.6 mg, 0.315 mmol) in MeCN (2.0 mL) at reflux. After being stirred at reflux for 15 min, *t*-BuI (113 μL, 0.945 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 40 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/acetone= 25 : 1) to afford indole **13ra** (47.2 mg, 56%) as a white solid; Mp: 152-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, br, 1H), 7.97-7.91 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.57-7.46 (m, 2H), 7.46-7.37 (m, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 4.14 (q, *J* = 7.6 Hz, 2H), 3.17 (t, *J* = 8.0 Hz, 2H), 2.74 (t, *J* = 8.0 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 130.8, 130.4, 128.8, 125.4, 123.9, 122.9, 121.8, 120.2, 119.6, 119.4, 118.8, 116.8, 60.4, 35.3, 20.7, 14.2; HRMS (ESI) *m/z* calcd for $C_{17}H_{18}O_2N$ $[M+H]^+$ 268.1332, found 268.1333.

Ethyl 3-(3*H*-benz[*e*]indole-3-yl)propanoate (13sa) [Scheme 30] To a solution of cyclopropyl acetal **10d** (37.4 mg, 0.200 mmol) in MeCN (10 mL) were added 2-naphthylhydrazine hydrochloride **9s** (78.1 mg, 0.401 mmol) and *t*-BuI (143 μL, 1.20 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 15 min, *t*-BuI (72 μL, 0.600 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13sa** (19.0 mg, 36%) as a white solid; Mp: 91-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.2 Hz, 1H), 8.33 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.60-7.55 (m, 2H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.44-7.40 (m, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.49 (t, *J* = 7.2 Hz, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 133.3, 129.7, 129.1, 128.9, 125.9, 123.5, 123.1, 122.9, 119.9, 117.8, 112.9, 60.4, 34.6, 23.5, 14.2; One carbon peak could not be detected probably due to overlapping; HRMS (ESI) *m/z* calcd for $C_{17}H_{18}O_2N$ $[M+H]^+$ 268.1332, found 268.1332.

Ethyl 3-(5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)propanoate (13ta) [Scheme 30] To a solution of cyclopropyl acetal **10d** (44.3 mg, 0.238 mmol) in MeCN (14 mL) were added 3,4-dihydroquinonyl (2*H*)-amine hydrochloride **9u** (87.9 mg, 0.476 mmol) and *t*-BuI (170 μL, 1.43 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 15 min, *t*-BuI (85 μL, 0.715 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ta** (22.5 mg, 37%) as a yellow solid; Mp: 45-50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 1H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.88 (s, 1H), 4.19-4.06 (m, 4H), 3.08 (t, *J* = 7.8 Hz, 2H), 2.97 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 7.8 Hz, 2H), 2.27-2.15 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 125.0, 123.6, 121.7, 119.1, 118.4, 116.4, 113.5, 60.3, 43.8, 35.4, 24.7, 22.9, 21.0, 14.2; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_2N$ $[M+H]^+$ 258.1489, found 258.1488.

Ethyl 3-(5*H*-[1,3]dioxolo[4,5-*f*]indol-7-yl)propanoate (13ua) [Scheme 30] To a solution of cyclopropyl acetal **10d** (42.7 mg, 0.229 mmol) in MeCN (14 mL) were added 1,3-benzodioxol-5-yl hydrazine hydrochloride **9u** (86.4 mg, 0.458 mmol) and *t*-BuI (164 μL, 1.37 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 15 min, *t*-BuI (82 μL, 0.685 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45

min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ua** (31.7 mg, 53%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 6.97 (s, 1H), 6.88 (d, *J* = 2.8 Hz, 1H), 6.81 (s, 1H), 5.93 (s, 2H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 145.0, 142.8, 131.0, 121.1, 120.0, 115.3, 100.6, 97.4, 92.0, 60.4, 34.9, 20.7, 14.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_4N$ $[M+H]^+$ 262.1074, found 262.1073.

Ethyl 3-(5-methoxy-1-methyl-1*H*-indol-3-yl)propanoate (13va) [Scheme 30] To a solution of *N*-(4-methoxyphenyl)methylhydrazine hydrochloride **9v** (119 mg, 0.631 mmol) and *t*-BuI (225 μL, 1.89 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d'** (58.7 mg, 0.315 mmol) in MeCN (2.0 mL) at reflux. After being stirred at reflux for 37 min, *t*-BuI (117 μL, 0.945 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 1 h. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13va** (56.6 mg, 69%) as a brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.83 (s, 1H), 4.14 (q, *J* = 7.6 Hz, 3H), 3.86 (s, 3H), 3.69 (s, 3H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.68 (t, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 153.6, 132.3, 127.8, 126.8, 112.9, 111.7, 109.9, 100.6, 60.3, 55.9, 35.0, 32.7, 20.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_3N$ $[M+H]^+$ 262.1438, found 262.1438.

Ethyl 3-(1-methyl-1*H*-indol-3-yl)propanoate (13wa) [Scheme 30] To a solution of 1-methyl-1-phenylhydrazine **9w** (70 μL, 0.593 mmol) and *t*-BuI (212 μL, 1.78 mmol) in MeCN (14 mL) was added cyclopropyl acetal **10d'** (55.2 mg, 0.297 mmol) in MeCN (2.0 mL) at reflux. After being stirred at reflux for 17 min, *t*-BuI (106 μL, 0.891 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 50 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13wa** (19.9 mg, 29%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 1H), 7.33-7.18 (m, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.87 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 136.9, 127.5, 126.3, 121.5, 118.8, 118.7, 113.5, 109.2, 60.3, 35.2, 32.6, 20.5, 14.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_2N$ $[M+H]^+$ 232.1332, found 232.1333.

Ethyl 5-(5-methoxy-1*H*-indol-3-yl)-3-pentenoate (13ab) [Scheme 31] To a solution of cyclopropyl α,β-saturated ester **10e** (35.9 mg, 0.169 mmol) in MeCN (10 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (59.0 mg, 0.338 mmol) and *t*-BuI (121 μL, 1.01 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 15 min, *t*-BuI (61 μL, 0.505 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ab** (dr = 1.7 : 1, 20.3 mg, 44%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.33-7.16 (m, 1H), 7.05-6.99 (m, 1H), 6.98-6.92 (m, 1H), 6.92-6.74 (m, 1H), 5.98-5.64 (m, 2H), 4.30-4.07 (m, 2H), 3.86 (s, 1.1H), 3.85 (s, 1.9H), 3.50-3.45 (m, 2H), 3.25 (dd, *J* = 7.2, 0.8 Hz, 0.7H), 3.07 (dd, *J* = 6.4, 0.9 Hz, 1.3H), 1.26 (t, *J* = 7.2 Hz, 1.1H), 1.24 (t, *J* = 7.2 Hz, 1.9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 172.1, 154.0, 154.0, 133.1, 131.7, 131.5, 127.8, 127.7, 122.7, 122.6, 122.4, 121.7, 114.3, 114.3, 112.3, 112.2, 111.9, 111.9, 101.0, 100.8, 60.8, 60.7, 56.0, 38.1, 33.1, 28.7, 23.6, 14.3; Three carbon peaks of diastereomers could not be detected probably due to overlapping; HRMS (ESI) (*E*/*Z* mixture) *m/z* calcd for $C_{16}H_{20}O_3N$ $[M+H]^+$ 274.1438, found 274.1436.

Ethyl 3-(5-methoxy-1*H*-indol-3-yl)butanoate (13ac) [Scheme 31] To a solution of 4-methoxyphenylhydrazine hydrochloride **9a** (42.6 mg, 0.243 mmol) and *t*-BuI (87.0 μL, 0.732 mmol) in MeCN (8.0 mL) was added cyclopropyl acetal **10f** (24.4 mg, 0.122 mmol) in MeCN (1.0 mL) at reflux. After being stirred at reflux for 17 min, *t*-BuI (44 μL, 0.366 mmol) was added to the reaction mixture. After being stirred at reflux for 35 min, *t*-BuI (44 μL, 0.366 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 20 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford indole **13ac** (23.8 mg, 75%) as an orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, br, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 3.63-3.51 (m, 1H), 2.80 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.55 (dd, *J* = 15.2, 8.8 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 153.8, 131.6, 126.7, 120.8, 120.6, 112.1, 111.8, 101.1, 60.3, 56.0, 42.3, 27.9, 21.0, 14.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_3N$ $[M+H]^+$ 262.1438, found 262.1439.

***N*,*N*-Diethyl-3-(5-methoxy-1*H*-indol-3-yl)propanamide (13ad) [Scheme 31].** To a solution of cyclopropyl amide **10g** (42.2 mg, 0.198 mmol) in MeCN (12 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (69.1 mg, 0.396 mmol) and *t*-BuI (142 μL, 1.19 mmol) at

room temperature. The mixture was stirred at reflux. After being stirred at reflux for 15 min, *t*-BuI (71 μL, 0.595 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 45 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 1 : 2) to afford indole **13ad** (33.1 mg, 61%) as a white solid; Mp: 101-105°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br, 1H), 7.25 (d, *J* = 4.0 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.99 (d, *J* = 1.6 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.85 (s, 3H), 3.40 (q, *J* = 7.2 Hz, 2H), 3.23 (q, *J* = 7.2 Hz, 2H), 3.10 (dd, *J* = 9.6, 7.2 Hz, 2H), 2.70-2.60 (m, 2H), 1.14-1.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 153.8, 131.4, 127.6, 122.4, 115.2, 112.1, 111.9, 100.5, 55.9, 41.9, 40.1, 33.8, 21.1, 14.2, 13.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}O_2N_2$ $[M+H]^+$ 275.1754, found 275.1754.

3-(5-Methoxy-1*H*-indol-3-yl)-1-(1-piperidinyl)-1-propanone (13ae) [Scheme 31]. To a solution of cyclopropyl amide **10h** (30.7 mg, 0.136 mmol) in MeCN (10 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (47.6 mg, 0.272 mmol) and *t*-BuI (97 μL, 0.816 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 12 min, *t*-BuI (49 μL, 0.408 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 33 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 1 : 2) to afford indole **13ae** (19.6 mg, 50%) as a pale orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.84 (dd, *J* = 9.2, 2.8 Hz), 3.85 (s, 3H), 3.57-3.55 (m, 2H), 3.31 (t, *J* = 5.6 Hz, 2H), 3.10-3.06 (m, 2H), 2.75-2.65 (m, 2H), 1.64-1.54 (m, 2H), 1.54-1.46 (m, 2H), 1.45-1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 153.9, 131.4, 127.6, 122.3, 115.3, 112.1, 111.8, 100.5, 55.9, 46.6, 42.7, 33.9, 26.3, 25.5, 24.5, 21.1; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}O_2N_2$ $[M+H]^+$ 287.1754, found 287.1755.

***N*-Methoxy-3-(5-methoxy-1*H*-indol-3-yl)-*N*-methylpropanamide (13af) [Scheme 31]** To a solution of cyclopropyl amide **10j** (206 mg, 1.02 mmol) in MeCN (50 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (358 mg, 2.05 mmol) and *t*-BuI (730 μL, 6.12 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 15 min, *t*-BuI (365 μL, 3.06 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 35 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 1 : 3) to afford indole **13af** (139 mg, 52%) as a pale orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H),

6.83 (dd, J = 8.8, 2.4 Hz, 1H), 3.85 (s, 3H), 3.57 (s, 3H), 3.18 (s, 3H), 3.07 (t, J = 7.2 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 153.7, 131.4, 127.5, 122.4, 115.0, 112.0, 111.9, 100.4, 61.1, 55.9, 32.5, 32.1, 20.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}O_3N_2$ $[M+H]^+$ 263.1391, found 263.1390.

***S*-Benzyl 3-(5-methoxy-1*H*-indol-3-yl)propanethioate (13ag) [Scheme 31]** To a solution of cyclopropyl thioester **10i** (38.1 mg, 0.144 mmol) in MeCN (10 mL) were added 4-methoxyphenylhydrazine hydrochloride **9a** (50.3 mg, 0.288 mmol) and *t*-BuI (103 μL, 0.864 mmol) at room temperature. The mixture was stirred at reflux. After being stirred at reflux for 18 min, *t*-BuI (365 μL, 3.06 mmol) was added to the reaction mixture. The mixture was stirred at reflux for additional 42 min. Then the mixture was cooled to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (hexane/EtOAc = 7 : 3) to afford the indole **13ag** (34.4 mg, 74%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.52-7.16 (m, 6H), 7.01 (s, 1H), 6.93 (s, 1H), 6.86 (d, J = 8.5 Hz, 1H), 4.13 (s, 2H), 3.86 (s, 3H), 3.11 (t, J = 7.6 Hz, 2H), 2.96 (dd, J = 8.2, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 154.0, 137.6, 131.3, 128.8, 128.6, 127.4, 127.2, 122.3, 114.1, 112.3, 111.9, 100.4, 55.9, 44.2, 33.2, 21.1; One carbon peak could not be detected probably due to overlapping; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}O_2NNa$ $[M+Na]^+$ 348.1029, found 348.1026.

5-(5-Methoxy-1*H*-indol-3-yl)-1-(4-methoxyphenyl)pent-1-yn-3-one (51) [Scheme 32]. To a solution of 4-ethynylanisole (116 mg, 0.874 mmol) in THF (1 mL) was added *n*-BuLi (46.8 mg, 0.73 mmol) at −78 °C. After stirred at −78 °C for 30 min, the mixture was transferred through cannula to cooled (−78 °C) solution of indole **13af** (76.5 mg, 0.29 mmol) in THF (1 mL) and stirred for 5 min at −78 °C. Then the mixture was stirred for further 1 h at −10 °C followed by cooled to −78 °C, quenched with saturated aqueous NH_4Cl and warm to room temperature. The resulting mixture was diluted with water, extracted with ethyl acetate three times, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 7 : 3) to afford ynone **51** (57.8 mg, 59%) as a brown solid; Mp: 76-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, br, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.25 (s, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.92-6.83 (m, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.19-3.15 (m, 2H), 3.08-3.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 161.6, 154.0, 135.1, 131.4, 127.5, 122.3, 114.4, 114.3, 112.2, 111.9, 111.7, 100.5, 92.3, 87.8, 55.9, 55.4, 45.7, 19.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{20}O_3N$ $[M+H]^+$ 334.1438, found 334.1440.

2-Methoxy-6-(4-methoxyphenyl)-9,10-dihydrocyclohepta[*b*]indol-8(5*H*)-one (52) [Scheme 32]. To a solution of ynone **51** (21.8 mg, 0.065 mmol) in MeCN (2 mL) was added $NaAuCl_4 \cdot 2H_2O$ (1.30

mg, 0.003 mmol). The mixture was stirred at room temperature for 12 h and then, diluted with EtOAc. The mixture was washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 7 : 3) to afford **52** (22.1 mg, quant.) as a yellow solid; Mp: 188-191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, br, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.08-6.96 (m, 3H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.18 (s, 1H), 3.883 (s, 3H), 3.876 (s, 3H), 3.21-3.08 (m, 2H), 2.97-2.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 160.6, 154.5, 145.1, 132.2, 131.8, 131.0, 130.2, 127.4, 127.2, 120.7, 115.8, 114.3, 112.3, 99.9, 55.8, 55.4, 42.7, 18.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{20}O_3N$ $[M+H]^+$ 334.1438, found 334.1434.

1-(4-Methoxyphenyl)spiro[(4-methoxyphenyl)-cyclohex[6]ene-2,3'-indol]-5-one (53)

[Scheme 32]. To a solution of ynone **51** (20.9 mg, 0.063 mmol) in CH_2Cl_2 (1 mL) was added AgOTf (1.67 mg, 0.0065 mmol). After stirred at room temperature for 3 h, the mixture was concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 7 : 3) to afford **53** (18 mg, 86%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 6.97 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.87 (d, *J* = 2.8 Hz, 1H), 6.77-6.72 (m, 2H), 6.70-6.64 (m, 2H), 6.47 (s, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 2.95-2.80 (m, 1H), 2.76-2.62 (m, 1H), 2.61-2.48 (m, 1H), 1.86-1.74 (m, 1H), 0.96-0.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 174.0, 161.0, 159.1, 157.4, 148.3, 142.6, 129.7, 128.2, 127.4, 122.9, 114.0, 113.8, 109.3, 61.5, 60.4, 55.8, 55.2, 34.1, 32.2, 14.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{20}O_3N$ $[M+H]^+$ 334.1438, found 334.1438.

第 4 節　第 2 章第 1 節の実験

Di-*tert*-butyl 1-cyclopropylhydrazine-1,2-dicarboxylate (66) [Scheme 39]. To a solution of cyclopropylboronic acid **65** (8.59 g, 100 mmol) in DMF (60 mL) were added di-*tert*-butyl azodicarboxylate (7.41 g, 32.0 mmol) and $Cu(OAc)_2$ (908 mg, 5.00 mmol). The mixture was stirred at 80 °C for 8 h, and then cooled to room temperature. After the mixture was cooled to 0 °C, H_2O (100 mL) and Et_2O (200 mL) were added. The organic layer was washed with H_2O and brine, and dried over $MgSO_4$. Then, the mixture was filtered and concentrated. The residue was purified with silica gel column chromatography (hexane/EtOAc = 9 : 1) to afford protected *N*-cyclopropylhydrazine **66** (5.75 g, 21% yield) as a yellow oil. The spectral data were identical with those reported in the literature. [41)]

Cyclopropylhydrazine ditosylate (67) [Scheme 39]. To a solution of protected *N*-cyclopropyl hydrazine **66** (5.75g, 21.0 mmol) in MeCN (105 mL) was added *p*-toluenesulfonic acid monohydrate (16.0 g, 84.0 mmol). The mixture was stirred at 60 °C for 1 h, and then cooled to room temperature, filtered with KIRIYAMA funnel to afford *N*-cyclopropylhydrazine tosylate **67** (6.26 g, 71% yield) as a white solid. The spectral data were identical with those reported in the literature. [41)]

Methyl 2-(naphthalen-2-yl)-2-oxoacetate (70aa) [Scheme 40]. To a suspension of magnesium (703 mg, 28.9 mmol) in THF (7.30 mL), was added I_2 slowly. To the resulted mixture was added the solution of 2-bromonaphthalene **68** (5.00 g, 24.1 mmol) in THF (12 mL). After cooled to −78 °C, dimethyloxalate (1.90 g, 15.9 mmol) solution in THF was added to the reaction mixture and stirred at −78 °C for 1 h. Then, the mixture was quenched with 1 M HCl and the aqueous phase was extracted with ethyl acetate and the combined organic extracts were dried over $MgSO_4$, filtered and evaporated. 2-(Naphthalen-2-yl)-2-oxoacetate **70aa** (571 mg, 11%) was obtained after purification by flash column chlomatography (hexane/EtOAc); The spectral data were identical with those reported in the literature.[79)]

Methyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(naphthalen-2-yl)acetate (14aa) [Scheme 40]. To a solution of methyl 2-(naphthalene-2-yl)-2-oxoacetate **70aa** (571 mg, 2.66 mmol) in MeOH (120 mL) were added cyclopropylhydrazine ditosylate **67** (1.11 g, 2.66 mmol) and pyridine (430 μL, 5.33 mmol). The mixture was stirred at room temperature for 18 h, and then evaporated. **14aa** (320 mg, 45%) was obtained as a white solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 72-77 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 7.96 (s, 1H), 7.84-7.78 (m, 3H), 7.66 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.47-7.41 (m, 2H), 3.81 (s, 3H), 3.12-3.07 (m, 1H), 0.85-0.79 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.1, 134.4, 133.2, 132.5, 128.2, 127.5, 127.2, 127.1, 126.6, 126.0, 125.8,

125.7, 51.4, 31.9, 6.3; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}O_2N_2$ $[M+H]^+$ 269.1285, found 269.1284.

[Table 3, entry 1] *N*-Cyclopropylhydrazone **14aa** (42.4 mg, 0.158 mmol), $[Cp^*RhCl_2]_2$ (9.8 mg, 0.0158 mmol), $Cu(OAc)_2$ (28.7 mg, 0.158 mmol), K_2CO_3 (21.8 mg, 0.158 mmol) and MS4A (100 mg) were dissolved in xylene (1.60 mL). The mixture was stirred at reflux for 16 h. Then, the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was analyzed by ^{1}H NMR ($CDCl_3$). Pyrazole **16aa** was calculated as 13% NMR yield.

Methyl 2-(naphthalen-2-yl)-2-(1*H*-pyrazol-1-yl)acetate (**16aa**). Physical state: yellow solid; Mp: 97-99 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89-7.84 (m, 4H), 7.61 (d, J = 2.0 Hz, 1H), 7.54-7.47 (m, 3H), 7.42 (d, J = 2.0 Hz, 1H), 6.40 (s, 1H), 6.27 (t, J = 2.0 Hz, 1H), 3.83 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.5, 140.0, 133.4, 133.1, 131.0, 129.3, 129.1, 128.2, 128.0, 127.7, 127.0, 126.7, 125.5, 106.1, 67.9, 52.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}O_2N_2$ $[M+H]^+$ 267.1128, found 267.1127.

[Table 3, entry 3] *N*-Cyclopropylhydrazone **14aa** (30.7 mg, 0.110 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol) and MS4A (100 mg) were dissolved in xylene (1.00 mL). The mixture was stirred at reflux for 14 h. Then, the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was analyzed by ^{1}H NMR ($CDCl_3$). Pyrazole **16aa** was calculated as 49% NMR yield.

[Table 3, entry 4] *N*-Cyclopropylhydrazone **14aa** (46.8 mg, 0.175 mmol), $Pd(TFA)_2$ (5.8 mg, 0.017 mmol) and MS4A (100 mg) were dissolved in xylene (1.70 mL). The mixture was stirred at reflux for 16 h. Then, the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was analyzed by ^{1}H NMR ($CDCl_3$). Pyrazole **16aa** was calculated as 42% NMR yield.

[Table 3, entry 5] *N*-Cyclopropylhydrazone **14aa** (35.1 mg, 0.130 mmol), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol), AgOAc (43.4 mg, 0.260 mmol) and MS4A (100 mg) were dissolved in xylene (1.30 mL). The mixture was stirred at reflux for 16 h. Then, the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was analyzed by ^{1}H NMR ($CDCl_3$). Pyrazole **16aa** was calculated as 39% NMR yield.

[Table 3, entry 6] *N*-Cyclopropylhydrazone **14aa** (38.6 mg, 0.144 mmol), $Pd(OAc)_2$ (3.2 mg, 0.014 mmol), HFIP (48.4 mg, 0.288 mmol) and MS4A (100 mg) were dissolved in xylene (1.40 mL). The mixture was stirred at reflux for 15 h. Then, the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by PTLC (hexane/EtOAc = 7 : 3) to afford pyrazole **16aa** (26.4 mg, 69%).

[Table 3, entry 8] *N*-Cyclopropylhydrazone **14aa** (32.1 mg, 0.120 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol) and MS4A (100 mg) were dissolved in *t*-AmylOH (1.20 mL). The mixture was stirred at reflux for 4 h. Then, the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by PTLC (hexane/EtOAc = 7 : 3) to afford pyrazole **16aa** (25.6 mg, 80%).

第 5 節　第 2 章第 2 節の実験

General procedure for preparation of cyclopropylhydrazones [Table 4]. To a solution of α-keto esters in MeOH were added cyclopropylhydrazine **67** (1.0 eq.) and pyridine (2.0 eq.). The mixture was stirred at room temperature for several hours, and then evaporated. The crude product was purified by column chromatography to afford cyclopropylhydrazones **14ab-as**.

Methyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-phenylacetate (14ab) [Table 4, entry 1]. Following to the general procedure using commercially available methyl benzoylformate **70ab** (1.20 g, 7.20 mmol), cyclopropylhydrazine **67** (3.00 g, 7.20 mmol) and pyridine (1.20 mL, 14 mmol), **14ab** (775 mg, 49%) was obtained as a yellow oil after purification by flash column chromatography (hexane/EtOAc = 10 : 1); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.50-7.48 (m, 2H), 7.34-7.31 (m, 2H), 7.27-7.24 (m, 1H), 3.77 (s, 3H), 3.07-3.03 (m, 1H), 0.82-0.75 (m, 4H); ^{13}C-NMR (151 MHz, $CDCl_3$) δ 163.9, 137.0, 128.4, 127.8, 127.0, 126.1, 51.3, 31.8, 6.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}O_2N_2$ $[M+H]^+$ 219.1128, found 219.1128.

Ethyl 2-(2-cyclopropylhydrazineylidene)-2-phenylacetate (14ac) [Table 4, entry 2]. Following to the general procedure using commercially available ethyl benzoylformate **70ac** (534 mg, 3.00 mmol), cyclopropylhydrazine **67** (1.25 mg, 3.00 mmol) and pyridine (484 μL, 6.00 mmol), **14ac** (45.6 mg, 7%) and **14ac'** (*E*-isomer of **14ac**, 21.0 mg, 3%) were obtained after purification by flash column chromatography (hexane/EtOAc = 4 : 1);

Ethyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-phenylacetate (14ac). Physical state: yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.53-7.50 (m, 2H), 7.34-7.30 (m, 2H), 7.27-7.23 (m, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.07-3.02 (m, 1H), 1.31 (t, *J* = 7.6 Hz, 3H), 0.81-0.76 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6, 137.1, 128.3, 127.8, 126.9, 126.3, 60.4, 31.8, 14.2, 6.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_2N_2$ $[M+H]^+$ 233.1285, found 233.1286.

Ethyl (*E*)-2-(2-cyclopropylhydrazineylidene)-2-phenylacetate (14ac'). Physical state: yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48-7.37 (m, 3H), 7.27-7.22 (m, 2H), 6.41 (s, 1H), 4.32-4.26 (m, 2H), 2.90-2.87 (m, 1H), 1.33-1.29 (m, 3H), 0.73-0.63 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.4, 133.6, 130.5, 129.2, 129.0, 129.0, 61.1, 31.1, 14.3, 6.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_2N_2$ $[M+H]^+$ 233.1285, found 233.1284.

Ethyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(4-methoxyphenyl)acetate (14ad) [Table 4, entry 3]. Following to the general procedure, commercially available ethyl 4-methoxybenzoylformate **70ad**

(208 mg, 1.00 mmol), cyclopropylhydrazine **67** (417 mg, 1.00 mmol) and pyridine (161 µL, 2.00 mmol) were used and the reaction time was 4 h. **14ad** (128 mg, 12%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47-7.43 (m, 2H), 6.88-6.85 (m, 2H), 4.26 (q, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 3.05-2.99 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.79-0.74 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6, 158.7, 129.8, 129.5, 126.3, 113.2, 60.4, 55.3, 31.7, 14.2, 6.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}O_3N_2$ $[M+H]^+$ 263.1390, found 263.1388.

Ethyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(*p*-tolyl)acetate (14ae) [Table 4, entry 4]. Following to the general procedure, commercially available ethyl 4-methylbenzoylformate **70ae** (326 mg, 1.70 mmol), cyclopropylhydrazine **67** (700 mg, 1.68 mmol) and pyridine (270 µL, 3.40 mmol) were used and the reaction time was 2 h. **14ae** (207 mg, 49%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 4.28-4.23 (m, 2H), 3.05-3.00 (m, 1H), 2.34 (s, 3H), 1.32-1.29 (m, 3H), 0.79-0.75 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6, 136.7, 134.3, 128.5, 128.2, 126.5, 60.3, 31.8, 21.2, 14.2, 6.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}O_2N_2$ $[M+H]^+$ 247.1441, found 247.1441.

Ethyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(4-fluorophenyl)acetate (14af) [Table 4, entry 5]. Following to the general procedure, commercially available ethyl-(4-fluorobenzoyl)formate **70af** (334 mg, 1.70 mmol), cyclopropylhydrazine **67** (700 mg, 1.68 mmol) and pyridine (270 µL, 3.40 mmol) were used and the reaction time was 2 h. **14af** (212 mg, 50%) was obtained as a yellow solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 35-40 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 7.50-7.46 (m, 2H), 7.00 (t, *J* = 8.8 Hz, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.06-3.01 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.3 (d, $J_{C\text{-}F}$ = 245.6 Hz), 160.8, 133.2 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 2.89 Hz), 130.0 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 7.71 Hz), 125.3, 114.6 (d, $J_{C\text{-}C\text{-}F}$ = 21.2 Hz), 60.5, 31.8, 14.2, 6.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_2N_2F$ $[M+H]^+$ 251.1190, found 251.1192.

Ethyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(4-chlorophenyl)acetate (14ag) [Table 4, entry 6]. Following to the general procedure, commercially available ethyl-(4-chlorobenzoyl)formate **70ag** (360 mg, 1.70 mmol), cyclopropylhydrazine **67** (700 mg, 1.68 mmol) and pyridine (270 µL, 3.40 mmol) were used and the reaction time was 5 h. **14ag** (207 mg, 46%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 7.48-7.45 (m, 2H), 7.30-7.26 (m, 2H), 4.26 (q, *J* = 6.8 Hz, 2H), 3.07-3.01 (m, 1H), 1.31 (t, *J* = 6.8 Hz, 3H), 0.80-0.77 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.3, 135.6, 132.6, 129.5, 127.9, 125.0, 60.5, 31.9, 14.2, 6.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_2N_2{}^{35}Cl$ $[M+H]^+$ 267.0895, found 267.0895, $C_{13}H_{16}O_2N_2{}^{37}Cl$ $[M+H]^+$ 269.0865, found 269.0866.

Ethyl (*Z*)-2-(4-bromophenyl)-2-(2-cyclopropylhydrazineylidene)acetate (14ah) [Table 4, entry 7]. Following to the general procedure, commercially available ethyl-(4-bromobenzoyl)formate **70ah** (617 mg, 2.40 mmol), cyclopropylhydrazine **67** (1.00 g, 2.40 mmol) and pyridine (400 μL, 4.80 mmol) were used and the reaction time was 5 h. **14ah** (403 mg, 54%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 7.45-7.38 (m, 4H), 4.26 (q, *J* = 7.6 Hz, 2H), 3.07-3.01 (m, 1H), 1.31 (t, *J* = 7.6 Hz, 3H), 0.80-0.77 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.3, 136.0, 130.8, 129.9, 124.9, 120.9, 60.5, 31.9, 14.2, 6.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{16}O_2N_2{}^{79}Br$ $[M+H]^+$ 311.0390, found 311.0391, $C_{13}H_{16}O_2N_2{}^{81}Br$ $[M+H]^+$ 313.0369, found 313.0371.

Methyl (*Z*)-4-(1-(2-cyclopropylhydrazineylidene)-2-methoxy-2-oxoethyl)benzoate (14ai) [Table 4, entry 8]. Following to the general procedure, methyl-(4-methoxycarbonyl)benzoylformate **70ai** (165 mg, 0.743 mmol), cyclopropylhydrazine **67** (291 mg, 0.700 mmol) and pyridine (113 μL, 1.40 mmol) were used and the reaction time was 3 h. **14ai** (79.7 mg, 41%) was obtained as a white solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 75 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 8.00-7.97 (m, 2H), 7.62-7.59 (m, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 3.11-3.06 (m, 1H), 0.84-0.80 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.1, 163.8, 141.5, 129.1, 128.2, 127.9, 124.6, 52.0, 51.4, 32.1, 6.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}O_4N_2$ $[M+H]^+$ 277.1183, found 277.1182.

Ethyl (*Z*)-2-(4-cyanophenyl)-2-(2-cyclopropylhydrazineylidene)acetate (14aj) [Table 4, entry 9]. Following to the general procedure, commercially available ethyl 4-cyanobenzoylformate **70aj** (203 mg, 1.00 mmol), cyclopropylhydrazine **67** (416 mg, 1.00 mmol) and pyridine (161 μL, 2.00 mmol) were used and the reaction time was 5 h. **14aj** (133 mg, 51%) was obtained as a white solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 66-70 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 7.68 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.59 (dd, *J* = 6.8, 1.6 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.12-3.06 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 0.84-0.81 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.1, 141.6, 131.6, 128.4, 123.8, 119.3, 109.7, 60.7, 32.2, 14.2, 6.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}O_2N_3$ $[M+H]^+$ 258.1237, found 258.1239.

Methyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(*o*-tolyl)acetate (14ak) [Table 4, entry 10]. Following to the general procedure, methyl 2-methylbenzoylformate **70ak** (115 mg, 0.645 mmol), cyclopropylhydrazine **67** (268 mg, 0.643 mmol) and pyridine (103 μL, 1.28 mmol) were used. The mixture was stirred at room temperature for 18 h. Then the mixture was heated up to 50 °C and stirred for 8 h. After the same work-up as the general procedure, **14ak** (20.2 mg, 14%) was obtained as a white solid after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 7.24-7.17 (m, 4H), 3.69 (s, 3H), 3.04-2.99 (m, 1H), 2.22 (s, 3H), 0.77-0.75 (m, 4H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.0, 137.2, 136.4, 130.2, 130.0, 127.8, 126.1, 125.6, 51.3, 31.6, 19.8, 6.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_2N_2$ $[M+H]^+$ 233.1285, found 233.1286.

Methyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(2-methoxyphenyl)acetate (14al) [Table 4, entry 11]. Following to the general procedure, 2-methoxybenzoylformate **70al** (159 mg, 0.819 mmol), cyclopropylhydrazine **67** (342 mg, 0.821 mmol) and pyridine (132 μL, 1.64 mmol) were used and the reaction time was 17 h. **14al** (16.7 mg, 8%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 7.31-7.26 (m, 2H), 6.99-6.95 (m, 1H), 6.88-6.86 (m, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.02-2.97 (m, 1H), 0.77-0.72 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.0, 157.8, 130.5, 129.2, 126.8, 125.3, 120.7, 110.8, 55.6, 51.2, 31.4, 6.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_3N_2$ $[M+H]^+$ 249.1234, found 249.1231.

Methyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(*m*-tolyl)acetate (14am) [Table 4, entry 12]. Following to the general procedure, 3-methylbenzoylformate **70am** (132 mg, 0.741 mmol), cyclopropylhydrazine **67** (309 mg, 0.742 mmol) and pyridine (119 μL, 1.48 mmol) were used and the reaction time was 22 h. **14am** (112 mg, 65%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 7.29-7.26 (m, 2H), 7.23-7.20 (m, 1H), 7.08 (d, J = 8.0 Hz, 1H), 3.77 (s, 3H), 3.06-3.03 (m, 1H), 2.36 (s, 3H), 0.80-0.76 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.0, 137.4, 136.9, 129.0, 128.0, 127.7, 126.3, 125.6, 51.3, 31.8, 21.5, 6.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_2N_2$ $[M+H]^+$ 233.1285, found 233.1284.

Methyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(3-methoxyphenyl)acetate (14an) [Table 4, entry 13]. Following to the general procedure, 3-methoxybenzoylformate **70an** (84.2 mg, 0.433 mmol), cyclopropylhydrazine **67** (181 mg, 0.434 mmol) and pyridine (69.0 μL, 0.86 mmol) were used and the reaction time was 21 h. **14an** (26.5 mg, 25%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 7.26-7.22 (m, 1H), 7.11-7.06 (m, 2H), 6.84-6.81 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.07-3.02 (m, 1H), 0.81-0.76 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.9, 159.1, 138.3, 128.7, 125.7, 121.0, 114.2, 112.5, 55.2, 51.3, 31.9, 6.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_3N_2$ $[M+H]^+$ 249.1233, found 249.1234.

Methyl (*Z*)-2-(3-cyanophenyl)-2-(2-cyclopropylhydrazineylidene)acetate (14ao) [Table 4, entry 14]. Following to the general procedure, 3-cyanobenzoylformate **70ao** (189 mg, 1.00 mmol), cyclopropylhydrazine **67** (416 mg, 1.00 mmol) and pyridine (161 μL, 2.00 mmol) were used and the reaction time was 24 h. **14ao** (110 mg, 45%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 7.84 (d, J = 0.8 Hz, 1H), 7.77 (dd, J = 8.0, 1.2 Hz, 1H), 7.52 (dd, J = 7.2, 0.8 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 3.81 (s, 3H), 3.11-3.05 (m, 1H), 0.83 (d, J = 5.6 Hz, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.4, 138.2, 132.4,

131.8, 130.1, 128.6, 123.2, 119.2, 111.9, 51.5, 32.2, 6.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_2N_3$ $[M+H]^+$ 244.1081, found 244.1079.

(Methyl (*Z*)-2-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-cyclopropylhydrazineylidene)acetate (14ap) [Table 4, entry 15]. Following to the general procedure, 3,4-methylenedioxybenzoylformate **70ap** (400 mg, 1.67 mmol), cyclopropylhydrazine **67** (696 mg, 1.67 mmol) and pyridine (270 µL, 3.34 mmol) were used and the reaction time was 17 h. **14ap** (117 mg, 27%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.00-6.96 (m, 2H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.94 (s, 2H), 3.77 (s, 3H), 3.05-3.00 (m, 1H), 0.79-0.75 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.8, 147.1, 146.7, 131.1, 125.7, 122.1, 109.1, 107.8, 100.9, 51.3, 31.8, 6.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_4N_2$ $[M+H]^+$ 263.1026, found 263.1027.

Methyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(thiophen-2-yl)acetate (14aq) [Table 4, entry 16]. Following to the general procedure, methyl 2-oxo-2-(thiophen-2-yl)acetate **70aq** (181 mg, 1.06 mmol), cyclopropylhydrazine **67** (443 mg, 1.06 mmol) and pyridine (171 µL, 2.12 mmol) were used and the reaction time was 22 h. **14aq** (52.8 mg, 22%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 7.31 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.13 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.96 (dd, *J* = 5.2, 3.6 Hz, 1H), 3.86 (s, 3H), 3.08-3.04 (m, 1H), 0.86-0.76 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.1, 141.1, 127.0, 124.0, 123.8, 121.3, 51.4, 32.1, 6.2; HRMS (ESI) *m/z* calcd for $C_{10}H_{13}O_2N_2S$ $[M+H]^+$ 225.0692, found 225.0691.

Methyl (*Z*)-2-(benzofuran-3-yl)-2-(2-cyclopropylhydrazineylidene)acetate (14ar) [Table 4, entry 17]. Following to the general procedure, ethyl 2-(benzofuran-3-yl)-2-oxoacetate **70ar** (207 mg, 0.948 mmol), cyclopropylhydrazine **67** (396 mg, 0.948 mmol) and pyridine (153 µL, 1.90 mmol) were used and the reaction time was 3 h. **14ar** (79.0 mg, 31%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.25-8.23 (m, 1H), 7.98 (s, 1H), 7.47-7.45 (m, 1H), 7.33-7.25 (m, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.15-3.09 (m, 1H), 1.41 (t, *J* = 7.2 Hz, 3H), 0.88-0.83 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.2, 154.9, 143.0, 126.2, 124.3, 123.3, 122.7, 120.1, 117.1, 111.0, 60.7, 31.9, 14.2, 6.2; HRMS (ESI) *m/z* calcd for $C_{15}H_{17}O_3N_2$ $[M+H]^+$ 273.1234, found 273.1234.

Methyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(naphthalen-1-yl)acetate (14as) [Table 4, entry 18]. Following to the general procedure, ethyl 2-(naphthalen-1-yl)-2-oxoacetate **70as** (175 mg, 0.815 mmol), cyclopropylhydrazine **67** (339 mg, 0.815 mmol) and pyridine (132 µL, 1.63 mmol) were used and the reaction time was 22 h. **14as** (60.3 mg, 28%) was obtained as a brown solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 87-90 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.84 (s, 1H), 7.85-7.81 (m, 2H), 7.76 (t, *J* = 4.4 Hz, 1H), 7.49-7.41 (m, 4H), 3.60 (d, *J* = 1.6 Hz, 3H), 3.09-3.03

(m, 1H), 0.83-0.74 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.5, 134.4, 133.7, 132.8, 128.3, 128.3, 127.8, 125.8, 125.5, 125.3, 125.3, 125.1, 51.3, 31.7, 6.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}O_2N_2$ $[M+H]^+$ 269.1285, found 269.1287.

General procedure for preparation of α-keto esters 70ak-70ap, 70as [Table 5]. To a solution of ketone (1.0 eq.) in pyridine (*c* = 2.0 M) was added SeO_2 (1.5 eq.) and stirred at 100 °C under argon overnight. The mixture was cooled in an ice bath and then MS4A and MeOH were added (1.8 eq.). After the mixture was stirred for 10 min, $SOCl_2$ (5.0 eq.) was added slowly and stirred at room temperature overnight. Then, 60% $HClO_4$ aq. (2.70 mL) and MeCN (27.3 mL) were poured into the flask and stirred for 30 min. Excess acid was neutralized by saturated aqueous Na_2CO_3 and filtered through Celite®. Then, the aqueous phase was extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chlomatography (hexane/EtOAc) to afford α-keto esters.

Methyl 4-(2-methoxy-2-oxoacetyl)benzoate (70ai) [Table 5, entry 1]. Following to the general procedure using 4-methoxycarbonylacetophenone **71ai** (1.78 g, 10.0 mmol), SeO_2 (1.66 g, 15.0 mmol), pyridine (5.00 mL), MS4A (60 mg), MeOH (7.50 mL), $SOCl_2$ (3.75 mL), 60% $HClO_4$ aq. (2.70 mL) and MeCN (27.3 mL), methyl 4-(2-methoxy-2-oxoacetyl)benzoate **70ai** (242 mg, 11%) was obtained as a white solid after purification by flash column chromatography (hexane/EtOAc); Mp: 96-101 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 6.8 Hz, 2H), 8.11-8.09 (m, 2H), 4.00 (d, *J* = 2.0 Hz, 3H), 3.97 (d, *J* = 2.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 185.2, 165.9, 163.3, 135.6, 135.4, 130.0, 129.9, 53.0, 52.6; HRMS (ESI) *m/z* calcd for $C_{11}H_{10}O_5Na$ $[M+Na]^+$ 245.0420, found 245.0423.

Methyl 2-oxo-2-(*o*-tolyl)acetate (70ak) [Table 5, entry 2]. Following to the general procedure using 2-methylacetophenone **71ak** (1.34 g, 10.0 mmol), SeO_2 (1.66 g, 15.0 mmol), pyridine (5.00 mL), MS4A (60 mg), MeOH (7.50 mL), $SOCl_2$ (3.75 mL), 60% $HClO_4$ aq. (2.70 mL) and MeCN (27.3 mL), methyl 2- methyl 2-oxo-2-(*o*-tolyl)acetate **70ak** (755 mg, 56%) was obtained after purification by flash column chromatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [80)]

Methyl 2-(2-methoxyphenyl)-2-oxoacetate (70al) [Table 5, entry 3]. Following to the general procedure using 2-methoxyacetophenone **71al** (751 mg, 5.00 mmol), SeO_2 (832 mg, 7.50 mmol), pyridine (2.50 mL), MS4A (300 mg), MeOH (3.60 mL), $SOCl_2$ (1.89 mL), 60% $HClO_4$ aq. (1.30 mL) and MeCN (13.7 mL), methyl 2-(2-methoxyphenyl)-2-oxoacetate **70al** (159 mg, 16%) was obtained as a colorless oil after purification by flash column chromatography (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J*

= 8.4 Hz, 1H), 3.91 (d, *J* = 2.4 Hz, 3H), 3.87 (d, *J* = 3.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 186.3, 165.6, 160.3, 136.4, 130.6, 122.7, 121.3, 112.0, 56.2, 52.4; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}O_4$ $[M+H]^+$ 195.0652, found 195.0654.

Methyl 2-oxo-2-(*m*-tolyl)acetate (70am) [Table 5, entry 4]. Following to the general procedure using 3-methylacetophenone **71am** (537 mg, 4.00 mmol), SeO_2 (666 mg, 6.00 mmol), pyridine (2.00 mL), MS4A (50 mg), MeOH (3.00 mL), $SOCl_2$ (1.5 mL), 60% $HClO_4$ aq. (1.20 mL) and MeCN (12.1 mL), 3- methyl 2-oxo-2-(*m*-tolyl)acetate **70am** (544 mg, 76%) was obtained after purification by flash column chromatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [80)]

Methyl 2-(3-methoxyphenyl)-2-oxoacetate (70an) [Table 5, entry 5]. Following to the general procedure using 3-methoxyacetophenone **71an** (751 mg, 5.00 mmol), SeO_2 (832 mg, 7.50 mmol), pyridine (2.50 mL), MS4A (300 mg), MeOH (3.60 mL), $SOCl_2$ (1.89 mL), 60% $HClO_4$ aq. (1.30 mL) and MeCN (13.7 mL), methyl 2-(3-methoxyphenyl)-2-oxoacetate **70an** (84.2 mg, 9%) was obtained after purification by flash column chromatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [81)]

Methyl 2-(3-cyanophenyl)-2-oxoacetate (70ao) [Table 5, entry 6]. Following to the general procedure using 3-cyanoacetophenone **70ao** (728 mg, 5.00 mmol), SeO_2 (832 mg, 7.50 mmol), pyridine (2.50 mL), MS4A (300 mg), MeOH (3.60 mL), $SOCl_2$ (1.89 mL), 60% $HClO_4$ aq. (1.30 mL) and MeCN (13.7 mL), methyl 2-(3-cyanophenyl)-2-oxoacetate **70ao** (198 mg, 21%) was obtained as a colorless oil after purification by flash column chromatography (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.70-7.66 (m, 1H), 4.02 (d, *J* = 1.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 183.3, 162.5, 137.5, 133.9, 133.8, 133.4, 129.9, 117.4, 113.6, 53.3; HRMS (ESI) *m/z* calcd for $C_{10}H_7O_3NNa$ $[M+Na]^+$ 212.0318, found 212.0321.

Methyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2-oxoacetate (70ap) [Table 5, entry 7]. Following to the general procedure using 3,4-methylenedioxyacetophenone **71ap** (1.64 g, 10.0 mmol), SeO_2 (1.66 g, 15.0 mmol), pyridine (5.00 mL), MS4A (60 mg), MeOH (7.50 mL), $SOCl_2$ (3.75 mL), 60% $HClO_4$ aq. (2.70 mL) and MeCN (27.3 mL), methyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2-oxoacetate **70ap** (1.08 g, 52%) was obtained after purification by flash column chromatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [82)]

Methyl 2-(naphthalen-1-yl)-2-oxoacetate (70as) [Table 5, entry 8]. Following to the general procedure using 1-acetonaphthone **71as** (681 mg, 4.00 mmol), SeO_2 (666 mg, 6.00 mmol), pyridine

(2.00 mL), MS4A (50 mg), MeOH (3.00 mL), $SOCl_2$ (1.50 mL), 60% $HClO_4$ aq. (1.20 mL) and MeCN (12.1 mL), methyl 2-(naphthalen-1-yl)-2-oxoacetate **70as** (594 mg, 69%) was obtained after purification by flash column chromatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [79)]

Methyl 2-oxo-2-(thiophen-2-yl)acetate (70aq) [Scheme 41]. To a solution of thiopheneglyoxylic acid **72** (625 mg, 4.00 mmol) in THF (20 mL) were added DBU (657 μL, 4.40 mmol) and MeI (1.20 mL, 20 mmol). The mixture was stirred at room temperature overnight, and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O three times and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Methyl 2-oxo-2-(thiophen-2-yl)acetate **70aq** (664 mg, 97%) was obtained after purification by flash column chlomatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [80)]

Ethyl 2-(benzofuran-3-yl)acetate (74) [Scheme 42]. To a solution of coumaranone **73** (671 mg, 5.00 mmol) in toluene (50 mL) was added ethyl triphenylphosphoranylidene acetate (2.61 g, 7.50 mmol) and stirred at reflux for 17 h. Then, the mixture was evaporated. Ethyl 2-(benzofuran-3-yl)acetate **74** (888 mg, 87%) was obtained after purification by flash column chromatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [48)]

Ethyl 2-(benzofuran-3-yl)-2-oxoacetate (70ar) [Scheme 42] To a solution of ethyl 2-(benzofuran-3-yl)acetate **74** (888 mg, 4.35 mmol) in 1,4-dioxane (6.00 mL) was added SeO_2 (965 mg, 8.70 mmol) and stirred at reflux for 4 h. Then, the resulting mixture was filtered through Celite® and the solution was evaporated. Ethyl 2-(benzofuran-3-yl)-2-oxoacetate **70ar** (682 mg, 72%) was obtained after purification by flash column chromatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [49)]

4,4,5,5-Tetramethyl-2-(2-phenylcyclopropyl)-1,3,2-dioxaborolane (76) [Scheme 43]. Et_2Zn (1M in hexane, 8.69 mL, 8.69 mmol) was added to CH_2Cl_2 (6.7 mL) at 0 °C. To the solution was added a solution of TFA (0.67 mL) in CH_2Cl_2 (6.7 mL) slowly. Then, the mixture was stirred at 0 °C for 30 min. Next, a solution of diiodomethane (700 μL, 8.69 mmol) in CH_2Cl_2 (6.7 mL) was added and the resulting reaction mixture was stirred for an additional 20 min at 0 °C. To the resulting solution was added *trans*-2-phenylvinylboronic acid pinacol ester **75** in CH_2Cl_2 (6.7 mL), and the mixture was allowed to warm to room temperature and stirred for 12 h. Then, the mixture was quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$ three times. The collected organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to afford crude cyclopropylboronate **76**. The spectral data were identical with those reported in the literature. [83)]

(2-Phenylcyclopropyl)boronic acid (77) [Scheme 43]. To a solution of the crude cyclopropylboronate **76** in THF/H_2O (4:1, 25 mL) was added $NaIO_4$ (1.28 g, 6.00 mmol) and stirred at room temperature for 15 min. Then, 1.0 M HCl aq. (5.1 mL) was added to the mixture and stirred for 14 h. The reaction mixture was diluted with water and extracted with EtOAc three times. The collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated to afford crude cyclopropylboronic acid **77**. The spectral data were identical with those reported in the literature. [50] The residue was dissolved in DMF (5.0 mL).

Di-*tert*-butyl 1-(2-phenylcyclopropyl)hydrazine-1,2-dicarboxylate (78) [Scheme 43]. To the crude cyclopropylboronic acid **77** (736 mg) were added di-*tert*-butyl azodicarboxylate (523 mg, 2.27 mmol) and $Cu(OAc)_2$ (41.0 mg, 0.23 mmol). The mixture was stirred at 80 °C for 15 h, and then cooled to 0 °C and diluted with water and Et_2O. The organic layer was collected and washed with water and brine. The resulting solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc) to afford di-*tert*-butyl 1-(2-phenylcyclopropyl)hydrazine-1,2-dicarboxylate **78** as a yellow oil (357 mg, 24% from **75**); ^{1}H-NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.26-7.24 (m, 2H), 7.18-7.12 (m, 3H), 6.43 (s, 0.7H), 6.16 (s, 0.2H), 3.13 (s, 0.6H), 3.05 (s, 0.08H), 2.28 (s, 1H), 1.46 (d, J = 16.0 Hz, 18H), 1.37 (s, 0.3H), 1.19 (s, 0.9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.7, 140.6, 128.2, 126.5, 125.9, 81.5, 81.2, 41.0, 28.2, 28.2, 16.3; Two carbon peak could not be detected probably due to overlapping; HRMS (ESI) *m/z* calcd for $C_{19}H_{28}O_4N_2Na$ $[M+Na]^+$ 371.1941, found 371.1943.

***N*-(2-Phenyl)cyclopropylhydrazine tosylate (79) [Scheme 43].** To a solution of di-*tert*-butyl 1-(2-phenylcyclopropyl)hydrazine-1,2-dicarboxylate **78** (5.75 g, 21.0 mmol) in MeCN (105 mL) was added *p*-toluenesulfonic acid (16.0 g, 84.0 mmol). The mixture was stirred at 60 °C for 1 h, and then cooled to room temperature, filtered with KIRIYAMA funnel to afford *N*-(2-phenyl)cyclopropyl hydrazinetosylate **79** (206 mg, 64%) as a white solid; Mp: 148 °C (decomp.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.51-8.66 (m, 2H), 7.49-7.47 (m, 2H), 7.27-7.23 (m, 2H), 7.17-7.08 (m, 5H), 2.67 (s, 1H), 2.28 (s, 3H), 2.11 (s, 1H), 1.17-1.09 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 145.5, 140.5, 137.8, 128.2, 128.2, 126.1, 125.8, 125.5, 40.4, 23.5, 20.8, 15.5; HRMS (ESI) *m/z* calcd for $C_9H_{13}N_2$ $[M+H]^+$ 149.1073, found 149.1074.

Ethyl (*Z*)-2-phenyl-2-(2-(2-phenylcyclopropyl)hydrazineylidene)acetate (14at) [Scheme 43]. To a solution of ethyl benzoylformate **70ac** (114 mg, 0.640 mmol) in MeOH (6.4 mL), were added cyclopropylhydrazine **79** (315 mg, 0.983 mmol) and pyridine (103 μL, 1.28 mmol). The mixture was stirred at room temperature for 13 h, and then evaporated. The crude product was purified by flash column chlomatography (hexane/EtOAc) to afford cyclopropylhydrazone **14at** (94 mg, 48%) as a

colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 7.56-7.53 (m, 2H), 7.35-7.24 (m, 5H), 7.20-7.16 (m, 1H), 7.12-7.09 (m, 2H), 4.29 (q, *J* = 6.8 Hz, 2H), 3.25-3.21 (m, 1H), 2.32-2.27 (m, 1H), 1.60-1.55 (m, 1H), 1.32 (t, *J* = 6.8 Hz, 3H), 1.29-1.26 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6, 140.8, 137.0, 128.4, 128.3, 127.8, 127.0, 126.5, 126.0, 125.9, 60.5, 41.8, 24.7, 15.4, 14.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}O_2N_2$ $[M+H]^+$ 309.1598, found 309.1598.

Methyl (*E*)-2-(2-cyclopropylhydrazineylidene)acetate (14au) [Scheme 44]. To a solution of commercially available methyl 2-hydroxy-2-methoxy acetate **84** (100 mg, 0.831 mmol) in MeOH (3.00 mL) were added cyclopropylhydrazine **67** (346 mg, 0.831 mmol) and AcONa (136 mg, 1.66 mmol). The mixture was stirred at room temperature for 3 h. The mixture was evaporated and extracted with $CHCl_3$ three times. Then, the mixture was dried over $MgSO_4$, filtered and evaporated. Methyl (*E*)-2-(2-cyclopropylhydrazineylidene)acetate **14au** (84.2 mg, 65%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.75 (s, 1H), 3.82 (s, 3H), 2.49-2.46 (m, 1H), 0.87-0.82 (m, 2H), 0.65-0.61 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.3, 122.5, 51.8, 26.5, 6.4; HRMS (ESI) *m/z* calcd for $C_6H_{11}O_2N_2$ $[M+H]^+$ 143.0815, found 143.0815.

General procedure for preparation of cyclopropylhydrazones [Table 6]. To a solution of α-keto esters in MeOH were added cyclopropylhydrazine **67** (1.0 eq.) and pyridine (2.0 eq.). The mixture was stirred at room temperature for several hours and then evaporated. The crude product was purified by column chromatography to afford cyclopropylhydrazones **14av-az, 14ba-bc, 14ca**.

Ethyl (*E*)-2-(2-cyclopropylhydrazinylidene)propanoate (14av) [Table 6, entry 1]. Following to the general procedure, commercially available ethyl pyruvate **81av** (116 mg, 1.00 mmol), cyclopropylhydrazine **67** (416 mg, 1.00 mmol) and pyridine (161 µL, 2.00 mmol) were used and the reaction time was 9 h. **14av** (150 mg, 88%) was obtained as a white solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 54-58 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.31 (q, *J* = 5.2 Hz, 2H), 3.09-2.87 (m, 1H), 1.91 (s, 3H), 1.36 (t, *J* = 5.2 Hz, 3H), 0.82-0.68 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 132.6, 61.1, 31.3, 14.5, 10.2, 6.8; HRMS (ESI) *m/z* calcd for $C_8H_{15}O_2N_2$ $[M+H]^+$ 171.1128, found 171.1127.

Methyl (*E*)-2-(2-cyclopropylhydrazinylidene)-3-phenylpropanoate (14aw) [Table 6, entry 2]. Following to the general procedure, methyl-2-oxo-3-phenylpropanoate **81aw** (125 mg, 0.701 mmol), cyclopropylhydrazine **67** (291 mg, 0.699 mmol) and pyridine (113 µL, 1.40 mmol) were used and the reaction time was 4 h. **14aw** (65.7 mg, 40%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.2 Hz, 2H), 7.24-7.20 (m, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 6.20 (s, 1H), 3.85 (s, 3H), 3.84 (s, 2H), 2.89-2.83 (m, 1H), 0.69-

0.64 (m, 2H), 0.55-0.51 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.7, 135.0, 133.2, 128.9, 127.8, 126.8, 52.4, 31.3, 30.8, 6.6; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_2N_2$ $[M+H]^+$ 233.1285, found 233.1285.

Ethyl (*Z*)-2-cyclopentyl-2-(2-cyclopropylhydrazineylidene)acetate (14ax) [Table 6, entry 3]. Following to the general procedure, ethyl-2-cyclopentyl-2-oxo acetate **81ax** (170 mg, 1.00 mmol), cyclopropylhydrazine **67** (416 mg, 1.00 mmol) and pyridine (161 µL, 2.00 mmol) were used and the reaction time was 7 h. **14ax** (110 mg, 49%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.99-2.91 (m, 1H), 2.89-2.84 (m, 1H), 1.82-1.77 (m, 2H), 1.69-1.54 (m, 6H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.68-0.66 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.7, 129.5, 59.8, 42.6, 31.3, 31.0, 25.3, 14.2, 5.9; HRMS (ESI) *m/z* calcd for $C_{12}H_{21}O_2N_2$ $[M+H]^+$ 225.1598, found 225.1599.

Methyl (*Z*)-2-(2-cyclopropylhydrazinylidene)-2-*tert*-butylacetate (14ay) [Table 6, entry 4]. Following to the general procedure, methyl 2-oxo-2-*tert*-butyl acetate **81ay** (132 mg, 0.915 mmol), cyclopropylhydrazine **67** (383 mg, 0.915 mmol) and pyridine (149 µL, 1.84 mmol) were used and the reaction time was 4 h. **14ay** (97.3 mg, 53%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 3.76 (s, 3H), 2.87-2.82 (m, 1H), 1.18 (s, 9H), 0.69-0.64 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.3, 133.9, 50.6, 36.3, 31.4, 29.0, 5.7; HRMS (ESI) *m/z* calcd for $C_{10}H_{19}O_2N_2$ $[M+H]^+$ 199.1441, found 199.1442.

(*E*)-3-(2-Cyclopropylhydrazineylidene)-4,4-dimethyldihydrofuran-2(3*H*)-one (14az) [Table 6, entry 5]. Following to the general procedure, commercially available 2-keto pantoyl lactone **81az** (100 mg, 0.780 mmol), cyclopropylhydrazine **67** (325 mg, 0.780 mmol) and pyridine (126 µL, 1.56 mmol) were used and the reaction time was 2 h. Hydrazone **14az** (95.0 mg, 67%) was obtained as a white solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 96 °C (decomp.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 4.01 (s, 2H), 3.00-2.95 (m, 1H), 1.40 (s, 6H), 0.78-0.73 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.3, 133.7, 77.6, 37.2, 31.9, 22.6, 6.8; HRMS (ESI) *m/z* calcd for $C_9H_{15}O_2N_2$ $[M+H]^+$ 183.1128, found 183.1128.

2-(2-Cyclopropylhydrazineylidene)-1,2-diphenylethan-1-one (14ba) [Table 6, entry 6]. Following to the general procedure, commercially available benzil **81ba** (147 mg, 0.699 mmol), cyclopropylhydrazine **67** (291 mg, 0.699 mmol) and pyridine (113 µL, 1.40 mmol) were used and the reaction time was 2 h. **14ba** (dr = 3.2 : 1, 62.7 mg, 24%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.01-7.97 (m, 6H), 7.53-7.49 (m, 12H), 7.46-7.38 (m, 10H), 7.28-7.25 (m, 10H), 7.24-7.18 (m, 2H), 6.67 (s, 3H), 3.11-3.06 (m, 1H), 2.89-2.84 (m, 3H), 0.87-0.77 (m, 4H), 0.71-0.67 (m, 12H); ^{13}C-NMR (100 MHz,

$CDCl_3$) δ 190.7, 141.3, 138.5, 131.9, 131.2, 130.6, 130.5, 129.9, 129.3, 129.2, 129.0, 128.1, 127.9, 127.6, 127.0, 32.3, 31.5, 6.4, 6.3; Five carbon peaks of diastereomers could not be detected probably due to overlapping; HRMS (ESI) (*E/Z* mixture) *m/z* calcd for $C_{17}H_{17}ON_2$ $[M+H]^+$ 265.1335, found 265.1336.

(*E*)-2-(2-Cyclopropylhydrazineylidene)-1-phenylpropan-1-one (14bb) [Table 6, entry 7]. Following to the general procedure, commercially available 1-phenyl-1,2-propanedione **81bb** (104 mg, 0.700 mmol), cyclopropylhydrazine **67** (291 mg, 0.700 mmol) and pyridine (161 µL, 1.40 mmol) were used and the reaction time was 10 h. **14bb** (97.9 mg, 69%) was obtained as a yellow solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 60 °C (decomp.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 6.8 Hz, 2H), 7.49-7.46 (m, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 6.21 (s, 1H), 2.95-2.90 (m, 1H), 1.98 (s, 3H), 0.74-0.71 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.4, 139.9, 137.9, 131.1, 130.6, 127.5, 31.5, 8.8, 6.5; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}ON_2$ $[M+H]^+$ 203.1179, found 203.1180.

(1*R*,4*S*)-3-(2-Cyclopropylhydrazineylidene)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (14bc) [Table 6, entry 8]. Following to the general procedure, commercially available camphorquinone **81bc** (166 mg, 1.00 mmol), cyclopropylhydrazine **67** (416 mg, 1.00 mmol) and pyridine (161 µL, 2.00 mmol) were used and the reaction time was 9 h. **14bc** (*E/Z* = 100:7, 40.6 mg, 18%) was obtained as a white solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 87-93 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 1H), 2.90-2.84 (m, 1H), 2.66 (d, *J* = 4.4 Hz, 1H), 2.48 (d, *J* = 4.4 Hz, 0.07H), 1.97-1.89 (m, 1H), 1.75-1.68 (m, 1H), 1.54-1.47 (m, 1H), 1.42-1.34 (m, 1H), 0.99 (s, 3H), 0.94 (s, 3H), 0.89-0.91 (s, 0.19H), 0.83 (s, 3H), 0.69-0.64 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.1, 203.5, 146.5, 141.7, 59.3, 57.8, 50.7, 47.7, 45.7, 45.3, 31.4, 31.1, 30.9, 30.1, 26.0, 23.6, 20.4, 18.5, 18.1, 9.1, 8.7, 6.9, 6.7, 6.3, 6.2; One carbon peak could not be detected probably due to overlapping; HRMS (ESI) *m/z* calcd for $C_{13}H_{21}ON_2$ $[M+H]^+$ 221.1648, found 221.1648.

(*E*)-2-(2-Cyclopropylhydrazineylidene)-2-(4-nitrophenyl)-1-(piperidin-1-yl)ethan-1-one (14ca) [Table 6, entry 9]. To a solution of 1-(4-nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione **81ca** (127 mg, 0.569 mmol) in EtOH (5.70 mL), cyclopropylhydrazine **67** (237 mg, 0.569 mmol) and pyridine (92.0 µL, 1.14 mmol) were added. The mixture was stirred at room temperature for 12 h, then heated 70 °C and stirred overnight. The mixture was evaporated. Hydrazone **14ca** (61.4 mg, 34%) was obtained as a yellow solid after purification by Biotage Isolera® (hexane/EtOAc); Mp: 99 °C (decomp.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.2 Hz, 2H), 7.68 (d, *J* = 11.2 Hz, 2H), 6.53 (s, 1H), 3.73 (s, 2H), 3.18 (t, *J* = 5.6 Hz, 2H), 2.95-2.89 (m, 1H), 1.66 (s, 4H), 1.42 (s, 2H), 0.76-0.67 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.1, 146.9, 140.7, 136.9, 125.1, 124.0, 47.2, 42.2, 31.5, 26.8, 25.7, 24.3, 6.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}O_3N_4$ $[M+H]^+$ 317.1608, found 317.1607.

Methyl-2-oxo-3-phenylpropanoate (81aw) [Table 7, entry 1]. To a solution of phenylpyruvic acid **82aw** (657 mg, 4.00 mmol) in THF (20 mL) were added DBU (657 µL, 4.40 mmol) and MeI (1.20 mL, 20 mmol). The mixture was stirred at room temperature overnight, and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O three times and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Methyl-2-oxo-3-phenylpropanoate **81aw** (342 mg, 48%) was obtained as a yellow oil after purification by flash column chlomatography (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 6.6 Hz, 2H), 7.29-7.25 (m, 1H), 6.53 (s, 1H), 6.45 (s, 1H), 3.92 (d, *J* = 1.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.7, 139.0, 134.0, 129.9, 128.5, 128.0, 111.2, 53.3; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}O_3$ $[M+H]^+$ 179.0703, found 179.0703.

Methyl 2-oxo-2-*tert*-butylacetate (81ay) [Table 7, entry 2]. To a solution of 3,3-dimethyl-2-oxobutanoic acid **82ay** (1.30 g, 10.0 mmol) in THF (50 mL) were added DBU (1.64 mL, 11.0 mmol) and MeI (3.11 mL, 50.0 mmol). The mixture was stirred at room temperature overnight, and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O three times and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Methyl 2-oxo-2-*tert*-butylacetate **81ay** (1.54 g, quant.) was obtained after purification by flash column chlomatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [84)]

Ethyl-2-cyclopentyl-2-oxoacetate (81ax) [Scheme 45]. To a solution of diethyloxalate (466 µL, 3.00 mmol) in THF (5.00 mL), was added cyclopropylmagnesium bromide **83** solution in THF (3.00 mL, 3.00 mmol). The mixture was stirred at −78 °C. Then, the mixture warmed up to −10 °C and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O three times and the combined organic extracts were dried over Na_2SO_4, filtered and evaporated. Ethyl-2-cyclopentyl-2-oxo acetate **81ax** (245 mg, 48%) was obtained as a colorless oil after purification by flash column chlomatography (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.36-4.30 (m, 2H), 3.54-3.46 (m, 1H), 1.90-1.81 (m, 4H), 1.65-1.64 (m, 4H), 1.39-1.35 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.7, 161.9, 62.2, 47.4, 28.3, 26.0, 14.0; HRMS (ESI) *m/z* calcd for $C_9H_{14}O_3Na$ $[M+Na]^+$ 193.0835, found 193.0837.

1-(4-Nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (81ca) [Scheme 46]. To a solution of 4-nitroacetophenone **84** (330 mg, 2.00 mmol) in toluene (5.0 mL) were added piperidine (218 µL, 2.20 mmol) and CuI (38.0 mg, 0.200 mmol). The mixture was stirred at 65 °C under O_2 for 5 h. After H_2O was added into the resulting mixture, the aqueous phase was extracted with EtOAc three times and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. 1-(4-nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione **81ca** (286 mg, 55%) was obtained after

purification by flash column chromatography (hexane/EtOAc); The spectral data were identical with those reported in the literature. [51)]

General Procedure for ring opening reaction of *N*-cyclopropylhydrazones [Scheme 47]. *N*-cyclopropylhydrazone (1.0 eq.), $Pd(OAc)_2$ (0.10 eq.) and MS4A were dissolved in *t*-AmylOH (*c* = 0.10 M). The mixture was stirred at reflux for 5-28 h. Then, the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by PTLC to afford pyrazole**.**

Methyl 2-phenyl-2-(1*H*-pyrazole-1yl)acetate (16ab) [Scheme 47]. Following to the general procedure, hydrazone **14ab** (32.2 mg, 0.148 mmol), $Pd(OAc)_2$ (3.3 mg, 0.015 mmol) and MS4A (100 mg) were used and the reaction time was 23 h. Pyrazole **16ab** (20.2 mg, 64%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.6 Hz, 1H), 7.42-7.37 (m, 6H), 6.26 (t, *J* = 2.0 Hz, 1H), 6.23 (s, 1H), 3.80 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.4, 139.9, 133.8, 129.4, 129.2, 129.2, 128.4, 106.1, 67.8, 52.9; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}O_2N_2$ $[M+H]^+$ 217.0972, found 217.0973.

Ethyl 2-phenyl-2-(1*H*-pyrazole-1yl)acetate (16ac) [Scheme 47]. Following to the general procedure, **14ac** (22.8 mg, 0.0982 mmol), $Pd(OAc)_2$ (2.2 mg, 0.0098 mmol) and MS4A (86.0 mg) were used and the reaction time was 7 h. Pyrazole **16ac** (12.5 mg, 55%) was obtained as a yellow solid after purification by PTLC (hexane/EtOAc = 3 : 1);
Following to the general procedure, **14ac'** (21.0 mg, 0.0904 mmol), $Pd(OAc)_2$ (2.0 mg, 0.0090 mmol) and MS4A (79.0 mg) were used and the reaction time was 6 h. **16ac** (11.1 mg, 54%) was obtained as a yellow solid after purification by PTLC (hexane/EtOAc = 3 : 1); Mp: 43-47 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.0 Hz, 1H), 7.40-7.38 (m, 6H), 6.26 (t, *J* = 2.4 Hz, 1H), 6.21 (s, 1H), 4.33-4.20 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.0, 139.8, 134.0, 129.3, 129.2, 129.1, 128.4, 106.0, 67.9, 62.1, 14.0; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2N_2$ $[M+H]^+$ 231.1128, found 231.1130.

Ethyl 2-(4-methoxyphenyl)-2-(1*H*-pyrazole-1yl)acetate (16ad) [Scheme 47]. Following to the general procedure, hydrazone **14ad** (34.2 mg, 0.130 mmol), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol) and MS4A (100 mg) were used and the reaction time was 5 h. Pyrazole **16ad** (15.8 mg, 47%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.2 Hz, 1H), 7.36-7.33 (m, 3H), 6.95-6.92 (m, 2H), 6.25 (t, *J* = 1.6 Hz, 1H), 6.15 (s, 1H), 4.33-4.20 (m, 2H), 3.82 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.2, 160.3, 139.8, 129.9, 129.1, 125.8, 114.5, 105.9, 67.3, 62.0, 55.3, 14.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}O_3N_2$ $[M+H]^+$ 261.1234, found 261.1232.

Ethyl 2-(4-methylphenyl)-2-(1*H*-pyrazole-1yl)acetate (16ae) [Scheme 47]. Following to the general procedure, hydrazone **14ae** (35.4 mg, 0.140 mmol), $Pd(OAc)_2$ (3.2 mg, 0.014 mmol) and MS4A (100 mg) were used and the reaction time was 24 h. Pyrazole **16ae** (22.4 mg, 64%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.31-7.28 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.25 (t, *J* = 1.6 Hz, 1H), 6.18 (s, 1H), 4.34-4.20 (m, 2H), 2.37 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.1, 139.8, 139.3, 130.8, 129.8, 129.1, 128.4, 105.9, 67.6, 62.0, 21.2, 14.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}O_2N_2$ $[M+H]^+$ 245.1285, found 245.1284.

Ethyl 2-(4-fluorophenyl)-2-(1*H*-pyrazole-1yl)acetate (16af) [Scheme 47]. Following to the general procedure, hydrazone **14af** (32.0 mg, 0.128 mmol), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol) and MS4A (100 mg) were used and the reaction time was 6 h. Pyrazole **16af** (18.5 mg, 58%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 2.0 Hz, 1H), 7.42-7.37 (m, 3H), 7.13-7.08 (m, 2H), 6.29 (t, *J* = 2.4 Hz, 1H), 6.19 (s, 1H), 4.34-4.21 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.8, 163.1 (d, $J_{C\text{-}F}$ = 249.5 Hz), 140.0, 130.3 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.67 Hz), 129.9 (d, $J_{C\text{-}C\text{-}C\text{-}C\text{-}F}$ = 2.89 Hz), 129.1, 116.2 (d, $J_{C\text{-}C\text{-}F}$ = 22.2 Hz), 106.2, 67.1, 62.2, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_2N_2F$ $[M+H]^+$ 249.1034, found 249.1035.

Ethyl 2-(4-chlorophenyl)-2-(1*H*-pyrazole-1yl)acetate (16ag) [Scheme 47]. Following to the general procedure, hydrazone **14ag** (37.9 mg, 0.142 mmol), $Pd(OAc)_2$ (3.2 mg, 0.014 mmol) and MS4A (100 mg) were used and the reaction time was 12 h. Pyrazole **16ag** (26.9 mg, 72%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 2.0 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.40-7.38 (m, 2H), 7.34-7.32 (m, 2H), 6.29 (t, *J* = 2.4 Hz, 1H), 6.17 (s, 1H), 4.34-4.21 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.5, 140.0, 135.4, 132.6, 129.7, 129.3, 129.2, 106.3, 67.1, 62.3, 14.0; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_2N_2{}^{35}Cl$ $[M+H]^+$ 265.0738, found 265.0738, $C_{13}H_{14}O_2N_2{}^{37}Cl$ $[M+H]^+$ 267.0709, found 267.0708.

Ethyl 2-(4-bromophenyl)-2-(1*H*-pyrazole-1yl)acetate (16ah) [Scheme 47]. Following to the general procedure, hydrazone **14ah** (40.6 mg, 0.130 mmol), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol) and MS4A (100 mg) were used and the reaction time was 24 h. Pyrazole **16ah** (3.5 mg, 9%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56-7.52 (m, 3H), 7.43 (d, *J* = 2.8 Hz, 1H), 7.26-7.24 (m, 2H), 6.28 (t, *J* = 2.0 Hz, 1H), 6.14 (s, 1H), 4.33-4.20 (m, 2H), 1.26 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.5, 140.0, 133.1, 132.3, 129.9, 129.2, 123.6, 106.3, 67.2, 62.3, 14.0; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_2N_2{}^{79}Br$ $[M+H]^+$

309.0233, found 309.0232, $C_{13}H_{14}O_2N_2{}^{81}Br$ $[M+H]^+$ 311.0213, found 311.0211.

Methyl 2-(4-methoxycarbonylphenyl)-2-(1*H*-pyrazole-1yl)acetate (16ai) [Scheme 47]. Following to the general procedure, hydrazone **14ai** (26.6 mg, 0.0962 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol) and MS4A (82.0 mg) were used and the reaction time was 24 h. Pyrazole **16ai** (15.9 mg, 60%) was obtained as a colorless oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09-8.07 (m, 2H), 7.59 (s, 1H), 7.47-7.44 (m, 3H), 6.31 (d, *J* = 0.8 Hz, 1H), 6.29 (s, 1H), 3.93 (s, 3H), 3.83 (t, *J* = 0.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.8, 166.3, 140.1, 138.7, 131.0, 130.3, 129.4, 128.3, 106.5, 67.4, 53.1, 52.3; HRMS (ESI) *m/z* calcd for $C_{14}H_{15}O_4N_2$ $[M+H]^+$ 275.1026, found 275.1025.

Ethyl 2-(4-cyanophenyl)-2-(1*H*-pyrazole-1yl)acetate (16aj) [Scheme 47]. Following to the general procedure, hydrazone **14aj** (42.6 mg, 0.165 mmol), $Pd(OAc)_2$ (3.7 mg, 0.017 mmol) and MS4A (100 mg) were used and the reaction time was 24 h. Pyrazole **16aj** (15.6 mg, 37%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 6.35 (t, *J* = 2.4 Hz, 1H), 6.25 (s, 1H), 4.37-4.25 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.7, 140.3, 139.5, 132.7, 129.5, 128.8, 118.1, 113.1, 106.8, 67.2, 62.6, 14.0; HRMS (ESI) *m/z* calcd for $C_{14}H_{14}O_2N_3$ $[M+H]^+$ 256.1081, found 256.1081.

Methyl 2-(2-methylphenyl)-2-(1*H*-pyrazole-1yl)acetate (16ak) [Scheme 47]. Following to the general procedure, hydrazone **14ak** (20.2 mg, 0.0873 mmol), $Pd(OAc)_2$ (2.0 mg, 0.0089 mmol) and MS4A (74.0 mg) were used and the reaction time was 18 h. Pyrazole **16ak** (11.7 mg, 58%) was obtained as a white solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 80-82 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J* = 1.2 Hz, 1H), 7.34-7.23 (m, 4H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.43 (s, 1H), 6.23 (t, *J* = 2.4 Hz, 1H), 3.80 (s, 3H), 2.24 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.1, 139.9, 138.0, 132.0, 131.3, 129.5, 129.1, 127.6, 126.6, 106.0, 65.0, 52.8, 19.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2N_2$ $[M+H]^+$ 231.1128, found 231.1126.

Methyl 2-(2-methoxyphenyl)-2-(1*H*-pyrazole-1yl)acetate (16al) [Scheme 47]. Following to the general procedure, **14al** (16.7 mg, 0.0673 mmol), $Pd(OAc)_2$ (1.5 mg, 0.0067 mmol) and MS4A (60.0 mg) were used and the reaction time was 9 h. **16al** (10.0 mg, 60%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.6 Hz, 1H), 7.41-7.36 (m, 2H), 7.29-7.26 (m, 1H), 7.02-6.94 (m, 2H), 6.53 (s, 1H), 6.26 (t, *J* = 2.0 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.0, 157.0, 139.7, 130.7, 129.5, 129.2, 122.9, 121.0, 111.2, 105.8, 62.6, 55.7, 52.8; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_3N_2$ $[M+H]^+$ 247.1077, found 247.1075.

Methyl 2-(3-methylphenyl)-2-(1*H*-pyrazole-1yl)acetate (16am) [Scheme 47]. Following to the general procedure, hydrazone **14am** (26.8 mg, 0.115 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol) and MS4A (98.0 mg) were used and the reaction time was 9 h. Pyrazole **16am** (10.3 mg, 39%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.33-7.29 (m, 1H), 7.21 (t, *J* = 8.0 Hz, 3H), 6.27 (t, *J* = 2.4 Hz, 1H), 6.20 (s, 1H), 3.81 (s, 3H), 2.37 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.6, 139.9, 139.1, 133.5, 130.2, 129.2, 129.1, 129.1, 125.4, 106.0, 67.8, 52.9, 21.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2N_2$ $[M+H]^+$ 231.1128, found 231.1128.

Methyl 2-(3-methoxyphenyl)-2-(1*H*-pyrazole-1yl)acetate (16an) [Scheme 47]. Following to the general procedure, hydrazone **14an** (26.3 mg, 0.110 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol) and MS4A (95.0 mg) were used and the reaction time was 6 h. Pyrazole **16an** (16.1 mg, 62%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.2 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 6.99-6.92 (m, 3H), 6.28 (t, *J* = 2.0 Hz, 1H), 6.20 (s, 1H), 3.81 (s, 1H), 3.80 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.3, 160.1, 139.9, 135.1, 130.2, 129.3, 120.5, 114.8, 114.2, 106.1, 67.7, 55.3, 52.9; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_3N_2$ $[M+H]^+$ 247.1077, found 247.1076.

Methyl 2-(3-cyanophenyl)-2-(1*H*-pyrazole-1yl)acetate (16ao) [Scheme 47]. Following to the general procedure, hydrazone **14ao** (48.0 mg, 0.200 mmol), $Pd(OAc)_2$ (4.5 mg, 0.020 mmol) and MS4A (168 mg) were used and the reaction time was 24 h. Pyrazole **16ao** (32.1 mg, 68%) was obtained as a yellow solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 101-103 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70-7.51 (m, 6H), 6.35 (d, *J* = 2.0 Hz, 1H), 6.23 (s, 1H), 3.85 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2, 140.5, 136.1, 132.7, 132.4, 131.6, 129.9, 129.4, 118.0, 113.4, 106.9, 66.8, 53.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}O_2N_3$ $[M+H]^+$ 242.0924, found 242.0922.

Methyl 2-(3,4-methylenedioxyphenyl)-2-(1*H*-pyrazole-1yl)acetate (16ap) [Scheme 47]. *N*-cyclopropylhydrazone **14ap** (33.8 mg, 0.129 mmol), $Pd(OAc)_2$ (2.9 mg, 0.013 mmol) and MS4A (110 mg) were dissolved in *t*-AmylOH (1.29 mL). The mixture was stirred at reflux for 19 h. Then the mixture was transferred to sealed tube and stirred at 150 °C for 9 h. After the same work-up as general procedure, pyrazole **16ap** (11.0 mg, 33%) was obtained as a yellow solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 49- 52 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.6 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 6.90-6.88 (m, 2H), 6.84-6.82 (m, 1H), 6.28 (t, *J* = 2.4 Hz, 1H), 6.12 (s, 1H), 6.00 (s, 2H), 3.80 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.5, 148.5, 148.3, 140.0, 129.1, 127.2, 122.5, 108.8, 108.7, 106.0, 101.6, 67.4, 52.9; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}O_4N_2Na$ $[M+Na]^+$ 283.0689, found 283.0687.

Methyl 2-(1*H*-pyrazole-1yl)-2-(thiophen-2-yl)acetate (16aq) [Scheme 47]. Following to the general procedure, hydrazone **14aq** (25.5 mg, 0.114 mmol), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) and MS4A (97.0 mg) were used and the reaction time was 18 h. Pyrazole **16aq** (18.8 mg, 74%) was obtained as a yellow solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 41-45 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.6 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.40 (dd, *J* = 5.2, 0.8 Hz 1H), 7.19-7.18 (m, 1H), 7.04 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.44 (s, 1H), 6.30 (t, *J* = 2.0 Hz, 1H), 3.83 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.6, 140.1, 135.1, 129.0, 128.5, 127.7, 127.1, 106.3, 62.9, 53.2; HRMS (ESI) *m/z* calcd for $C_{10}H_{11}O_2N_2S$ $[M+H]^+$ 223.0536, found 223.0533.

Ethyl 2-(benzofuran-3-yl)-2-(1*H*-pyrazole-1yl)acetate (16ar) [Scheme 47]. Following to the general procedure, hydrazone **14ar** (26.1 mg, 0.0958 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol) and MS4A (86.0 mg) were used and the reaction time was 10 h. Pyrazole **16ar** (15.5 mg, 60%) was obtained as a yellow solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 49-52 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.54-7.51 (m, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.39-7.32 (m, 2H), 7.26-7.21 (m, 1H), 6.42 (d, *J* = 1.2 Hz, 1H), 6.27 (t, *J* = 2.0 Hz, 1H), 4.36-4.24 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2, 155.4, 144.3, 140.0, 129.2, 125.7, 125.3, 123.4, 120.0, 114.5, 111.8, 106.3, 62.4, 59.7, 14.0; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}O_3N_2$ $[M+H]^+$ 271.1077, found 271.1075.

Methyl 2-(naphthalen-1-yl)-2-(1*H*-pyrazole-1yl)acetate (16as) [Scheme 47]. Following to the general procedure, hydrazone **14as** (24.7 mg, 0.0921 mmol), $Pd(OAc)_2$ (2.1 mg, 0.0092 mmol) and MS4A (77.0 mg) were used and the reaction time was 10 h. Pyrazole **16as** (15.3 mg, 62%) was obtained as a yellow solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 81-86 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94-7.87 (m, 3H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.53-7.47 (m, 4H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.02 (s, 1H), 6.19 (t, *J* = 2.0 Hz, 1H), 3.85 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.1, 140.1, 134.0, 131.5, 130.5, 129.4, 128.9, 127.5, 126.4, 126.1, 125.1, 122.7, 106.1, 64.9, 52.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}O_2N_2$ $[M+H]^+$ 267.1128, found 267.1130.

Methyl 2-phenyl-2-(5-phenyl-1*H*-pyrazole-1yl)acetate (16at) [Scheme 47]. *N*-cyclopropylhydrazone **14at** (30.2 mg, 0.0980 mmol), $Pd(OAc)_2$ (2.2 mg, 0.0098 mmol) and MS4A (87.0 mg) were dissolved in *t*-AmylOH (980 μL). After the mixture was stirred at 140 °C in a sealed tube for 21 h, $Pd(OAc)_2$ (2.2 mg, 0.0098 mmol) was added and stirred for 4 h. Then, the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by PTLC (Hexane/EtOAc = 7 : 3) to afford pyrazole **16at** as a yellow oil (11.4 mg, 38%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.44 (t, *J* = 2.0 Hz, 3H), 7.35 (s, 7H), 6.33 (s, 1H), 6.02 (s, 1H), 4.22 (q, *J* = 7.6 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.6, 144.6, 139.8, 135.1,

130.4, 129.2, 128.9, 128.8, 128.7, 128.5, 106.4, 64.6, 62.0, 14.0; One carbon peak could not be detected probably due to overlapping; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}O_2N_2$ $[M+H]^+$ 307.1441, found 307.1439.

General procedure for ring opening reaction of *N*-cyclopropylhydrazones [Scheme 48]. *N*-cyclopropylhydrazone (1.0 eq.), $Pd(OAc)_2$ (0.10 eq.) and MS4A were dissolved in *t*-AmylOH (*c* = 0.10 M). The mixture was stirred at reflux for 5-32 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by PTLC to afford pyrazole**.**

Methyl 2-(1*H*-pyrazol-1-yl)acetate (16au) [Scheme 48]. Following to the general procedure, hydrazone **14au** (12.0 mg, 0.0844 mmol), $Pd(OAc)_2$ (1.9 mg, 0.0085 mmol) and MS4A (100 mg) were used and the reaction time was 32 h. Pyrazole **16au** (4.1 mg, 35%) was obtained as a brown oil after purification by PTLC (hexane/EtOAc = 1 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 6.34 (t, *J* = 2.0 Hz, 1H), 4.95 (s, 2H), 3.78 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.3, 140.2, 130.6, 106.6, 52.9, 52.7; HRMS (ESI) *m/z* calcd for $C_6H_9O_2N_2$ $[M+H]^+$ 141.0659, found 141.0658.

Ethyl 2-(1*H*-pyrazol-1-yl)propanoate (16av) [Scheme 48]. Following to the general procedure, hydrazone **14av** (20.0 mg, 0.117 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol) and MS4A (100 mg) were used and the reaction time was 8 h. Pyrazole **16av** (15.3 mg, 78%) was obtained as a brown oil after purification of silica gel short column (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 0.8 Hz, 2H), 6.32 (t, *J* = 0.8 Hz, 1H), 5.11 (q, *J* = 7.2 Hz, 1H), 4.23-4.17 (m, 2H), 1.81-1.79 (m, 3H), 1.27-1.23 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.6, 139.5, 128.1, 106.0, 61.7, 59.5, 17.5, 14.0; HRMS (ESI) *m/z* calcd for $C_8H_{13}O_2N_2$ $[M+H]^+$ 169.0972, found 169.0970.

Methyl 3-phenyl-2-(1*H*-pyrazol-1-yl)propanoate (16aw) [Scheme 48]. Following to the general procedure, hydrazone **14aw** (23.7 mg, 0.102 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol) and MS4A (83.0 mg) were used and the reaction time was 5 h. Pyrazole **16aw** (10.3 mg, 44%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.25-7.19 (m, 3H), 7.02 (dd, *J* = 7.6, 2.0 Hz, 2H), 6.23 (t, *J* = 2.4 Hz, 1H), 5.15 (t, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 3.49 (d, *J* = 7.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.8, 139.8, 136.1, 129.5, 128.9, 128.5, 127.0, 105.9, 65.6, 52.7, 38.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2N_2$ $[M+H]^+$ 231.1126, found 231.1128.

Ethyl 2-cyclopentyl-2-(1*H*-pyrazol-1-yl)acetate (16ax) [Scheme 48]. Following to the general procedure, hydrazone **14ax** (24.3 mg, 0.109 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol) and MS4A (93.0

mg) were used and the reaction time was 12 h. Pyrazole **16ax** (16.5 mg, 68%) was obtained as a colorless oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 1.2 Hz, 1H), 6.31 (t, *J* = 1.6 Hz, 1H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.26-4.13 (m, 2H), 2.77-2.67 (m, 1H), 1.89-1.81 (m, 1H), 1.75-1.51 (m, 6H), 1.45-1.35 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.0, 139.0, 128.3, 106.1, 69.0, 61.5, 42.7, 29.6, 29.6, 25.3, 24.8, 14.1; HRMS (ESI) *m/z* calcd for $C_{12}H_{19}O_2N_2$ $[M+H]^+$ 223.1441, found 223.1442.

Methyl 3,3-dimethyl-2-(1*H*-pyrazol-1-yl)butanoate (16ay) [Scheme 48]. *N*-cyclopropylhydrazone **14ay** (21.0 mg, 0.106 mmol), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol) and MS4A (91.0 mg) were dissolved in *t*-AmylOH (1.06 mL). After the mixture was stirred at 130 °C in a sealed tube for 13 h, $Pd(OAc)_2$ (2.4 mg, 0.011 mmol) was added and stirred for 11 h. After the same work-up as general procedure, pyrazole **16ay** (3.8 mg, 18%) was obtained as a colorless oil after purification by PTLC (Hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 6.30 (t, *J* = 2.0 Hz, 1H), 4.94 (s, 1H), 3.75 (s, 3H), 1.02 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.6, 138.4, 129.7, 105.8, 73.0, 52.0, 36.0, 26.9; HRMS (ESI) *m/z* calcd for $C_{10}H_{17}O_2N_2$ $[M+H]^+$ 197.1284, found 197.1285.

4,4-Dimethyl-3-(1*H*-pyrazol-1-yl)dihydrofuran-2(3*H*)-one (16az) [Scheme 48]. Following to the general procedure, hydrazone **14az** (32.1 mg, 0.175 mmol), $Pd(OAc)_2$ (3.9 mg, 0.017 mmol) and MS4A (100 mg) were used and the reaction time was 13 h. Pyrazole **16az** (27.0 mg, 86%) was obtained as a white solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 78-81 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.2 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 6.33 (t, *J* = 2.0 Hz, 1H), 4.90 (s, 1H), 4.25 (d, *J* = 8.8 Hz, 1H), 4.12 (d, *J* = 9.2 Hz, 1H), 1.35 (s, 3H), 0.80 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.9, 140.6, 130.2, 106.0, 69.0, 41.9, 24.3, 20.0; HRMS (ESI) *m/z* calcd for $C_9H_{13}O_2N_2$ $[M+H]^+$ 181.0972, found 181.0970.

1,2-Diphenyl-2-(1*H*-pyrazol-1-yl)ethan-1-one (16ba) [Scheme 48]. Following to the general procedure, hydrazone **14ba** (17.9 mg, 0.0680 mmol), $Pd(OAc)_2$ (1.5 mg, 0.0067 mmol) and MS4A (60.0 mg) were used and the reaction time was 17 h. Pyrazole **16ba** (6.8 mg, 38%) was obtained as a yellow solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 95-98 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.59-7.52 (m, 2H), 7.44-7.38 (m, 8H), 7.22 (s, 1H), 6.30 (t, *J* = 2.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.6, 139.6, 134.7, 134.1, 133.8, 129.8, 129.5, 129.4, 129.1, 128.9, 128.8, 106.0, 70.1; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}ON_2$ $[M+H]^+$ 263.1179, found 263.1178.

1-Phenyl-2-(1*H*-pyrazol-1-yl)propan-1-one (16bb) [Scheme 48]. Following to the general procedure, hydrazone **14bb** (26.9 mg, 0.134 mmol), $Pd(OAc)_2$ (3.0 mg, 0.013 mmol) and MS4A (118

mg) were used and the reaction time was 7 h. Pyrazole **16bb** (11.8 mg, 44%) was obtained as a brown solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 79 °C (decomp); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.58-7.52 (m, 3H), 7.44 (t, *J* = 7.8 Hz, 2H), 6.29 (s, 1H), 6.08 (q, *J* = 7.2 Hz, 1H), 1.76 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.6, 139.4, 134.6, 133.8, 128.8, 128.7, 127.9, 106.4, 60.9, 18.0; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}ON_2$ $[M+H]^+$ 201.1022, found 201.1023.

(1*R*,4*S*)-1,7,7-Trimethyl-3-(1*H*-pyrazol-1-yl)bicyclo[2.2.1]heptan-2-one (16bc) [Scheme 48]. Following to the general procedure, hydrazone **14bc** (19.1 mg, 0.0867 mmol), $Pd(OAc)_2$ (2.0 mg, 0.0089 mmol) and MS4A (74.0 mg) were used and the reaction time was 5 h. Pyrazole **16bc** (11.3 mg, 59%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 6.27-6.26 (m, 1H), 5.01 (d, *J* = 4.4 Hz, 1H), 2.63 (t, *J* = 4.4 Hz, 1H), 1.85-1.49 (m, 4H), 1.07 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 212.4, 139.9, 129.1, 105.3, 67.4, 59.2, 49.5, 43.9, 30.8, 19.8, 19.7, 19.1, 9.5; HRMS (ESI) *m/z* calcd for $C_{13}H_{19}ON_2$ $[M+H]^+$ 219.1492, found 219.1490.

2-(4-Nitrophenyl)-1-(piperidin-1-yl)-2-(1*H*-pyrazol-1-yl)ethan-1-one (16ca) [Scheme 48]. Following to the general procedure, hydrazone **14ca** (26.5 mg, 0.0838 mmol), $Pd(OAc)_2$ (1.9 mg, 0.0084 mmol) and MS4A (75 mg) were used and the reaction time was 9 h. Pyrazole **16ca** (14.3 mg, 54%) was obtained as a yellow solid after purification by PTLC (hexane/EtOAc = 7 : 3); Mp: 93-98 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25-8.21 (m, 2H), 7.58 (d, *J* = 1.2 Hz, 1H), 7.54 (d, *J* = 2.8 Hz, 1H), 7.44-7.42 (m, 2H), 6.64 (s, 1H), 6.34 (t, *J* = 2.4 Hz, 1H), 3.71-3.58 (m, 2H), 3.45-3.29 (m, 2H), 1.64-1.54 (m, 4H), 1.36-1.25 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.7, 148.0, 142.7, 140.0, 129.7, 129.0, 124.1, 106.9, 64.9, 47.0, 43.8, 26.1, 25.4, 24.2; HRMS (ESI) *m/z* calcd for $C_{16}H_{19}O_3N_4$ $[M+H]^+$315.1452, found 315.1450.

第 6 節　第 2 章第 3 節の実験

Ethyl 2-(((*E*)-allylidene)hydrazineylidene)-2-phenylacetate (15ac) and ethyl 2-phenyl-2-(1*H*-pyrazol-1-yl)acetate (16ac) [Scheme 50]. *N*-cyclopropylhydrazone **14ac** (23.6 mg, 0.102 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol) and MS4A (92.0 mg) were dissolved in *t*-AmylOH (1.0 mL). The mixture was stirred at reflux under air for 30 min. After cooled to room temperature, the mixture was filtered through Celite® and evaporated. The residue was analyzed by ^1H NMR ($CDCl_3$) using triphenyl methane (21.5 mg, 0.0880 mmol) as internal standard. The azine **15ac** was calculated as 22% NMR yield, pyrazole **16ac** as 4% and *N*-cyclopropylhydrazone **14ac** as 43%.

N-cyclopropylhydrazone **14ac** (26.5 mg, 0.114 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol) and MS4A (100 mg) were dissolved in *t*-AmylOH (1.1 mL). The mixture was stirred at reflux under air for 1 h. After cooled to room temperature, the mixture was filtered through Celite® and evaporated. The residue was analyzed by ^1H NMR ($CDCl_3$) using triphenyl methane (22.1mg, 0.0904 mmol) as internal standard. The azine **15ac** was calculated as 26% NMR yield, pyrazole **16ac** as 19% and *N*-cyclopropylhydrazone **14ac** as 17%.

N-cyclopropylhydrazone **14ac** (26.1 mg, 0.112 mmol), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) and MS4A (100 mg) were dissolved in *t*-AmylOH (1.1 mL). The mixture was stirred at reflux under air for 2 h. After cooled to room temperature, the mixture was filtered through Celite® and evaporated. The residue was analyzed by ^1H NMR ($CDCl_3$) using triphenyl methane (23.0 mg, 0.0941 mmol) as internal standard. The azine **15ac** was calculated as 15% NMR yield, pyrazole **16ac** as 42% and *N*-cyclopropylhydrazone **14ac** as 2%.

N-cyclopropylhydrazone **14ac** (26.6 mg, 0.115 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol) and MS4A (100 mg) were dissolved in *t*-AmylOH (1.2 mL). The mixture was stirred at reflux under air for 17 h. After cooled to room temperature, the mixture was filtered through Celite® and evaporated. The residue was analyzed by ^1H NMR ($CDCl_3$) using triphenyl methane (24.0 mg, 0.0982 mmol) as internal standard. The pyrazole **16ac** as 44% NMR yield.

Methyl 2-phenyl-2-(1*H*-pyrazol-1-yl)acetate (16ab) [Scheme 58]. *N*-Cyclopropylhydrazone **14ab** (25.9 mg, 0.120 mmol) and $Pd(OAc)_2$ (2.6 mg, 0.012 mmol) were dissolved in *t*-AmylOH (1.2 mL). The mixture was stirred at reflux under Ar for 15 h. After cooled to room temperature, the mixture was filtered through Celite® and evaporated. The residue was analyzed by ^1H NMR ($CDCl_3$) using triphenyl methane as internal standard. The pyrazole **16ab** was calculated as 34% NMR yield.

Methyl 2-phenyl-2-(1*H*-pyrazol-1-yl)acetate (16ab) [Scheme 58]. *N*-Cyclopropylhydrazone **14ab** (26.1 mg, 0.120 mmol) and $Pd(OAc)_2$ (2.6 mg, 0.012 mmol) were dissolved in *t*-AmylOH (1.2 mL). The mixture was stirred at reflux under air for 15 h. After cooled to room temperature, the mixture was filtered through Celite® and evaporated. The residue was analyzed by ^1H NMR ($CDCl_3$) using triphenyl methane as internal standard. The pyrazole **16ab** was calculated as 60% NMR yield.

Ethyl 2-hydrazineylidene-2-phenylacetate (85) [Scheme 59, eq. 1]. To a solution of hydrazine monohydrate (600 μL, 10.0 mmol) in H_2O/AcOH = 1 : 1 (800 μL), ethylbenzoylformate **70ac** (795 μL, 5.00 mmol) was added dropwise. The mixture was stirred at room temperature overnight. The resulting mixture was diluted with water and extracted with EtOAc three times. The collected organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford crude ethyl phenylglyoxylate hydrazone **85**. The spectral data were identical with those reported in the literature. [85)]

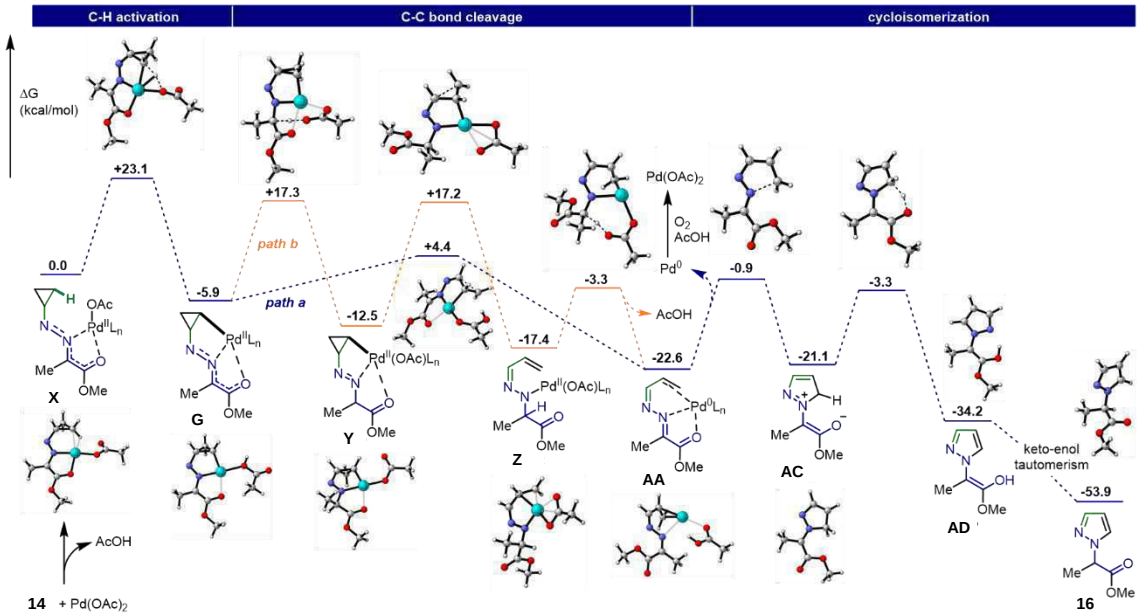
Ethyl 2-((allylidene)hydrazineylidene)-2-phenylacetate (15ac) [Scheme 59, eq. 1]. To a solution of crude hydrazone **85** in Et_2O (5.0 mL) were added acrolein (67.0 μL, 1.00 mmol) and AcOH (20 μL). The mixture was stirred at room temperature for 4 h, and then evaporated. Azine **15ac** (66.0 mg, 29%, from **70ac**) was obtained as a yellow oil after purification with flash column chromatography (hexane/EtOAc = 7 : 3); ^1H-NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.6 Hz, 1H), 7.80-7.78 (m, 2H), 7.55-7.42 (m, 4H), 6.71-6.61 (m, 1H), 5.89-5.85 (m, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.6, 164.3, 161.7, 134.3, 131.6, 131.5, 129.4, 128.8, 127.5, 61.6, 14.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}O_2N_2$ $[M+H]^+$ 231.1128, found 231.1127.

Ethyl 2-phenyl-2-(1*H*-pyrazol-1-yl)acetate (16ac) [Scheme 59, eq. 2]. Azine **15ac** (24.8 mg, 0.108 mmol) and $Pd(OAc)_2$ (2.4 mg, 0.011 mmol), MS4A (92.0 mg) were dissolved in *t*-AmylOH (1.1 mL). The mixture was stirred at reflux under air for 8 h. After cooled to room temperature, the mixture was filtered through Celite® and evaporated. The residue was purified by PTLC (hexane/EtOAc = 7 : 3) to afford pyrazole **16ac** (17.8 mg, 72%).

Ethyl 2-phenyl-2-(1*H*-pyrazol-1-yl)acetate (16ac) [Scheme 59, eq. 3]. Azine **15ac** (27.2 mg, 0.118 mmol) and MS4A (100 mg) were dissolved in *t*-AmylOH (1.2 mL). The mixture was stirred at reflux under air for 7 h. After cooled to room temperature, the mixture was filtered through Celite® and evaporated. The residue was purified by PTLC (hexane/EtOAc = 7 : 3) to afford pyrazole **16ac** (21.1 mg, 78%).

DFT calculations [Scheme 52].

The molecular geometries for each transition states were first estimated with the *Reaction plus* software package, based on the nudged elastic band method, [86] and were subsequently re-optimized using the Gaussian 16 software package. [87] Once the stationary points were obtained at M06/6-31g+(d,p)/Lanl2DZ level, [88–90] the harmonic vibrational frequencies were calculated at the same level to estimate the Gibbs free energy. The nature of the stationary points was characterized *via* vibrational analysis. All of the Gibbs free energy values reported in this paper were calculated for a temperature of 298.15 K. The transition structure reported was optimized without constraints and the intrinsic reaction coordinate (IRC) route was calculated in both directions toward the corresponding minima for each transition-state structure. The IRC calculation failed to reach the energy minima on the potential energy surface for the transition states, and we therefore carried out geometry optimizations as a continuation of the IRC path. For each optimized structure (potential energy minimum or transition state computed at M06/6-31g+(d,p)/Lanl2DZ level of theory), additional single-point energy calculations were performed at M06/6-31g+(d,p)/Lanl2DZ (PhCl or benzonitrile) level of theory. [91] The 3D optimized structural figures in this paper were displayed by the CYLview visualization program. [92]



X

Calculation Method = RM06
Formula = C9H14N2O4Pd
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Charge = 0
Spin = Singlet
Solvation = None
E(RM06) = -887.78168 Hartree
RMS Gradient Norm = 1.0837e-05 Hartree/Bohr
Imaginary Freq = 0
Dipole Moment = 2.1913874 Debye
Polarizability (?) = 170.13133 a.u.
Point Group = C1
Molecular Mass = 319.99884 amu
Job cpu time: 0 days 0 hours 23 minutes 20.0 seconds.

Thermo Tab Data Section:
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Pressure = 1 atm
Frequencies scaled by = 1
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Zero-point Energy Correction = 0.232184 Hartree
Thermal Correction to Energy = 0.250628 Hartree
Thermal Correction to Enthalpy = 0.251572 Hartree
Thermal Correction to Free Energy = 0.184001 Hartree
EE + Zero-point Energy = -887.54949 Hartree
EE + Thermal Energy Correction = -887.53105 Hartree

EE + Thermal Enthalpy Correction = -887.5301 Hartree

EE + Thermal Free Energy Correction = -887.59767 Hartree

E (Thermal) = 157.271 kcal/mol

Heat Capacity (Cv) = 64.289 cal/mol-kelvin

Entropy (S) = 142.215 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ

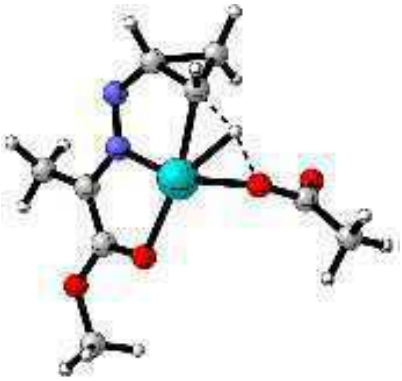
Solvation = scrf=solvent=chlorobenzene

E(RM06) = -887.79633 Hartree

0 1

C	-1.39369000	3.25818400	0.57803100
H	-1.14675300	3.08587200	1.62143600
H	-2.03096200	4.11602300	0.39061400
C	-1.63310900	1.99191300	-0.26784600
H	-1.82717600	1.13480600	0.44008900
H	-2.37382300	2.04312200	-1.05898100
C	-0.38022200	2.87092500	-0.43111700
H	-0.37259400	3.45132700	-1.35137800
N	0.96134200	2.47829200	-0.05875200
N	1.12748900	1.19959100	-0.06061700
C	2.33111900	0.59815000	0.15676300
C	3.55633900	1.39789300	0.40755900
H	3.44577800	2.01547000	1.30865300
H	3.75158900	2.08785400	-0.42419500
H	4.41668400	0.73615700	0.53224400
C	2.24565400	-0.80040200	0.06592900
O	-1.85767300	-1.47722100	-0.49081300
O	3.37558700	-1.51301400	0.22436200
C	3.28609200	-2.96555200	0.12422600
H	2.93146300	-3.25278800	-0.86813200
H	4.30208700	-3.31516100	0.29637200
H	2.60001300	-3.35293600	0.88066200
Pd	-0.41511700	-0.07256500	-0.26413300
O	1.13790300	-1.44486700	-0.17257200
C	-2.93392800	-1.33228200	0.26639700
O	-3.11441800	-0.35634700	1.03160200

C	-3.92442000	-2.45370500	0.13201300
H	-4.82278300	-2.22358500	0.70713300
H	-3.47747200	-3.38335300	0.50020300
H	-4.17665700	-2.60916800	-0.92136200



TS of **X** to **G**

Calculation Method = RM06

Formula = C9H14N2O4Pd

Basis Set = 6-31g+(d,p)/ Lanl2DZ

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -887.74231 Hartree

RMS Gradient Norm = 4.685e-06 Hartree/Bohr

Imaginary Freq = 1

Dipole Moment = 1.5120655 Debye

Polarizability (?) = 167.351 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 22 minutes 53.7 seconds.

Thermo Tab Data Section:

Imaginary Freq = 1

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -887.74231 Hartree

Zero-point Energy Correction = 0.227197 Hartree

Thermal Correction to Energy = 0.245043 Hartree

Thermal Correction to Enthalpy = 0.245988 Hartree

Thermal Correction to Free Energy = 0.179848 Hartree

EE + Zero-point Energy = -887.51512 Hartree

EE + Thermal Energy Correction = -887.49727 Hartree

EE + Thermal Enthalpy Correction = -887.49632 Hartree

EE + Thermal Free Energy Correction = -887.56246 Hartree

E (Thermal) = 153.767 kcal/mol

Heat Capacity (Cv) = 63.537 cal/mol-kelvin

Entropy (S) = 139.203 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ

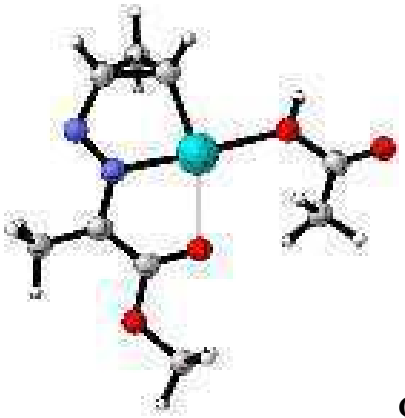
Solvation = scrf=solvent=chlorobenzene

E(RM06) = -887.75533 Hartree

0 1

C	1.62368000	-2.59764400	0.76307800
H	1.47767600	-1.99724900	1.65804800
H	2.36499700	-3.38641500	0.85933200
C	1.54322800	-1.82645000	-0.55688800
H	2.12478400	-0.62372400	-0.45712900
H	2.11362500	-2.17056800	-1.42085000
C	0.44285400	-2.84580800	-0.11683100
H	0.46013400	-3.77991700	-0.67260300
N	-0.90640700	-2.46891600	0.20541100
N	-1.14028000	-1.21298600	0.00289900
C	-2.33817300	-0.60346100	0.20093700
C	-3.53492400	-1.38125900	0.60955000
H	-3.36995100	-1.87969000	1.57448600
H	-3.75603400	-2.17178600	-0.11956200
H	-4.40053400	-0.72009900	0.69301600
C	-2.25264700	0.79308400	0.02969300
O	2.42223900	0.73481200	-0.66188800
O	-3.38236300	1.50571000	0.21408800
C	-3.30363100	2.95159300	0.05915400
H	-2.98460600	3.20554800	-0.95441500
H	-4.31438900	3.30543100	0.25323600
H	-2.59450700	3.36965200	0.77733400

Pd	0.38024300	-0.02673500	-0.45779300
O	-1.16013600	1.41756700	-0.28031500
C	2.91381000	1.29285300	0.47907800
O	2.64677900	0.85918500	1.60440400
C	3.80942900	2.46103200	0.20423000
H	4.19966100	2.85805900	1.14260800
H	3.24765900	3.23666300	-0.32684900
H	4.63319800	2.15536300	-0.44866000



G

Calculation Method = RM06

Formula = C9H14N2O4Pd

Basis Set = 6-31g+(d,p)/ Lanl2DZ

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -887.7949 Hartree

RMS Gradient Norm = 2.579e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 2.2356329 Debye

Polarizability (?) = 159.36867 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 23 minutes 38.6 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

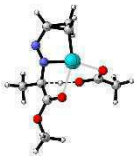
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -887.7949 Hartree
Zero-point Energy Correction = 0.233266 Hartree
Thermal Correction to Energy = 0.251315 Hartree
Thermal Correction to Enthalpy = 0.25226 Hartree
Thermal Correction to Free Energy = 0.185593 Hartree
EE + Zero-point Energy = -887.56163 Hartree
EE + Thermal Energy Correction = -887.54358 Hartree
EE + Thermal Enthalpy Correction = -887.54264 Hartree
EE + Thermal Free Energy Correction = -887.60931 Hartree
E (Thermal) = 157.703 kcal/mol
Heat Capacity (Cv) = 64.505 cal/mol-kelvin
Entropy (S) = 140.312 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -887.80721 Hartree

0 1

C	0.10497700	3.28615100	0.90114600
H	0.41474800	2.75965600	1.80084700
H	-0.22610700	4.30819600	1.07499700
C	-0.50600300	2.49941400	-0.23436900
H	-3.09505100	0.90432900	0.65033200
H	-1.29986400	2.95317600	-0.82890400
C	0.92630900	3.00863300	-0.35750700
H	1.15661300	3.85111500	-1.00143700
N	1.98656600	2.04529900	-0.30778900
N	1.52302100	0.84085100	-0.17257200
C	2.32722600	-0.25517800	-0.05226000
C	3.80556600	-0.09920300	-0.07964100
H	4.14087000	0.57679700	0.71872500
H	4.13541600	0.35251700	-1.02529800
H	4.29137000	-1.06954100	0.04224500
C	1.62429300	-1.46705100	0.07964600

O	-2.59692400	0.21805100	0.16356600
O	2.39091000	-2.59067400	0.15292700
C	1.70954000	-3.85656000	0.33236000
H	1.06040400	-4.06843300	-0.52173500
H	2.50626000	-4.59576600	0.40245100
H	1.10873800	-3.84428300	1.24581200
Pd	-0.44903700	0.49418300	-0.04246600
O	0.33952400	-1.58288200	0.14469800
C	-3.36126000	-0.94737300	-0.02428500
O	-4.49359700	-0.99168700	0.42749500
C	-2.62153700	-1.97275800	-0.79314000
H	-3.25011600	-2.85627500	-0.90675000
H	-1.67585200	-2.22875700	-0.29659800
H	-2.35281800	-1.57711400	-1.77991600



TS of **G** to **Y**

Calculation Method = RM06

Formula = C9H14N2O4Pd

Basis Set = 6-31g+(d,p)/ Lanl2DZ

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -887.75283 Hartree

RMS Gradient Norm = 3.079e-06 Hartree/Bohr

Imaginary Freq = 1

Dipole Moment = 1.2492467 Debye

Polarizability (?) = 151.41867 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 21 minutes 57.8 seconds.

Thermo Tab Data Section:

Imaginary Freq = 1

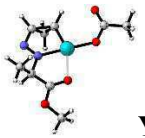
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -887.75283 Hartree
Zero-point Energy Correction = 0.227816 Hartree
Thermal Correction to Energy = 0.245466 Hartree
Thermal Correction to Enthalpy = 0.246411 Hartree
Thermal Correction to Free Energy = 0.181762 Hartree
EE + Zero-point Energy = -887.52502 Hartree
EE + Thermal Energy Correction = -887.50737 Hartree
EE + Thermal Enthalpy Correction = -887.50642 Hartree
EE + Thermal Free Energy Correction = -887.57107 Hartree
E (Thermal) = 154.033 kcal/mol
Heat Capacity (Cv) = 63.106 cal/mol-kelvin
Entropy (S) = 136.065 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -887.76644 Hartree

0 1

C	2.96950300	-0.64925600	0.84725200
H	2.41423400	0.03363200	1.48716400
H	4.03601100	-0.69153300	1.05636800
C	2.48147200	-0.88702500	-0.54143200
H	-0.65761000	0.32110700	1.25476200
H	3.20260300	-1.03602500	-1.34543400
C	2.25124300	-1.97371000	0.52040200
H	2.81966100	-2.89569000	0.55293800
N	0.92733600	-2.07198600	1.05556700
N	0.10887200	-1.36783500	0.38043800
C	-1.13176100	-0.90036700	0.93475800
C	-1.68932200	-1.64068100	2.11853600
H	-0.93091800	-1.71110900	2.90374600
H	-1.99651300	-2.66053900	1.85284600
H	-2.56065500	-1.10979100	2.51012400
C	-2.00478600	-0.44399100	-0.15071600

O	-0.16045700	1.51408500	1.46146100
O	-3.32229700	-0.50642300	0.11963500
C	-4.23235600	0.10766200	-0.84235200
H	-4.15336500	-0.39959300	-1.80637300
H	-5.22231500	-0.02005900	-0.40945300
H	-3.98603700	1.16468600	-0.96745700
Pd	0.73019700	-0.07577600	-1.06614100
O	-1.57865100	0.09142300	-1.20811500
C	0.43320700	2.36577700	0.67250300
O	0.93972100	2.12115300	-0.47097600
C	0.51917600	3.76809100	1.21018000
H	-0.49125900	4.16501900	1.35603300
H	1.07413700	4.40801700	0.52288600
H	1.00471700	3.75539700	2.19147400



Y

Calculation Method = RM06

Formula = C9H14N2O4Pd

Basis Set = 6-31g+(d,p)/ Lanl2DZ

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -887.79844 Hartree

RMS Gradient Norm = 5.099e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 8.3631561 Debye

Polarizability (?) = 153.37267 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 19 minutes 10.4 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -887.79844 Hartree

Zero-point Energy Correction = 0.233387 Hartree

Thermal Correction to Energy = 0.251501 Hartree

Thermal Correction to Enthalpy = 0.252445 Hartree

Thermal Correction to Free Energy = 0.184618 Hartree

EE + Zero-point Energy = -887.56505 Hartree

EE + Thermal Energy Correction = -887.54694 Hartree

EE + Thermal Enthalpy Correction = -887.54599 Hartree

EE + Thermal Free Energy Correction = -887.61382 Hartree

E (Thermal) = 157.819 kcal/mol

Heat Capacity (Cv) = 63.63 cal/mol-kelvin

Entropy (S) = 142.755 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ

Solvation = scrf=solvent=chlorobenzene

E(RM06) = -887.81686 Hartree

0 1

C	-1.32995000	2.45515100	1.27936800
H	-0.77907600	2.03187300	2.11558900
H	-2.09425400	3.17403800	1.56664600
C	-1.50369200	1.66741000	0.02996600
H	3.04048300	1.24948500	0.74696800
H	-2.43223200	1.67865700	-0.53156300
C	-0.50273400	2.82792700	0.02655000
H	-0.70561900	3.78509000	-0.43851800
N	0.87976500	2.48970600	0.00166400
N	1.06814100	1.23035600	-0.01452900
C	2.47325600	0.77413800	-0.06399500
C	3.09139400	1.14035500	-1.41777500
H	3.05882800	2.22671100	-1.53905100
H	2.51754700	0.67650600	-2.22848200
H	4.12829300	0.79675000	-1.46409100
C	2.48012100	-0.71976300	0.13784600
O	-3.80857800	-0.09334000	-0.50079300

O	3.73345600	-1.18027400	0.29923800
C	3.90385200	-2.62374600	0.47372600
H	3.52578500	-3.14969800	-0.40565000
H	4.97571200	-2.76507100	0.59103400
H	3.35831600	-2.95520700	1.35989800
Pd	-0.48510000	-0.05760900	0.01699000
O	1.48719700	-1.46171100	0.13362400
C	-3.27910500	-1.18868300	-0.23233400
O	-1.99594800	-1.38192900	0.03620200
C	-4.07635600	-2.47023200	-0.18365800
H	-3.97179000	-2.93572100	0.80198300
H	-3.68463900	-3.17923900	-0.92079100
H	-5.12783600	-2.26190000	-0.38978200

TS of **Y** to **Z**

Calculation Method = RM06

Formula = C9H14N2O4Pd

Basis Set = 6-31g+(d,p)/ Lanl2DZ

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -887.74807 Hartree

RMS Gradient Norm = 1.21e-06 Hartree/Bohr

Imaginary Freq = 1

Dipole Moment = 3.5163017 Debye

Polarizability (?) = 165.46 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 22 minutes 25.3 seconds.

Thermo Tab Data Section:

Imaginary Freq = 1

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1
Electronic Energy (EE) = -887.74807 Hartree
Zero-point Energy Correction = 0.229215 Hartree
Thermal Correction to Energy = 0.247756 Hartree
Thermal Correction to Enthalpy = 0.2487 Hartree
Thermal Correction to Free Energy = 0.179023 Hartree
EE + Zero-point Energy = -887.51885 Hartree
EE + Thermal Energy Correction = -887.50031 Hartree
EE + Thermal Enthalpy Correction = -887.49937 Hartree
EE + Thermal Free Energy Correction = -887.56904 Hartree
E (Thermal) = 155.469 kcal/mol
Heat Capacity (Cv) = 64.244 cal/mol-kelvin
Entropy (S) = 146.647 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -887.76401 Hartree

0 1

C	0.75081100	2.98226400	-0.72367900
H	1.26366800	2.60775500	-1.60902000
H	0.20680600	3.91967600	-0.85104700
C	0.73206700	2.27716200	0.51396100
H	1.40611900	2.38407900	1.37126100
H	-1.14740400	-1.76314800	-0.31194900
C	-0.76926900	2.41568000	0.61644600
H	-1.26779800	3.35672900	0.81702000
N	-1.50971200	1.31810600	0.50787600
N	-0.89311500	0.23138900	0.12185500
C	-1.58691700	-1.04423000	0.39121000
C	-1.35917000	-1.48065800	1.82993000
H	-0.28500000	-1.58154400	2.02262600
H	-1.84343300	-2.44395700	2.01681700
H	-1.79034900	-0.74238700	2.51494000
C	-3.06389100	-0.91108400	0.07392100
O	-3.98154900	-1.09084100	0.86960700
O	-3.25643400	-0.59857800	-1.23417600

C	-4.63472500	-0.40881000	-1.66220800
H	-4.57217700	-0.17113700	-2.72226000
H	-5.09078400	0.41041700	-1.10029000
H	-5.21072200	-1.32299900	-1.49624000
Pd	1.10535400	0.29041700	0.05640000
O	3.24700500	0.11400800	-0.16378800
C	3.17342200	-1.17677500	-0.32290900
O	2.01792600	-1.74650500	-0.27296800
C	4.41105200	-1.95964400	-0.58914600
H	4.67207500	-1.88206000	-1.65133200
H	4.25158400	-3.01213200	-0.34639300
H	5.24508300	-1.55304600	-0.01121000

Z

Calculation Method = RM06
Formula = C9H14N2O4Pd
Basis Set = 6-31g+(d,p)/ Lanl2DZ
Charge = 0
Spin = Singlet
Solvation = None
E(RM06) = -887.8072 Hartree
RMS Gradient Norm = 3.581e-06 Hartree/Bohr
Imaginary Freq = 0
Dipole Moment = 2.4575257 Debye
Polarizability (?) = 161.44167 a.u.
Point Group = C1
Molecular Mass = 319.99884 amu
Job cpu time: 0 days 0 hours 20 minutes 18.3 seconds.

Thermo Tab Data Section:
Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm

Frequencies scaled by = 1
Electronic Energy (EE) = -887.8072 Hartree
Zero-point Energy Correction = 0.231918 Hartree
Thermal Correction to Energy = 0.250728 Hartree
Thermal Correction to Enthalpy = 0.251672 Hartree
Thermal Correction to Free Energy = 0.182309 Hartree
EE + Zero-point Energy = -887.57528 Hartree
EE + Thermal Energy Correction = -887.55647 Hartree
EE + Thermal Enthalpy Correction = -887.55552 Hartree
EE + Thermal Free Energy Correction = -887.62489 Hartree
E (Thermal) = 157.334 kcal/mol
Heat Capacity (Cv) = 65.258 cal/mol-kelvin
Entropy (S) = 145.987 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -887.82237 Hartree

0 1

C	1.39599200	2.52865100	-0.86117800
H	2.48179300	2.57120400	-0.92293600
H	0.84200800	2.59491200	-1.79560200
C	0.74352800	2.58002400	0.35512000
H	1.32218200	2.71302200	1.27276000
H	-0.96007900	-1.61095400	0.09816900
C	-0.74251500	2.65822600	0.45143600
H	-1.23529700	3.61334900	0.59712800
N	-1.47157600	1.59601500	0.35703000
N	-0.87857700	0.44133100	-0.01182400
C	-1.47451300	-0.77223800	0.58393600
C	-1.31859200	-0.83403300	2.09378000
H	-0.25431400	-0.81947900	2.35616500
H	-1.76553800	-1.74969800	2.49359000
H	-1.82442400	0.01919500	2.55909700
C	-2.93900200	-0.83034300	0.18031900

O	-3.88476100	-0.86977600	0.96375900
O	-3.08649800	-0.87220500	-1.16849900
C	-4.45209000	-0.89864500	-1.67067800
H	-4.35471100	-0.92633800	-2.75417600
H	-4.98748200	-0.00264400	-1.34590100
H	-4.97531900	-1.78361900	-1.29857300
Pd	1.12930500	0.41492200	-0.10205300
O	3.23915600	-0.33151400	-0.31391400
C	2.79708500	-1.52681300	-0.12963800
O	1.51431800	-1.68855500	0.06117400
C	3.69479000	-2.70924700	-0.14571500
H	3.48878500	-3.31509500	-1.03538600
H	3.50100200	-3.33786600	0.72874900
H	4.73860700	-2.39091700	-0.15953300

 **TS** of **Z** to **AA**

Calculation Method = RM06

Formula = C9H14N2O4Pd

Basis Set = 6-31g+(d,p)/ Lanl2DZ

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -887.7798 Hartree

RMS Gradient Norm = 8.375e-06 Hartree/Bohr

Imaginary Freq = 1

Dipole Moment = 4.2448469 Debye

Polarizability (?) = 163.79933 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 26 minutes 9.3 seconds.

Thermo Tab Data Section:

Imaginary Freq = 1

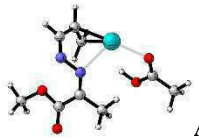
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -887.7798 Hartree
Zero-point Energy Correction = 0.225962 Hartree
Thermal Correction to Energy = 0.244582 Hartree
Thermal Correction to Enthalpy = 0.245527 Hartree
Thermal Correction to Free Energy = 0.177354 Hartree
EE + Zero-point Energy = -887.55384 Hartree
EE + Thermal Energy Correction = -887.53522 Hartree
EE + Thermal Enthalpy Correction = -887.53428 Hartree
EE + Thermal Free Energy Correction = -887.60245 Hartree
E (Thermal) = 153.478 kcal/mol
Heat Capacity (Cv) = 64.804 cal/mol-kelvin
Entropy (S) = 143.481 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -887.79501 Hartree

0 1

C	-0.13338400	1.95272500	-1.42000300
H	0.49707300	2.31849100	-2.22817800
H	-0.79897600	1.12300700	-1.66730100
C	-0.40128500	2.76876800	-0.30497100
H	-0.03751100	3.79493800	-0.29036800
H	0.09336700	-1.31992800	-0.04302500
C	-1.49024100	2.44252500	0.61090100
H	-2.21624300	3.19030900	0.91292900
N	-1.65452000	1.23685100	1.06630600
N	-0.63696700	0.38198100	1.08990700
C	-0.83503200	-0.98404000	0.83036000
C	-0.39388400	-1.87781800	1.98105200
H	0.58384700	-1.54369900	2.34677200
H	-0.31438600	-2.91263300	1.63565000
H	-1.11469900	-1.83612200	2.80605700
C	-2.08604600	-1.39039000	0.15063100

O	-2.75585100	-2.38821600	0.41821500
O	-2.38633100	-0.56347500	-0.90578700
C	-3.59027500	-0.89248700	-1.65246400
H	-3.66533000	-0.13069300	-2.42662200
H	-4.46138400	-0.86864400	-0.99269900
H	-3.49984100	-1.89011600	-2.08986000
Pd	1.13431900	1.15635700	0.10358500
O	2.62141800	-0.42601700	-0.06047300
C	2.26936400	-1.58891300	-0.46383800
O	1.04382800	-1.92481200	-0.71793400
C	3.31489900	-2.64316500	-0.66008300
H	3.20107800	-3.09508400	-1.65026800
H	3.17302600	-3.44142200	0.07714100
H	4.31248700	-2.21571900	-0.55029800



AA containing Pd

Calculation Method = RM06

Formula = C9H14N2O4Pd

Basis Set = 6-31g+(d,p)/ Lanl2DZ

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -887.81479 Hartree

RMS Gradient Norm = 8.16e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 2.8441742 Debye

Polarizability (?) = 158.77767 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 24 minutes 23.0 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -887.81479 Hartree

Zero-point Energy Correction = 0.231184 Hartree

Thermal Correction to Energy = 0.250709 Hartree

Thermal Correction to Enthalpy = 0.251653 Hartree

Thermal Correction to Free Energy = 0.179842 Hartree

EE + Zero-point Energy = -887.5836 Hartree

EE + Thermal Energy Correction = -887.56408 Hartree

EE + Thermal Enthalpy Correction = -887.56313 Hartree

EE + Thermal Free Energy Correction = -887.63494 Hartree

E (Thermal) = 157.322 kcal/mol

Heat Capacity (Cv) = 66.478 cal/mol-kelvin

Entropy (S) = 151.14 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ

Solvation = scrf=solvent=chlorobenzene

E(RM06) = -887.82831 Hartree

0 1

C	-0.23829800	-1.60680700	1.42524800
H	0.26062800	-1.94428900	2.33177900
H	-0.90438900	-0.75225500	1.54537100
C	-0.43315100	-2.50422200	0.36225800
H	-0.07043800	-3.52639600	0.47045800
H	1.40944500	0.70573000	1.33947700
C	-1.43639100	-2.31302400	-0.68466600
H	-1.99853400	-3.18023100	-1.02381500
N	-1.74297600	-1.20304300	-1.27758000
N	-0.95951300	-0.11318300	-1.19708800
C	-1.33036300	1.07179200	-0.81441400
C	-0.41700500	2.22295900	-1.08778400
H	0.46195700	1.86258100	-1.63043800
H	-0.10145800	2.71426000	-0.15754300
H	-0.92838800	2.98501900	-1.68830300
C	-2.58652100	1.39572900	-0.10973200
O	-3.03738200	2.54077300	-0.00094400

O	-3.19027600	0.30936300	0.45293500
C	-4.46008200	0.54915100	1.12162000
H	-4.77264600	-0.42463100	1.49335100
H	-5.18698700	0.95125600	0.41129200
H	-4.32737500	1.26290700	1.93907600
Pd	1.26591400	-1.16061300	-0.05920000
O	2.93701600	0.32536900	-0.40345800
C	2.91138500	1.35077000	0.30476300
O	2.01442300	1.50295900	1.29989600
C	3.81701500	2.51323700	0.13759300
H	4.26506200	2.78566800	1.09755200
H	3.23699500	3.37765000	-0.20661300
H	4.59171600	2.27929100	-0.59251100

AA without Pd

Calculation Method = 6-31g+(d,p)/ Lanl2DZ

Formula = C7H10N2O2

Basis Set = 6-31+G(d,p)

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -532.33693 Hartree

RMS Gradient Norm = 2.1995e-05 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 2.4582131 Debye

Polarizability (?) = 111.21333 a.u.

Point Group = C1

Molecular Mass = 154.07423 amu

Job cpu time: 0 days 0 hours 41 minutes 40.6 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -532.33693 Hartree

Zero-point Energy Correction = 0.165952 Hartree
Thermal Correction to Energy = 0.178043 Hartree
Thermal Correction to Enthalpy = 0.178987 Hartree
Thermal Correction to Free Energy = 0.126916 Hartree
EE + Zero-point Energy = -532.17098 Hartree
EE + Thermal Energy Correction = -532.15889 Hartree
EE + Thermal Enthalpy Correction = -532.15794 Hartree
EE + Thermal Free Energy Correction = -532.21001 Hartree
E (Thermal) = 111.724 kcal/mol
Heat Capacity (Cv) = 42.069 cal/mol-kelvin
Entropy (S) = 109.595 cal/mol-kelvin

Opt Tab Data Section:
Step number = 1
Maximum force = 3.9e-05 Converged
RMS force = 1.2e-05 Converged
Maximum displacement = 0.001532 Converged
RMS displacement = 0.000337 Converged
Predicted energy change = -3.728526e-08 Hartree

Basis Set = 6-31+G(d,p)
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -532.34408 Hartree

0 1

C	-1.96735300	-1.75352200	0.88658300
H	-2.20485300	-2.58110200	1.55051200
H	-0.93070000	-1.64006700	0.58288900
C	-2.94549300	-0.94649300	0.44928200
H	-3.96494400	-1.13519700	0.78763700
C	-2.83029900	0.16488800	-0.49010700
H	-3.76341200	0.62869300	-0.81230300
N	-1.77850300	0.69269700	-1.00765200
N	-0.56892200	0.17649600	-0.77971400
C	0.25643500	0.85641000	-0.06590300
C	-0.08408800	2.13395300	0.62206900
H	-0.63457600	2.78316600	-0.07011600

H	0.81459400	2.63670300	0.98337600
H	-0.74914400	1.94514200	1.47527200
C	1.64173900	0.31876200	0.08473400
O	2.53682300	0.94527100	0.61082800
O	1.78399400	-0.91901200	-0.39777200
C	3.09999300	-1.46047300	-0.29661300
H	3.04396000	-2.45937100	-0.72977800
H	3.41609900	-1.51131000	0.74975000
H	3.81281300	-0.84223000	-0.85040500

 **TS** of **AA** to **AC**

Calculation Method = RM06

Formula = C7H10N2O2

Basis Set = 6-31+G(d,p)

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -532.30381 Hartree

RMS Gradient Norm = 8.272e-06 Hartree/Bohr

Imaginary Freq = 1

Dipole Moment = 3.1603977 Debye

Polarizability (?) = 120.82133 a.u.

Point Group = C1

Molecular Mass = 154.07423 amu

Job cpu time: 0 days 0 hours 32 minutes 13.4 seconds.

Thermo Tab Data Section:

Imaginary Freq = 1

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -532.30381 Hartree

Zero-point Energy Correction = 0.165385 Hartree

Thermal Correction to Energy = 0.176443 Hartree

Thermal Correction to Enthalpy = 0.177388 Hartree
Thermal Correction to Free Energy = 0.128113 Hartree
EE + Zero-point Energy = -532.13843 Hartree
EE + Thermal Energy Correction = -532.12737 Hartree
EE + Thermal Enthalpy Correction = -532.12642 Hartree
EE + Thermal Free Energy Correction = -532.1757 Hartree
E (Thermal) = 110.72 kcal/mol
Heat Capacity (Cv) = 39.569 cal/mol-kelvin
Entropy (S) = 103.707 cal/mol-kelvin

Basis Set = 6-31+G(d,p)
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -532.31074 Hartree

0 1

C	1.36565900	-1.47777100	-0.59554500
H	0.83727400	-2.40111600	-0.35427700
H	0.98299500	-0.98660300	-1.48599800
C	2.70175600	-1.30216700	-0.21001500
H	3.33571100	-2.13093400	0.09557400
C	2.99751000	-0.01300600	0.21704200
H	3.98186300	0.31501100	0.54059200
N	1.98597800	0.82650900	0.45951800
N	0.81321600	0.25936800	0.25099800
C	-0.24861200	0.97443600	0.00723600
C	-0.17082900	2.43869200	-0.26050000
H	0.17178100	2.97542200	0.63311400
H	-1.14743200	2.82547800	-0.55788000
H	0.56770600	2.64161500	-1.04557900
C	-1.56614900	0.31620100	0.00857000
O	-2.61164300	0.91124300	-0.16126600
O	-1.50585900	-1.01658800	0.19662800
C	-2.76951200	-1.67673300	0.21089000
H	-2.55297000	-2.73335000	0.37353700
H	-3.29240000	-1.53361600	-0.73965700
H	-3.39780400	-1.28819500	1.01800200

AC

Calculation Method = RM06

Formula = C7H10N2O2

Basis Set = 6-31+G(d,p)

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -532.33931 Hartree

RMS Gradient Norm = 8.033e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 3.8677899 Debye

Polarizability (?) = 120.143 a.u.

Point Group = C1

Molecular Mass = 154.07423 amu

Job cpu time: 0 days 0 hours 39 minutes 27.2 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -532.33931 Hartree

Zero-point Energy Correction = 0.168121 Hartree

Thermal Correction to Energy = 0.178846 Hartree

Thermal Correction to Enthalpy = 0.17979 Hartree

Thermal Correction to Free Energy = 0.131803 Hartree

EE + Zero-point Energy = -532.17119 Hartree

EE + Thermal Energy Correction = -532.16046 Hartree

EE + Thermal Enthalpy Correction = -532.15952 Hartree

EE + Thermal Free Energy Correction = -532.2075 Hartree

E (Thermal) = 112.228 kcal/mol

Heat Capacity (Cv) = 39.607 cal/mol-kelvin

Entropy (S) = 100.997 cal/mol-kelvin

Basis Set = 6-31+G(d,p)
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -532.34663 Hartree

0 1

C	-1.08322300	-1.28660600	-0.00001900
H	-0.57260600	-1.69287800	-0.87996500
H	-0.57298400	-1.69268400	0.88027300
C	-2.55814300	-1.44122800	-0.00019200
H	-3.07976900	-2.38791100	-0.00029600
C	-3.06996600	-0.19602300	0.00008400
H	-4.11070200	0.10533600	0.00006800
N	-2.11957200	0.80785800	0.00014500
N	-0.94062300	0.20251200	0.00003800
C	0.18679700	0.92665800	0.00000900
C	0.03308000	2.40178400	-0.00005000
H	-0.54291300	2.73245100	-0.87491500
H	1.01588400	2.87483600	-0.00056900
H	-0.54184200	2.73268000	0.87545600
C	1.52258200	0.35505800	-0.00006900
O	2.53876500	1.02663000	-0.00008300
O	1.56126600	-1.00258900	-0.00008200
C	2.87417300	-1.56068800	0.00014000
H	2.73847100	-2.64319300	0.00007300
H	3.42772900	-1.24366700	0.88879500
H	3.42804500	-1.24362800	-0.88830100

TS of **AC** to **AD**

Calculation Method = RM06
Formula = C7H10N2O2
Basis Set = 6-31+G(d,p)

Charge = 0
Spin = Singlet
Solvation = None
E(RM06) = -532.30972 Hartree
RMS Gradient Norm = 5.406e-06 Hartree/Bohr
Imaginary Freq = 1
Dipole Moment = 1.3925487 Debye
Polarizability (?) = 118.89733 a.u.
Point Group = C1
Molecular Mass = 154.07423 amu
Job cpu time: 0 days 0 hours 30 minutes 55.2 seconds.

Thermo Tab Data Section:
Imaginary Freq = 1
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -532.30972 Hartree
Zero-point Energy Correction = 0.163737 Hartree
Thermal Correction to Energy = 0.173972 Hartree
Thermal Correction to Enthalpy = 0.174916 Hartree
Thermal Correction to Free Energy = 0.128093 Hartree
EE + Zero-point Energy = -532.14598 Hartree
EE + Thermal Energy Correction = -532.13574 Hartree
EE + Thermal Enthalpy Correction = -532.1348 Hartree
EE + Thermal Free Energy Correction = -532.18162 Hartree
E (Thermal) = 109.169 kcal/mol
Heat Capacity (Cv) = 38.125 cal/mol-kelvin
Entropy (S) = 98.548 cal/mol-kelvin

Basis Set = 6-31+G(d,p)
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -532.31463 Hartree

0 1

C	1.35975000	-1.13161400	0.37095200
H	1.09804200	-1.52351600	1.36051000

H	0.22190800	-1.57979400	-0.11119300
C	2.73328200	-1.20669400	-0.04857800
H	3.35145900	-2.09381700	-0.03855100
C	3.09315900	0.06620300	-0.39216900
H	4.04444800	0.43484300	-0.75402300
N	2.06058900	0.95602400	-0.25110300
N	1.05080700	0.25766800	0.20911900
C	-0.23274900	0.77044600	0.28249400
C	-0.39356700	2.24225500	0.14623300
H	0.24125000	2.76785700	0.86936100
H	-1.43380400	2.52392200	0.32034500
H	-0.09436800	2.59723100	-0.85028800
C	-1.24852800	-0.16827700	0.08438900
O	-1.07191000	-1.43080200	-0.01397500
O	-2.48564400	0.32847800	-0.07238100
C	-3.53247100	-0.61764300	-0.25887200
H	-4.45304000	-0.03307500	-0.28767300
H	-3.56375000	-1.33475100	0.56765100
H	-3.40472500	-1.16421500	-1.19810600

AD

Calculation Method = RM06

Formula = C7H10N2O2

Basis Set = 6-31+G(d,p)

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -532.3638 Hartree

RMS Gradient Norm = 1.518e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 0.90591136 Debye

Polarizability (?) = 110.10333 a.u.

Point Group = C1

Molecular Mass = 154.07423 amu
Job cpu time: 0 days 0 hours 35 minutes 25.4 seconds.

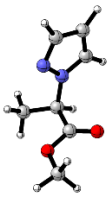
Thermo Tab Data Section:
Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -532.3638 Hartree
Zero-point Energy Correction = 0.169294 Hartree
Thermal Correction to Energy = 0.180003 Hartree
Thermal Correction to Enthalpy = 0.180947 Hartree
Thermal Correction to Free Energy = 0.131843 Hartree
EE + Zero-point Energy = -532.1945 Hartree
EE + Thermal Energy Correction = -532.18379 Hartree
EE + Thermal Enthalpy Correction = -532.18285 Hartree
EE + Thermal Free Energy Correction = -532.23195 Hartree
E (Thermal) = 112.953 kcal/mol
Heat Capacity (Cv) = 39.159 cal/mol-kelvin
Entropy (S) = 103.348 cal/mol-kelvin

Basis Set = 6-31+G(d,p)
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -532.3677 Hartree

0 1

C	-2.25712600	0.90275200	-0.00577300
H	-2.26387800	1.98328900	-0.01953300
H	0.26250800	-1.71201500	-0.01824300
C	-3.29649600	-0.01250800	0.00573300
H	-4.35530300	0.20263000	0.00440300
C	-2.66695300	-1.26029100	0.01890900
H	-3.10611100	-2.24960600	0.02992500
N	-1.33850800	-1.13114100	0.01738600
N	-1.09782100	0.19995900	0.00126000

C	0.22695100	0.71925000	-0.00114000
C	0.35436000	2.20186900	0.01921400
H	-0.09485100	2.66996500	-0.86912900
H	1.40979300	2.47918200	0.03918800
H	-0.12447400	2.64339400	0.90537900
C	1.28428500	-0.13111500	-0.03681200
O	1.22691500	-1.45898900	-0.04771200
O	2.52840800	0.37737200	-0.07589300
C	3.61603200	-0.52486700	0.07464200
H	4.51297000	0.09573800	0.04506400
H	3.64253400	-1.25650200	-0.73882300
H	3.56220600	-1.05541000	1.03144400



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Calculation Method = RM06

Formula = C7H10N2O2

Basis Set = 6-31+G(d,p)

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -532.39087 Hartree

RMS Gradient Norm = 7.07e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 1.8247174 Debye

Polarizability (?) = 98.595667 a.u.

Point Group = C1

Molecular Mass = 154.07423 amu

Job cpu time: 0 days 0 hours 30 minutes 44.0 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -532.39087 Hartree
Zero-point Energy Correction = 0.16991 Hartree
Thermal Correction to Energy = 0.180671 Hartree
Thermal Correction to Enthalpy = 0.181615 Hartree
Thermal Correction to Free Energy = 0.131783 Hartree
EE + Zero-point Energy = -532.22096 Hartree
EE + Thermal Energy Correction = -532.2102 Hartree
EE + Thermal Enthalpy Correction = -532.20926 Hartree
EE + Thermal Free Energy Correction = -532.25909 Hartree
E (Thermal) = 113.373 kcal/mol
Heat Capacity (Cv) = 38.569 cal/mol-kelvin
Entropy (S) = 104.88 cal/mol-kelvin

Basis Set = 6-31+G(d,p)
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -532.39914 Hartree

0 1

C	-2.04915400	-0.27029600	0.96610000
H	-1.98630400	-0.28592900	2.04671800
H	0.10677300	0.93401000	1.75935000
C	-2.99161200	-0.75957700	0.08852200
H	-3.91650900	-1.26324800	0.33128800
C	-2.47291600	-0.44992000	-1.18426300
H	-2.90240200	-0.65855700	-2.15656200
N	-1.30655300	0.18243200	-1.10650400
N	-1.07399800	0.29859900	0.21493500
C	0.19687300	0.84183300	0.66834000
C	0.47920800	2.19051600	0.04050800
H	0.53743200	2.10168900	-1.04703400
H	1.42598800	2.59487800	0.40986700
H	-0.32718200	2.88676000	0.29119500
C	1.25722100	-0.23582200	0.44411500

O	1.20870400	-1.31824200	0.97797000
O	2.22319300	0.14948900	-0.39163200
C	3.22251800	-0.83530500	-0.66678000
H	3.72756900	-1.13453100	0.25615600
H	3.92406500	-0.36367700	-1.35484200
H	2.76642100	-1.71715800	-1.12510400

 TS of **G** to **AA**

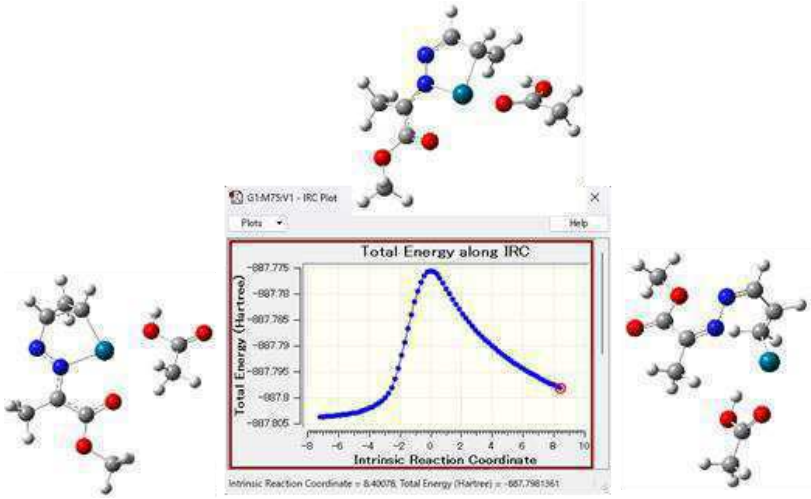
Calculation Method = RM06
Formula = C9H14N2O4Pd
Basis Set = 6-31g+(d,p)/ Lanl2DZ
Charge = 0
Spin = Singlet
Solvation = None
E(RM06) = -887.7756 Hartree
RMS Gradient Norm = 9.05e-07 Hartree/Bohr
Imaginary Freq = 1
Dipole Moment = 3.1007483 Debye
Polarizability (?) = 177.836 a.u.
Point Group = C1
Molecular Mass = 319.99884 amu
Job cpu time: 0 days 0 hours 19 minutes 4.7 seconds.

Thermo Tab Data Section:
Imaginary Freq = 1
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -887.7756 Hartree
Zero-point Energy Correction = 0.229774 Hartree
Thermal Correction to Energy = 0.248133 Hartree
Thermal Correction to Enthalpy = 0.249077 Hartree
Thermal Correction to Free Energy = 0.181798 Hartree

EE + Zero-point Energy = -887.54583 Hartree
EE + Thermal Energy Correction = -887.52747 Hartree
EE + Thermal Enthalpy Correction = -887.52652 Hartree
EE + Thermal Free Energy Correction = -887.5938 Hartree
E (Thermal) = 155.706 kcal/mol
Heat Capacity (Cv) = 64.309 cal/mol-kelvin
Entropy (S) = 141.601 cal/mol-kelvin

Basis Set = 6-31g+(d,p)/ Lanl2DZ
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -887.78706 Hartree

According to the IRC calculation, the transformation from **G** to **AA** proceeds via the TS like five-membered palladacycle to form alkene during releasing Pd, which coordinates to alkene terminus.



Calculation Type = IRC
Calculation Method =
Formula = C9H14N2O4Pd
Basis Set =
Charge = 0
Spin = Singlet
Solvation = None
E(RM06) = -887.7756 Hartree
RMS Gradient Norm = 9.39e-07 Hartree

Imaginary Freq =

Dipole Moment = 3.1008178 Debye

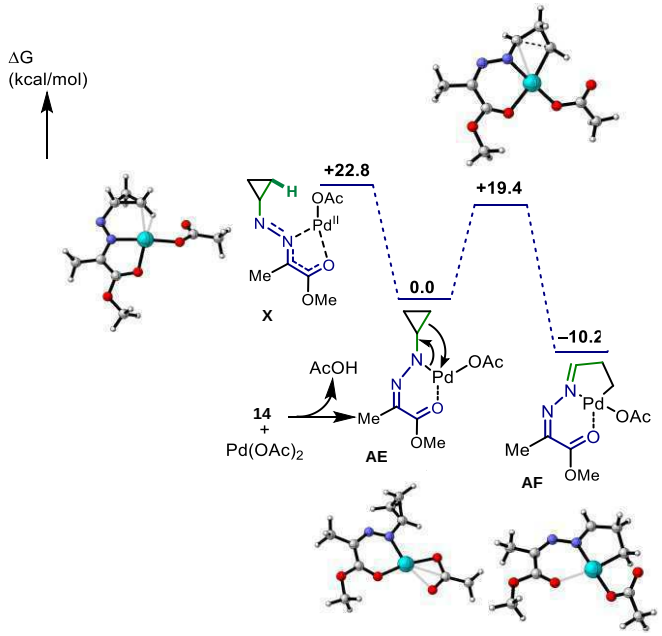
Polarizability (?) = 0 a.u.

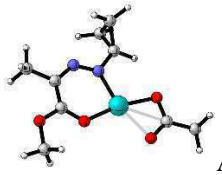
Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 9 hours 30 minutes 33.0 seconds.

DFT calculations [Scheme 54]





AE

Calculation Type = FREQ

Calculation Method = RM06

Basis Set = Gen

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -887.82426 Hartree

RMS Gradient Norm = 2.366e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 0.62056318 Debye

Polarizability (?) = 171.097 a.u.

Point Group = C1

Job cpu time: 0 days 0 hours 20 minutes 11.0 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -887.82426 Hartree
Zero-point Energy Correction = 0.234024 Hartree
Thermal Correction to Energy = 0.2523 Hartree
Thermal Correction to Enthalpy = 0.253245 Hartree
Thermal Correction to Free Energy = 0.185577 Hartree
EE + Zero-point Energy = -887.59024 Hartree
EE + Thermal Energy Correction = -887.57196 Hartree
EE + Thermal Enthalpy Correction = -887.57102 Hartree
EE + Thermal Free Energy Correction = -887.63868 Hartree
E (Thermal) = 158.321 kcal/mol
Heat Capacity (Cv) = 63.935 cal/mol-kelvin
Entropy (S) = 142.418 cal/mol-kelvin

Calculation Type = SP
Calculation Method = RM06
Basis Set = Gen
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -887.83427 Hartree

opt=calcfc freq gen m06 pseudo=read

0 1

C	0.05492700	3.69742500	0.80324200
H	-0.89455500	3.60111100	1.32153200
H	0.81712300	4.25968800	1.33305500
C	-0.00277100	3.75316500	-0.70451400
H	-0.98651800	3.68709800	-1.15936100
H	0.71889600	4.35494100	-1.24740800
C	0.49285100	2.51095900	-0.01229400
H	1.54828500	2.26991100	-0.06873000
N	-0.30838400	1.29966800	-0.03153200
N	-1.58341800	1.42770900	-0.02607900
C	-2.51384500	0.46949300	-0.01791000

C	-3.94812300	0.90548000	-0.03471600
H	-4.47621300	0.52762200	-0.91849800
H	-3.98532600	1.99769400	-0.04360900
H	-4.49317500	0.54027800	0.84395400
C	-2.19968600	-0.91386000	0.00234300
O	-1.03806000	-1.45269200	0.01554600
O	-3.27350800	-1.73662500	0.00952300
C	-3.02661200	-3.17261900	0.04172100
H	-2.47334600	-3.48073100	-0.84854300
H	-4.01795500	-3.62126900	0.06366000
H	-2.45254000	-3.43733000	0.93274700
Pd	0.70964800	-0.40642400	-0.00604600
O	2.70525100	0.28082900	-0.01675400
C	3.19060900	-0.93628300	-0.01320600
O	2.35278100	-1.91014900	-0.00619900
C	4.65852300	-1.14497000	0.00374600
H	5.07646500	-0.76220200	0.94197100
H	5.12483900	-0.58756400	-0.81394500
H	4.88589600	-2.20900700	-0.08280800

Pd 0

lanl2dz

****

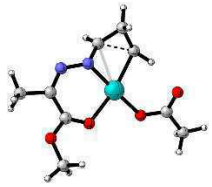
C H N O 0

6-31g+(d,p)

****

Pd 0

lanl2dz



TS of **AE** to **AF**

Calculation Type = FREQ

Calculation Method = RM06

Basis Set = Gen
Charge = 0
Spin = Singlet
Solvation = None
E(RM06) = -887.78269 Hartree
RMS Gradient Norm = 2.519e-06 Hartree/Bohr
Imaginary Freq = 1
Dipole Moment = 5.5019843 Debye
Polarizability (?) = 167.629 a.u.
Point Group = C1
Job cpu time: 0 days 0 hours 20 minutes 35.2 seconds.

Thermo Tab Data Section:
Imaginary Freq = 1
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -887.78269 Hartree
Zero-point Energy Correction = 0.230676 Hartree
Thermal Correction to Energy = 0.248893 Hartree
Thermal Correction to Enthalpy = 0.249837 Hartree
Thermal Correction to Free Energy = 0.182717 Hartree
EE + Zero-point Energy = -887.55202 Hartree
EE + Thermal Energy Correction = -887.5338 Hartree
EE + Thermal Enthalpy Correction = -887.53286 Hartree
EE + Thermal Free Energy Correction = -887.59998 Hartree
E (Thermal) = 156.183 kcal/mol
Heat Capacity (Cv) = 63.805 cal/mol-kelvin
Entropy (S) = 141.267 cal/mol-kelvin

Calculation Type = SP
Calculation Method = RM06
Basis Set = Gen
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -887.80055 Hartree

opt=(calcfc,qst3,noeigentest) freq m06/gen pseudo=read

Title Card Required

0 1

C	1.36031583	-1.02167937	0.02042227
H	1.92830965	-1.92476969	0.40882848
H	1.91270212	-0.64427253	-0.84422767
C	0.80690981	-0.07402812	1.07213035
H	0.78853833	-0.42463334	2.10798738
H	1.03955723	0.98827354	1.02877830
C	-0.16664061	-0.66767331	0.07516831
H	-0.55955762	-0.01431946	-0.72341561
N	-1.01830042	-1.77981258	0.47614022
N	-2.28215568	-1.75298376	0.12133420
C	-2.94228377	-2.90822631	0.02573132
C	-4.43742365	-2.84563993	-0.06259159
H	-4.79128281	-3.08089681	-1.07618547
H	-4.81820463	-1.84425934	0.19178550
H	-4.90699441	-3.56169670	0.62758972
C	-2.30609965	-4.23028150	-0.04033571
O	-1.10683161	-4.57614922	-0.09890035
O	-3.22689182	-5.24122594	-0.13784761
C	-2.68493492	-6.56725381	-0.41914242
H	-2.23420146	-6.56052179	-1.41741528
H	-3.57690919	-7.19815427	-0.36928983
H	-1.93486061	-6.83671468	0.33389277
Pd	0.35114256	-3.13295676	0.10036664
O	2.02598797	-6.14376181	0.07174311
C	2.67037717	-5.12205801	-0.13909957
O	2.14620384	-3.94147366	-0.24358549
C	4.17744571	-5.10158834	-0.31436459
H	4.55226422	-6.08176343	-0.62849707
H	4.67383088	-4.84013070	0.62673405
H	4.47613099	-4.35665881	-1.06054048

Title Card Required

0 1

C	1.71002372	-1.36971835	0.06966150
H	2.63348218	-1.63175976	0.59352854
H	1.90534788	-1.10358042	-0.97173056
C	0.78662493	-0.41259258	0.79179846
H	0.76636799	-0.66222170	1.88260971
H	1.10147229	0.64583276	0.72728611
C	-0.58061110	-0.61655578	0.18704796
H	-0.96908189	0.17558784	-0.46879529
N	-1.18856688	-1.74920643	0.47862950
N	-2.52607943	-1.81996493	0.15189645
C	-3.14269093	-2.95393339	0.01018239
C	-4.63133225	-2.90478970	-0.09203988
H	-4.98059673	-3.14241890	-1.10784701
H	-5.02430182	-1.90549356	0.16634232
H	-5.09535076	-3.63250654	0.59355096
C	-2.46264744	-4.30801480	-0.05274479
O	-1.28087769	-4.54688479	0.02689407
O	-3.38333537	-5.31176069	-0.24172000
C	-2.80793376	-6.63733298	-0.45562767
H	-2.34209902	-6.65190928	-1.44672590
H	-3.67834074	-7.29484571	-0.39252772
H	-2.05813985	-6.86040840	0.31510440
Pd	0.56079601	-3.02508065	0.14657902
O	1.89957548	-6.03979619	0.04407897
C	2.64853325	-5.08731293	-0.14675342
O	2.29922868	-3.84179008	-0.22051686
C	4.14901918	-5.21615644	-0.35021786
H	4.43077953	-6.22528042	-0.66123956
H	4.67764584	-4.98054612	0.58010186
H	4.48918832	-4.49974625	-1.10800525

Title Card Required

0 1

C	1.50923686	-1.17868102	0.03319980
H	2.24645429	-1.86102528	0.51557858
H	1.87733194	-0.81893281	-0.92333227
C	0.80791378	-0.21681373	0.96005122
H	0.79943519	-0.52571837	2.02186967
H	1.07235712	0.84725017	0.90841741
C	-0.34803648	-0.67442249	0.14412186
H	-0.67839464	-0.00514325	-0.67024481
N	-1.10679259	-1.75370775	0.55989081
N	-2.38717379	-1.79547576	0.12240480
C	-3.02803731	-2.92802516	0.00910789
C	-4.52069176	-2.87184419	-0.08154765
H	-4.87681245	-3.10854492	-1.09307317
H	-4.90647980	-1.87171697	0.17964601
H	-4.98440357	-3.59212651	0.61122400
C	-2.36622631	-4.27392649	-0.04458417
O	-1.17822531	-4.55987693	-0.04881863
O	-3.29528138	-5.27498245	-0.17966476
C	-2.74021873	-6.60105463	-0.43427579
H	-2.28180597	-6.60033365	-1.42923488
H	-3.62207753	-7.24386060	-0.37948514
H	-1.98846907	-6.84842109	0.32590518
Pd	0.41827797	-2.99989349	0.08450394
O	1.96659790	-6.08387811	0.05815262
C	2.65095538	-5.08563695	-0.14313083
O	2.20376211	-3.87280058	-0.23374985
C	4.15988724	-5.14426302	-0.32927973
H	4.49290122	-6.14042367	-0.64106283
H	4.67375263	-4.89936902	0.60660429
H	4.48239640	-4.41617270	-1.08158682

Pd 0

lanl2dz

****

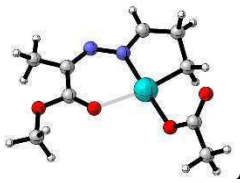
C H N O 0

6-31g+(d,p)

****

Pd 0

lanl2dz



AF

Calculation Type = FREQ

Calculation Method = RM06

Basis Set = Gen

Charge = 0

Spin = Singlet

Solvation = None

E(RM06) = -887.82668 Hartree

RMS Gradient Norm = 1.338e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 8.5028182 Debye

Polarizability (?) = 164.93433 a.u.

Point Group = C1

Job cpu time: 0 days 0 hours 20 minutes 6.0 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -887.82668 Hartree

Zero-point Energy Correction = 0.23233 Hartree

Thermal Correction to Energy = 0.250926 Hartree

Thermal Correction to Enthalpy = 0.251871 Hartree

Thermal Correction to Free Energy = 0.182821 Hartree

EE + Zero-point Energy = -887.59435 Hartree

EE + Thermal Energy Correction = -887.57575 Hartree

EE + Thermal Enthalpy Correction = -887.57481 Hartree
EE + Thermal Free Energy Correction = -887.64386 Hartree
E (Thermal) = 157.459 kcal/mol
Heat Capacity (Cv) = 64.772 cal/mol-kelvin
Entropy (S) = 145.328 cal/mol-kelvin

Calculation Type = SP
Calculation Method = RM06
Basis Set = Gen
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RM06) = -887.84791 Hartree

opt freq gen m06 pseudo=read

Title Card Required

0 1

C	-0.99876694	0.45006165	0.00000000
H	-1.91552194	0.70957065	0.53371900
H	-1.17530494	0.34798065	-1.07784500
C	-0.26347394	-0.76564835	0.58905700
H	-0.53865394	-0.87539535	1.65289900
H	-0.55168894	-1.71553235	0.11233100
C	1.20368806	-0.60385135	0.54135400
H	1.90714306	-1.43257435	0.64029400
N	1.67285706	0.60792965	0.40937600
N	3.07305006	0.66740665	0.41255700
C	3.71116106	1.79622665	0.40775000
C	5.20376906	1.69750365	0.41018400
H	5.63118406	2.20873965	-0.45957600
H	5.48925706	0.64437465	0.39473700
H	5.62637006	2.18192465	1.29727400
C	3.12943806	3.17716965	0.41318600
O	1.93824806	3.51608965	0.34511600

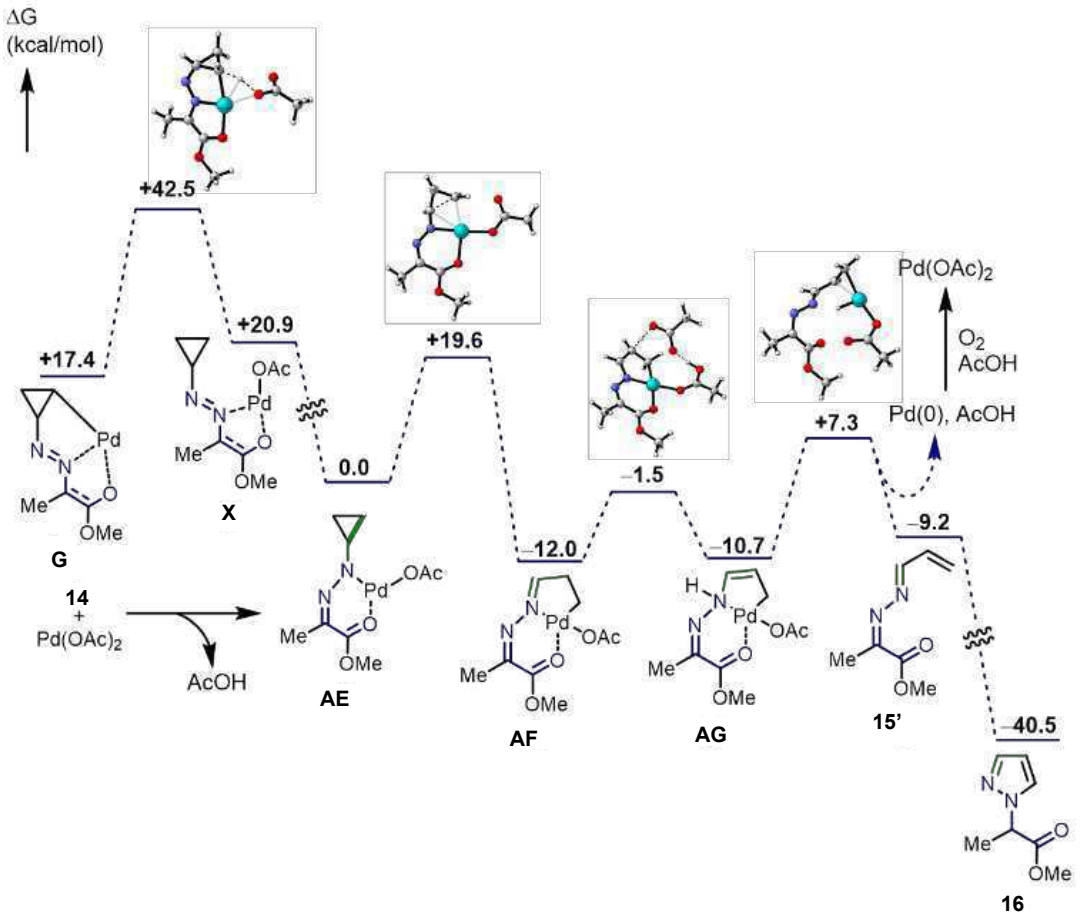
O	4.10583806	4.10483465	0.50751700
C	3.68809006	5.50701865	0.52505700
H	3.13892706	5.74005365	-0.38993000
H	4.61558506	6.07107765	0.59076700
H	3.04503706	5.68965165	1.38890900
Pd	0.24021806	2.04643665	0.17259400
O	-2.67538694	2.64992965	1.45841700
C	-2.33256794	3.47846465	0.58892600
O	-1.21635094	3.43631465	-0.11768800
C	-3.19947994	4.66684265	0.23889300
H	-4.10474094	4.65990065	0.84908800
H	-3.46386194	4.63384665	-0.82352400
H	-2.64294794	5.59521765	0.40594200

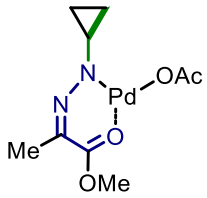
Pd 0
lanl2dz
****
C H N O 0
6-31g+(d,p)
****

Pd 0
lanl2dz

DFT calculations [Scheme 56].

The molecular geometries for each transition states were first estimated with the *Reaction plus* software package, based on the nudged elastic band method, [86] and were subsequently re-optimized using the Gaussian 16 software package. [87] Once the stationary points were obtained at B97D/6-31G+(d, p)-def2TZV (Lanl2DZ for Pd) level, [89, 90, 93, 94] the harmonic vibrational frequencies were calculated at the same level to estimate the Gibbs free energy. The nature of the stationary points was characterized *via* vibrational analysis. All of the Gibbs free energy values reported in this paper were calculated for a temperature of 298.15 K. The transition structure reported was optimized without constraints and the intrinsic reaction coordinate (IRC) route was calculated in both directions toward the corresponding minima for each transition-state structure. The IRC calculation failed to reach the energy minima on the potential energy surface for the transition states, and we therefore carried out geometry optimizations as a continuation of the IRC path. For each optimized structure (potential energy minimum or transition state computed at B97D/6-31G+(d, p)-def2TZV (Lanl2DZ for Pd) level), additional single-point energy calculations in the presence of chlorobenzene were performed at the same level. The 3D optimized structural figures in this paper were displayed by the CYLview visualization program. [92]





AE

Calculation Type = FREQ

Calculation Method = RB97D

Formula = C9H14N2O4Pd

Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = None

E(RB97D) = -888.148 Hartree

RMS Gradient Norm = 1.357e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 0.806392 Debye

Polarizability (?) = 186.15633 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 9 minutes 45.3 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -888.148 Hartree

Zero-point Energy Correction = 0.225096 Hartree

Thermal Correction to Energy = 0.244167 Hartree

Thermal Correction to Enthalpy = 0.245112 Hartree

Thermal Correction to Free Energy = 0.175058 Hartree

EE + Zero-point Energy = -887.9229 Hartree

EE + Thermal Energy Correction = -887.90383 Hartree

EE + Thermal Enthalpy Correction = -887.90289 Hartree

EE + Thermal Free Energy Correction = -887.97294 Hartree

E (Thermal) = 153.217 kcal/mol

Heat Capacity (Cv) = 66.252 cal/mol-kelvin

Entropy (S) = 147.439 cal/mol-kelvin

Calculation Type = SP

Calculation Method = RB97D

Formula = C9H14N2O4Pd

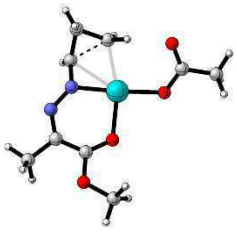
Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = scrf=solvent=chlorobenzene

E(RB97D) = -888.15772 Hartree



TS of **AE** to **AF**

Calculation Type = FREQ

Calculation Method = RB97D

Formula = C9H14N2O4Pd

Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = None

E(RB97D) = -888.109 Hartree

RMS Gradient Norm = 2.05e-07 Hartree/Bohr

Imaginary Freq = 1

Dipole Moment = 4.6693763 Debye

Polarizability (?) = 185.76033 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 11 minutes 19.5 seconds.

Thermo Tab Data Section:

Imaginary Freq = 1

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -888.109 Hartree

Zero-point Energy Correction = 0.22219 Hartree

Thermal Correction to Energy = 0.241022 Hartree

Thermal Correction to Enthalpy = 0.241966 Hartree

Thermal Correction to Free Energy = 0.173658 Hartree

EE + Zero-point Energy = -887.8868 Hartree

EE + Thermal Energy Correction = -887.86797 Hartree

EE + Thermal Enthalpy Correction = -887.86703 Hartree

EE + Thermal Free Energy Correction = -887.93534 Hartree

E (Thermal) = 151.243 kcal/mol

Heat Capacity (Cv) = 65.944 cal/mol-kelvin

Entropy (S) = 143.767 cal/mol-kelvin

Calculation Type = SP

Calculation Method = RB97D

Formula = C9H14N2O4Pd

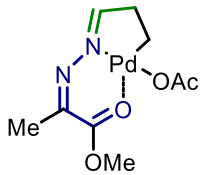
Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = scrf=solvent=chlorobenzene

E(RB97D) = -888.12516 Hartree



AF

Calculation Type = FREQ

Calculation Method = RB97D

Formula = C9H14N2O4Pd

Basis Set = Gen/def2TZV

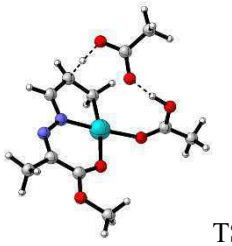
Charge = 0

Spin = Singlet

Solvation = None
E(RB97D) = -888.15572 Hartree
RMS Gradient Norm = 8.292e-06 Hartree/Bohr
Imaginary Freq = 0
Dipole Moment = 7.8355929 Debye
Polarizability (?) = 183.897 a.u.
Point Group = C1
Molecular Mass = 319.99884 amu
Job cpu time: 0 days 0 hours 10 minutes 3.1 seconds.

Thermo Tab Data Section:
Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -888.15572 Hartree
Zero-point Energy Correction = 0.223323 Hartree
Thermal Correction to Energy = 0.242619 Hartree
Thermal Correction to Enthalpy = 0.243564 Hartree
Thermal Correction to Free Energy = 0.172917 Hartree
EE + Zero-point Energy = -887.93239 Hartree
EE + Thermal Energy Correction = -887.9131 Hartree
EE + Thermal Enthalpy Correction = -887.91215 Hartree
EE + Thermal Free Energy Correction = -887.9828 Hartree
E (Thermal) = 152.246 kcal/mol
Heat Capacity (Cv) = 67.114 cal/mol-kelvin
Entropy (S) = 148.689 cal/mol-kelvin

Calculation Type = SP
Calculation Method = RB97D
Formula = C9H14N2O4Pd
Basis Set = Gen/def2TZV
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RB97D) = -888.17472 Hartree



TS of **AF** to **AG**

Calculation Type = FREQ

Calculation Method = RB97D

Formula = C11H18N2O6Pd

Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = None

E(RB97D) = -1117.0687 Hartree

RMS Gradient Norm = 6.51e-07 Hartree/Bohr

Imaginary Freq = 1

Dipole Moment = 3.1427077 Debye

Polarizability (?) = 226.46933 a.u.

Point Group = C1

Molecular Mass = 380.01997 amu

Job cpu time: 0 days 0 hours 20 minutes 42.0 seconds.

Thermo Tab Data Section:

Imaginary Freq = 1

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -1117.0687 Hartree

Zero-point Energy Correction = 0.27912 Hartree

Thermal Correction to Energy = 0.303315 Hartree

Thermal Correction to Enthalpy = 0.304259 Hartree

Thermal Correction to Free Energy = 0.222463 Hartree

EE + Zero-point Energy = -1116.7896 Hartree

EE + Thermal Energy Correction = -1116.7654 Hartree

EE + Thermal Enthalpy Correction = -1116.7645 Hartree

EE + Thermal Free Energy Correction = -1116.8463 Hartree

E (Thermal) = 190.333 kcal/mol

Heat Capacity (Cv) = 84.446 cal/mol-kelvin

Entropy (S) = 172.153 cal/mol-kelvin

Calculation Type = SP

Calculation Method = RB97D

Formula = C11H18N2O6Pd

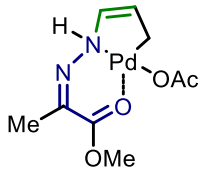
Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = scrf=solvent=chlorobenzene

E(RB97D) = -1117.0809 Hartree



AG

Calculation Type = FREQ

Calculation Method = RB97D

Formula = C11H18N2O6Pd

Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = None

E(RB97D) = -1117.0903 Hartree

RMS Gradient Norm = 5.662e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 3.4031855 Debye

Polarizability (?) = 210.37667 a.u.

Point Group = C1

Molecular Mass = 380.01997 amu

Job cpu time: 0 days 0 hours 20 minutes 15.9 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -1117.0903 Hartree

Zero-point Energy Correction = 0.284129 Hartree

Thermal Correction to Energy = 0.309021 Hartree

Thermal Correction to Enthalpy = 0.309965 Hartree

Thermal Correction to Free Energy = 0.227344 Hartree

EE + Zero-point Energy = -1116.8062 Hartree

EE + Thermal Energy Correction = -1116.7813 Hartree

EE + Thermal Enthalpy Correction = -1116.7804 Hartree

EE + Thermal Free Energy Correction = -1116.863 Hartree

E (Thermal) = 193.914 kcal/mol

Heat Capacity (Cv) = 86.506 cal/mol-kelvin

Entropy (S) = 173.891 cal/mol-kelvin

Calculation Type = SP

Calculation Method = RB97D

Formula = C11H18N2O6Pd

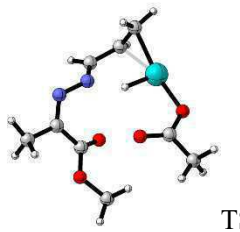
Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = scrf=solvent=chlorobenzene

E(RB97D) = -1117.1005 Hartree



TS of **AG** to **15'**

Calculation Type = FREQ

Calculation Method = RB97D

Formula = C9H14N2O4Pd

Basis Set = Gen/def2TZV

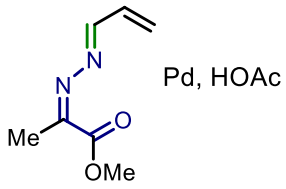
Charge = 0

Spin = Singlet

Solvation = None
E(RB97D) = -888.1084 Hartree
RMS Gradient Norm = 6.28e-07 Hartree/Bohr
Imaginary Freq = 1
Dipole Moment = 3.3307199 Debye
Polarizability (?) = 179.039 a.u.
Point Group = C1
Molecular Mass = 319.99884 amu
Job cpu time: 0 days 0 hours 12 minutes 12.4 seconds.

Thermo Tab Data Section:
Imaginary Freq = 1
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -888.1084 Hartree
Zero-point Energy Correction = 0.217867 Hartree
Thermal Correction to Energy = 0.237248 Hartree
Thermal Correction to Enthalpy = 0.238193 Hartree
Thermal Correction to Free Energy = 0.167882 Hartree
EE + Zero-point Energy = -887.89053 Hartree
EE + Thermal Energy Correction = -887.87115 Hartree
EE + Thermal Enthalpy Correction = -887.8702 Hartree
EE + Thermal Free Energy Correction = -887.94051 Hartree
E (Thermal) = 148.876 kcal/mol
Heat Capacity (Cv) = 67.511 cal/mol-kelvin
Entropy (S) = 147.981 cal/mol-kelvin

Calculation Type = SP
Calculation Method = RB97D
Formula = C9H14N2O4Pd
Basis Set = Gen/def2TZV
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RB97D) = -888.12573 Hartree



15''

Calculation Type = FREQ

Calculation Method = RB97D

Formula = C9H14N2O4Pd

Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = None

E(RB97D) = -888.14357 Hartree

RMS Gradient Norm = 7.35e-07 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 5.0263615 Debye

Polarizability (?) = 185.268 a.u.

Point Group = C1

Molecular Mass = 319.99884 amu

Job cpu time: 0 days 0 hours 10 minutes 33.0 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -888.14357 Hartree

Zero-point Energy Correction = 0.222602 Hartree

Thermal Correction to Energy = 0.242858 Hartree

Thermal Correction to Enthalpy = 0.243802 Hartree

Thermal Correction to Free Energy = 0.169869 Hartree

EE + Zero-point Energy = -887.92097 Hartree

EE + Thermal Energy Correction = -887.90071 Hartree

EE + Thermal Enthalpy Correction = -887.89977 Hartree

EE + Thermal Free Energy Correction = -887.9737 Hartree

E (Thermal) = 152.396 kcal/mol

Heat Capacity (Cv) = 68.508 cal/mol-kelvin

Entropy (S) = 155.607 cal/mol-kelvin

Calculation Type = SP

Calculation Method = RB97D

Formula = C9H14N2O4Pd

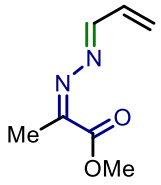
Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = scrf=solvent=chlorobenzene

E(RB97D) = -888.15397 Hartree



15'

Calculation Type = FREQ

Calculation Method = RB97D

Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = None

E(RB97D) = -532.19975 Hartree

RMS Gradient Norm = 1.208e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 1.9878389 Debye

Polarizability (?) = 114.66267 a.u.

Point Group = C1

Job cpu time: 0 days 0 hours 2 minutes 19.0 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0

Temperature = 298.15 Kelvin

Pressure = 1 atm

Frequencies scaled by = 1

Electronic Energy (EE) = -532.19975 Hartree

Zero-point Energy Correction = 0.160591 Hartree

Thermal Correction to Energy = 0.173441 Hartree

Thermal Correction to Enthalpy = 0.174385 Hartree

Thermal Correction to Free Energy = 0.119784 Hartree

EE + Zero-point Energy = -532.03916 Hartree

EE + Thermal Energy Correction = -532.02631 Hartree

EE + Thermal Enthalpy Correction = -532.02537 Hartree

EE + Thermal Free Energy Correction = -532.07997 Hartree

E (Thermal) = 108.836 kcal/mol

Heat Capacity (Cv) = 43.976 cal/mol-kelvin

Entropy (S) = 114.918 cal/mol-kelvin

Calculation Type = SP

Calculation Method = RB97D

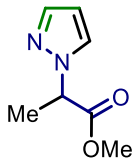
Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = scrf=solvent=chlorobenzene

E(RB97D) = -532.20711 Hartree



16

Calculation Type = FREQ

Calculation Method = RB97D

Basis Set = Gen/def2TZV

Charge = 0

Spin = Singlet

Solvation = None

E(RB97D) = -532.24546 Hartree

RMS Gradient Norm = 2.446e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 3.7857682 Debye
Polarizability (?) = 90.126333 a.u.
Point Group = C1
Job cpu time: 0 days 0 hours 2 minutes 1.0 seconds.

Thermo Tab Data Section:
Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -532.24546 Hartree
Zero-point Energy Correction = 0.164093 Hartree
Thermal Correction to Energy = 0.175653 Hartree
Thermal Correction to Enthalpy = 0.176597 Hartree
Thermal Correction to Free Energy = 0.12526 Hartree
EE + Zero-point Energy = -532.08137 Hartree
EE + Thermal Energy Correction = -532.06981 Hartree
EE + Thermal Enthalpy Correction = -532.06886 Hartree
EE + Thermal Free Energy Correction = -532.1202 Hartree
E (Thermal) = 110.224 kcal/mol
Heat Capacity (Cv) = 41.07 cal/mol-kelvin
Entropy (S) = 108.047 cal/mol-kelvin

Calculation Type = SP
Calculation Method = RB97D
Basis Set = Gen/def2TZV
Charge = 0
Spin = Singlet
Solvation = scrf=solvent=chlorobenzene
E(RB97D) = -532.25353 Hartree

第 7 節　第 3 章第 1 節の実験

[Table 8, entry 3]. *N*-Cyclopropylhydrazone **14ac** (21.4 mg, 0.0921 mmol), 4-iodotoluene (40.2 mg, 0.184 mmol), $Pd(OAc)_2$ (4.1 mg, 0.018 mmol), (*o*-tol)$_3$P (11.2 mg, 0.0368 mmol) and Cs_2CO_3 (59.9 mg, 0.184 mmol) were dissolved in xylene (1.84 mL). The mixture was stirred at 80 °C under argon for 17 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (5.9 mg, 0.037 mmol) was added. Then the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **18aa** (10.2 mg, 35%).

Ethyl 2-(5-(4-methylphenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18aa). white solid; Mp: 90-92 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 2.0 Hz, 1H), 7.35 (s, 4H), 7.26-7.24 (m, 5H), 6.30 (d, *J* = 1.6 Hz, 1H), 6.02 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.6, 144.7, 139.8, 138.9, 135.3, 129.5, 129.1, 128.7, 128.5, 127.5, 106.2, 64.5, 62.0, 21.3, 14.0; One carbon peak could not be detected probably due to overlapping; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}O_2N_2$ $[M+H]^+$ 321.1598, found 321.1598.

[Table 8, entry 4]. *N*-Cyclopropylhydrazone **14ac** (19.4 mg, 0.0835 mmol), 4-iodotoluene (36.4 mg, 0.167 mmol), $Pd(OAc)_2$ (3.8 mg, 0.017 mmol), (*o*-tol)$_3$P (10.2 mg, 0.0334 mmol) and Cs_2CO_3 (54.4 mg, 0.167 mmol) were dissolved in benzonitrile (1.67 mL). The mixture was stirred at 80 °C under argon for 5 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (5.4 mg, 0.033 mmol) was added. Then the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **18aa** (15.1 mg, 56%).

[Table 8, entry 5]. *N*-Cyclopropylhydrazone **14ac** (22.3 mg, 0.0960 mmol), 4-iodotoluene (41.9 mg, 0.192 mmol), $Pd(OAc)_2$ (4.3 mg, 0.019 mmol), (*o*-tol)$_3$P (11.7 mg, 0.0380 mmol) and Cs_2CO_3 (62.6 mg, 0.192 mmol) were dissolved in benzonitrile (1.92 mL). The mixture was stirred at 80 °C under argon for 12 h. After the formation of **17aa** was confirmed on TLC, the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **18aa** (14.2 mg, 46%).

[Table 8, entry 6]. *N*-Cyclopropylhydrazone **14ac** (18.7 mg, 0.0805 mmol), 4-iodotoluene (35.1 mg, 0.161 mmol), $Pd(OAc)_2$ (3.6 mg, 0.016 mmol), Ph_3P (8.45 mg, 0.0322 mmol) and Cs_2CO_3 (52.5 mg, 0.161 mmol) were dissolved in benzonitrile (1.61 mL). The mixture was stirred at 80 °C under argon for 2 h. After the formation of **17aa** was confirmed on TLC potassium ethyl xanthate (5.2 mg, 0.032

mmol) was added. Then the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The mixture was analyzed by ^{1}H NMR ($CDCl_3$). Pyrazole **18aa** was calculated as 36% NMR yield.

[Table 8, entry 7]. *N*-Cyclopropylhydrazone **14ac** (21.5 mg, 0.0926 mmol), 4-iodotoluene (40.6 mg, 0.186 mmol), $Pd(OAc)_2$ (4.2 mg, 0.019 mmol), (t-Bu)$_3$P (9.0 µL, 0.0372 mmol) and Cs_2CO_3 (60.6 mg, 0.190 mmol) were dissolved in benzonitrile (1.86 mL). The mixture was stirred at 80 °C under argon for 17 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (6.0 mg, 0.037 mmol) was added. Then the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The mixture was analyzed by ^{1}H NMR ($CDCl_3$). Pyrazole **18aa** was calculated as 10% NMR yield.

[Table 8, entry 8]. *N*-Cyclopropylhydrazone **14ac** (19.5 mg, 0.0840 mmol), 4-iodotoluene (36.6 mg, 0.168 mmol), $Pd(OAc)_2$ (3.8 mg, 0.017 mmol), Johnphos (10.0 mg, 0.0336 mmol) and Cs_2CO_3 (54.7 mg, 0.168 mmol) were dissolved in benzonitrile (1.68 mL). The mixture was stirred at 80 °C under argon for 17 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (5.4 mg, 0.034 mmol) was added. Then the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The mixture was analyzed by ^{1}H NMR ($CDCl_3$). Pyrazole **18aa** was calculated as 5% NMR yield.

[Table 8, entry 9]. *N*-Cyclopropylhydrazone **14ac** (19.3 mg, 0.0831 mmol), 4-iodotoluene (36.2 mg, 0.166 mmol), Herrmann catalyst (7.8 mg, 0.0083 mmol), and Cs_2CO_3 (54.1 mg, 0.166 mmol) were dissolved in benzonitrile (2.0 mL). The mixture was stirred at 80 °C under argon for 12 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (5.3 mg, 0.033 mmol) was added. Then the mixture was stirred at 150 °C for 5 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **18aa** (15.2 mg, 57%).

[Table 8, entry 10]. *N*-Cyclopropylhydrazone **14ac** (22.6 mg, 0.0972 mmol), 4-iodotoluene (42.4 mg, 0.195 mmol), Herrmann catalyst (9.1 mg, 0.0097 mmol), LiCl (0.82 mg, 0.019 mmol) and Cs_2CO_3 (63.2 mg, 0.194 mmol) were dissolved in benzonitrile (2.0 mL). The mixture was stirred at 80 °C under argon for 21 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (6.3 mg, 0.039 mmol) was added. Then the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **18aa** (16.9 mg, 54%).

[Table 8, entry 11]. *N*-Cyclopropylhydrazone **14ac** (18.4 mg, 0.0792 mmol), 4-iodotoluene (34.5 mg,

0.158 mmol), Herrmann catalyst (7.4 mg, 0.0079 mmol), *n*-Bu_4NOAc (4.8 mg, 0.016 mmol) and Cs_2CO_3 (51.5 mg, 0.158 mmol) were dissolved in benzonitrile (2.0 mL). The mixture was stirred at 80 °C under argon for 19 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (5.1 mg, 0.032 mmol) was added. Then the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **18aa** (15.5 mg, 61%).

[Table 8, entry 12]. *N*-Cyclopropylhydrazone **14ac** (18.0 mg, 0.0775 mmol), 4-iodotoluene (33.8 mg, 0.155 mmol), Herrmann catalyst (7.3 mg, 0.0078 mmol), *n*-Bu_4NI (5.8 mg, 0.016 mmol) and Cs_2CO_3 (50.8 mg, 0.156 mmol) were dissolved in benzonitrile (2.0 mL). The mixture was stirred at 80 °C under argon for 7 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (5.0 mg, 0.031 mmol) was added. Then the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **18aa** (15.2 mg, 61%).

[Table 8, entry 13]. *N*-Cyclopropylhydrazone **14ac** (19.8 mg, 0.0852 mmol), 4-iodotoluene (37.2 mg, 0.171 mmol), Herrmann catalyst (8.0 mg, 0.0085 mmol), *n*-Bu_4NOAc (5.1 mg, 0.017 mmol) and Et_3N (24 μL, 0.170 mmol) were dissolved in benzonitrile (1.7 mL). The mixture was stirred at 80 °C under argon for 36 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (5.5 mg, 0.034 mmol) was added. Then the mixture was stirred at 150 °C for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The mixture was analyzed by ^1H NMR ($CDCl_3$). Pyrazole **18aa** was calculated as 4% NMR yield.

[Table 8, entry 14]. *N*-Cyclopropylhydrazone **14ac** (19.4 mg, 0.0835 mmol), 4-iodotoluene (36.4 mg, 0.167 mmol), Herrmann catalyst (7.9 mg, 0.0084 mmol), *n*-Bu_4NOAc (5.1 mg, 0.017 mmol) and KOH (9.4 mg, 0.168 mmol) were dissolved in benzonitrile (2.0 mL). The mixture was stirred at 80 °C under argon for 65 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (5.3 mg, 0.033 mmol) was added. Then the mixture was stirred at 150 °C for 4.5 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **18aa** (13.7 mg, 51%).

[Table 8, entry 15]. *N*-Cyclopropylhydrazone **14ac** (21.8 mg, 0.0939 mmol), 4-iodotoluene (40.9 mg, 0.188 mmol), Herrmann catalyst (8.8 mg, 0.0094 mmol), *n*-Bu_4NOAc (5.7 mg, 0.019 mmol) and K_2CO_3 (26.0 mg, 0.188 mmol) were dissolved in benzonitrile (2.0 mL). The mixture stirred at 80 °C under argon for 67 h. After the formation of **17aa** was confirmed on TLC, potassium ethyl xanthate (6.0 mg, 0.038 mmol) was added. Then the mixture was stirred at 150 °C for 4.5 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified

by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **18aa** (17.5 mg, 58%).

第 8 節　第 3 章第 2 節の実験

Ethyl 2-phenyl-((3-(4-methylphenyl)allylidene)hydrazineylidene)acetate (17aa) [Scheme 67]. *N*-Cyclopropylhydrazone **14ac** (22.7 mg, 0.0977 mmol), *p*-tol-I (42.6 mg, 0.196 mmol), Herrmann catalyst (9.2 mg, 0.0098 mmol), *n*-Bu_4NI (7.2 mg, 0.020 mmol) and Cs_2CO_3 (63.9 mg, 0.196 mmol) were dissolved in benzonitrile (2.0 mL). The mixture was stirred at 80 °C under argon for 3 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford 5-arylated conjugated azine **17aa** (22.2 mg, 71%) as a yellow solid; Mp: 83 °C (decomp.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.8 Hz, 1H), 7.82-7.80 (m, 2H), 7.48-7.42 (m, 5H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.12-7.00 (m, 2H), 4.50 (q, J = 7.6 Hz, 2H), 2.38 (s, 3H), 1.43 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9, 165.0, 161.0, 144.3, 140.0, 132.9, 131.7, 131.4, 129.6, 128.8, 127.5, 127.5, 124.4, 61.5, 21.4, 14.3; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}O_2N_2$ $[M+H]^+$ 321.1598, found 321.1599.

Ethyl 2-phenyl-((3-(4-methylphenyl)allylidene)hydrazineylidene)acetate (17aa) [Scheme 69, eq. 1]. Azine **15ac** (21.0 mg, 0.0912 mmol), *N*-cyclopropylhydrazone **14ac** (4.7 mg, 0.0202 mmol), 4-iodotoluene (39.8 mg, 0.182 mmol), Herrmann catalyst (8.6 mg, 0.0091 mmol), *n*-Bu_4NI (6.7 mg, 0.018 mmol) and Cs_2CO_3 (59.3 mg, 0.182 mmol) were dissolved in benzonitrile (1.8 mL). The mixture was stirred at 80 °C under argon for 5 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by PTLC (hexane/EtOAc = 5 : 1) to afford 5-arylated conjugated azine **17aa** (23.4 mg, 58%, based on the subtracted amount of **14ac**).

Ethyl 2-phenyl-((3-(4-methylphenyl)allylidene)hydrazineylidene)acetate (17aa) [Scheme 69, eq. 2]. Azine **15ac** (24.1 mg, 0.105 mmol), *p*-tol-I (45.6 mg, 0.209 mmol), $Pd(OAc)_2$ (4.7 mg, 0.021 mmol), $(o\text{-tol})_3P$ (12.8 mg, 0.0420 mmol) and Cs_2CO_3 (68.4 mg, 0.210 mmol) were dissolved in benzonitrile (2.1 mL). The mixture was stirred at 80 °C under argon for 30 h. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by PTLC (hexane/EtOAc = 7 : 3) to afford 5-arylated conjugated azine **17aa** (6.6 mg, 20%).

Ethyl 2-(5-(4-methylphenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18aa) [Scheme 70]. Azine **15ac** (12.0 mg, 0.0380 mmol) was dissolved in benzonitrile (1.0 mL) and the mixture was stirred at 150 °C for 3 h. Then the resulting mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by PTLC (hexane/EtOAc = 5 : 1) to afford pyrazole **18aa** (7.5 mg, 63%).

第 9 節　第 3 章第 3 節の実験

General procedure for preparing cyclopropylhydrazones [Table 9]. To a solution of α-keto esters in MeOH were added cyclopropylhydrazine (1.0 eq.) and pyridine (2.0 eq.). The mixture was stirred at room temperature for several hours, and then evaporated. The crude product was purified by column chromatography to afford cyclopropylhydrazones.

Ethyl (*Z*)-2-(2-cyclopropylhydrazineylidene)-2-(naphthalen-2-yl)acetate (14da) [Table 9, entry 1]. Following to the general procedure, ethyl 2-(naphthalen-2-yl)-2-oxoacetate **70at** (228 mg, 1.00 mmol), cyclopropylhydrazine (416 mg, 1.00 mmol) and pyridine (161 μL, 2.00 mmol) were used and the reaction time was 16 h. **14da** (49.9 mg, 53%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 7.98 (s, 1H), 7.84-7.77 (m, 3H), 7.70-7.67 (m, 1H), 7.47-7.41 (m, 2H), 4.33-4.28 (m, 2H), 3.12-3.06 (m, 1H), 1.35-1.31 (m, 3H), 0.87-0.77 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.7, 134.5, 133.2, 132.5, 128.2, 127.4, 127.1, 127.0, 126.6, 126.3, 125.8, 125.7, 60.5, 31.9, 14.2, 6.3; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}O_2N_2$ $[M+H]^+$ 283.1441, found 283.1443.

(*Z*)-Ethyl 4-(ethoxycarbonyl)-2-(2-cyclopropyl hydrazinylidene)benzene acetate (14db) [Table 9, entry 2]. Following to the general procedure, ethyl 4-(2-ethoxy-2-oxoacetyl)benzoate **70au** (250 mg, 1.00 mmol), cyclopropylhydrazine (416 mg, 1.00 mmol) and pyridine (161 μL, 2.00 mmol) were used and the reaction time was 12 h. **14db** (188 mg, 62%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 4.40-4.34 (m, 2H), 4.30-4.25 (m, 2H), 3.10-3.05 (m, 1H), 1.41-1.37 (m, 3H), 1.33-1.30 (m, 3H), 0.85-0.77 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.6, 163.4, 141.5, 129.0, 128.4, 127.9, 124.9, 60.8, 60.5, 32.1, 14.3, 14.2, 6.2; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}O_4N_2$ $[M+H]^+$ 305.1496, found 305.1497.

General procedure of preparing α-keto ester [Table 10]. To a solution of ketone (1.0 eq.) in pyridine (7.0 eq.) was added SeO_2 (2.0 eq.). The mixture was stirred at 100 °C for 1 h. After the mixture was cooled to room temperature, the mixture was filtered with Celite®. Then 1M HCl was added and the mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to afford crude carboxylic acid. Then the crude mixture was dissolved in EtOH (10 mL) and H_2SO_4 (1.0 mL) was added. The mixture was stirred at reflux for 1 h and cooled to room temperature. Then the residue was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. α-Keto ester was obtained after purification with flash column chromatography.

Ethyl 2-(naphthalen-2-yl)-2-oxoacetate (70at) [Table 10, entry 1]. Following to the general procedure using commercially available 1-(naphthalen-2-yl)ethan-1-one **71at** (511 mg, 3.00 mmol), SeO_2 (666 mg, 6.00 mmol) and pyridine (1.70 mL, 21.0 mmol), ethyl 2-(naphthalen-2-yl)-2-oxoacetate **70at** (612 mg, 89%) was obtained after purification by flash column chromatography (hexane/EtOAc). The spectral data were identical with those reported in the literature. [95)]

Ethyl 4-(2-ethoxy-2-oxoacetyl)benzoate (70au) [Table 10, entry 2]. Following to the general procedure using commercially available ethyl 4-acetylbenzoate **71au** (577 mg, 3.00 mmol), SeO_2 (666 mg, 6.00 mmol) and pyridine (1.70 mL, 21.0 mmol), Ethyl 2-(naphthalen-2-yl)-2-oxoacetate **70au** (250 mg, 33%) was obtained after purification by flash column chromatography (hexane/EtOAc). The spectral data were identical with those reported in the literature. [96)]

1-Iodo-4-(methoxymethoxy)benzene (105af) [Scheme 71]. To a solution of 4-iodophenol **104** (1.10 g, 5.00 mmol) in THF (6.30 mL) was added NaH (180 mg, 7.50 mmol) at 0 °C. After stirred at 0 °C for 15 min, chloromethyl methyl ether (523 mg, 6.50 mmol) was added. The mixture was stirred at room temperature for 3 h. Then the mixture was diluted with Et_2O and washed with 3M NaOH aq. three times. The residue was dried over $MgSO_4$, filtered and evaporated. **105af** (1.32 g, 31%) was obtained after purification by Biotage Isolera® (hexane/EtOAc). The spectral data were identical with those reported in the literature. [97)]

***N*-(4-Iodophenyl)pivalamide (105ag) [Scheme 72].** To a solution of pivaloyl chloride (1.77 g, 14.7 mmol) in CH_2Cl_2 (12.0 mL), were added 4-iodoaniline **106** (657 mg, 3.00 mmol) and triethylamine (1.52 g, 15.0 mmol). The mixture was stirred at room temperature for 2 h. Then 1M HCl aq. (12 mL) was added and extracted with $CHCl_3$ three times. The residue was washed with saturated $NaHCO_3$ aq., dried over $MgSO_4$, filtered and evaporated. **105ag** (870 mg, 96%) was obtained after purification by Biotage Isolera® (hexane/EtOAc). The spectral data were identical with those reported in the literature. [98)]

General procedure for Heck type reaction of *N*-cyclopropylhydrazones [Scheme 73].
N-Cyclopropylhydrazone (1.0 eq.), iodoarene (2.0 eq.), Herrmann catalyst (0.10 eq.), *n*-Bu_4NI (0.20 eq.) and Cs_2CO_3 (2.0 eq.) were dissolved in benzonitrile (0.05 M). The mixture was stirred at 80 °C under argon for several hours. After the spot of *N*-cyclopropylhydrazone was disappeared on TLC, potassium ethyl xanthate (0.40 eq.) was added. Then the mixture was stirred at 150 °C for several hours. Then the mixture was cooled to room temperature, filtered through Celite® and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) or PTLC to afford pyrazoles.

Ethyl 2-(5-(4-*tert*-butylphenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18ab) [Scheme 73]. Following to the general procedure, **14ac** (21.0 mg, 0.0904 mmol), 1-(*tert*-butyl)-4-iodobenzene **105ab** (47.0 mg, 0.181 mmol), Herrmann catalyst (8.4 mg, 0.0090 mmol), *n*-Bu_4NI (6.7 mg, 0.018 mmol) and Cs_2CO_3 (59.0 mg, 0.181 mmol) were used. After the mixture was stirred at 80 °C for 3 h, potassium ethyl xanthate (5.8 mg, 0.036 mmol) was added and the mixture was stirred at 150 °C for 3 h. **18ab** (19.5 mg, 60%) was obtained as a colorless oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 2.0 Hz, 1H), 7.47-7.45 (m, 2H), 7.37-7.33 (m, 5H), 7.29-7.26 (m, 2H), 6.32 (d, *J* = 1.6 Hz, 1H), 6.06 (s, 1H), 4.22 (q, *J* = 7.6 Hz, 2H), 1.36 (s, 9H), 1.20 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.4, 151.6, 144.3, 139.5, 134.9, 128.5, 128.4, 128.2, 128.1, 127.0, 125.4, 105.9, 64.1, 61.7, 34.4, 30.9, 13.7; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}O_2N_2$ $[M+H]^+$ 363.2067, found 363.2066.

Ethyl 2-(5-(2-methylphenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18ac) [Scheme 73]. Following to the general procedure, **14ac** (20.5 mg, 0.0883 mmol), 2-iodotoluene **105ac** (38.6 mg, 0.177 mmol), Herrmann catalyst (8.3 mg, 0.0090 mmol), *n*-Bu_4NOAc (5.3 mg, 0.018 mmol) and Cs_2CO_3 (57.7 mg, 0.177 mmol) were used. After the mixture was stirred at 80 °C for 16 h, potassium ethyl xanthate (5.7 mg, 0.035 mmol) was added and the mixture was stirred at 150 °C for 4 h. **18ac** (15.7 mg, 56%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.2 Hz, 1H), 7.39-7.23 (m, 8H), 7.15 (d, *J* = 6.8 Hz, 1H), 6.25 (d, *J* = 1.6 Hz, 1H), 5.68 (s, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.6, 143.0, 139.7, 138.2, 134.9, 130.6, 130.4, 129.9, 129.4, 128.8, 128.5, 128.4, 125.8, 106.6, 64.4, 62.0, 19.8, 14.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}O_2N_2$ $[M+H]^+$ 321.1598, found 321.1594.

Ethyl 2-(5-phenyl-1*H*-pyrazol-1-yl)-2-phenylacetate (16at) [Scheme 73]. Following to the general procedure, **14ac** (20.4 mg, 0.0878 mmol), iodobenzene **105at** (35.9 mg, 0.176 mmol), Herrmann catalyst (8.2 mg, 0.0090 mmol), *n*-Bu_4NI (6.5 mg, 0.018 mmol) and Cs_2CO_3 (57.3 mg, 0.176 mmol) were used. After the mixture was stirred at 80 °C for 16 h, potassium ethyl xanthate (5.6 mg, 0.035

mmol) was added and the mixture was stirred at 150 °C for 4 h. **16at** (15.4 mg, 57%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc).

Following to the general procedure, **14ac** (468 mg, 2.02 mmol), iodobenzene **105at** (822mg, 4.03 mmol), Herrmann catalyst (189 mg, 0.202 mmol), *n*-Bu_4NI (149 mg, 0.404 mmol) and Cs_2CO_3 (1.32 g, 4.04 mmol) were used. After the mixture was stirred at 80 °C for 13 h, potassium ethyl xanthate (130 mg, 0.808 mmol) was added and the mixture was stirred at 150 °C for 3 h. **16at** (306 mg, 49%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc).

Ethyl 2-(5-(4-methoxyphenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18ad) [Scheme 73]. Following to the general procedure, **14ac** (20.2 mg, 0.0870 mmol), 4-iodoanisole **105ad** (40.7 mg, 0.174 mmol), Herrmann catalyst (8.2 mg, 0.0090 mmol), *n*-Bu_4NOAc (5.2 mg, 0.017 mmol) and Cs_2CO_3 (56.7 mg, 0.174 mmol) were used. After the mixture was stirred at 80 °C for 6 h, potassium ethyl xanthate (5.6 mg, 0.0350 mmol) was added and the resulting mixture was stirred at 150 °C for 2 h. **18ad** (12.9 mg, 44%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 1.6 Hz, 1H), 7.36 (s, 5H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.29 (d, *J* = 1.2 Hz, 1H), 6.01 (s, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.6, 160.0, 144.4, 139.8, 135.2, 130.5, 128.7, 128.5, 128.5, 122.6, 114.2, 106.2, 64.4, 62.0, 55.4, 14.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}O_3N_2$ $[M+H]^+$ 337.1547, found 337.1547.

Ethyl 2-(5-(2,4-dimethoxyphenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18ae) [Scheme 73]. Following to the general procedure, **14ac** (20.1 mg, 0.0870 mmol), 1-iodo-2,4-dimethoxybenzene **105ae** (45.7 mg, 0.170 mmol), Herrmann catalyst (8.1 mg, 0.0090 mmol), *n*-Bu_4NOAc (5.2 mg, 0.017 mmol) and Cs_2CO_3 (56.4 mg, 0.170 mmol) were used. After the mixture was stirred at 80 °C for 8 h, potassium ethyl xanthate (5.6 mg, 0.0350 mmol) was added and the mixture was stirred at 150 °C for 3 h. **18ae** (12.8 mg, 40%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz,$CDCl_3$) δ 7.63 (d, *J* = 1.6 Hz, 1H), 7.32-7.30 (m, 4H), 7.25 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.55-6.51 (m, 2H), 6.22 (d, *J* = 2.0 Hz, 1H), 5.80 (s, 1H), 4.23-4.18 (m, 2H), 3.85 (s, 3H), 3.64 (s, 3H), 1.19 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.9, 161.9, 157.9, 140.9, 139.8, 135.3, 132.7, 128.8, 128.3, 128.2, 111.6, 106.7, 104.7, 98.6, 64.4, 61.7, 55.5, 55.2, 14.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}O_4N_2$ $[M+H]^+$ 367.1652, found 367.1651.

Ethyl 2-(5-(4-methoxymethoxyphenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18af) [Scheme 73]. Following to the general procedure, **14ac** (20.4 mg, 0.0878 mmol), 1-iodo-4-(methoxymethoxy)benzene **105af** (46.4 mg, 0.176 mmol), Herrmann catalyst (8.2 mg, 0.0088 mmol), *n*-Bu_4NI (6.5 mg, 0.018 mmol) and Cs_2CO_3 (57.3 mg, 0.176 mmol) were used. After the mixture was

stirred at 80 °C for 12 h, potassium ethyl xanthate (5.6 mg, 0.035 mmol) was added and the mixture was stirred at 150 °C for 5 h. **18af** (20.2 mg, 63%) was obtained as a yellow oil after purification by Biotage Isolera® (hexane/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 1.2 Hz, 1H), 7.37 (s, 5H), 7.29-7.27 (m, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.31 (d, *J* = 2.0 Hz, 1H), 6.03 (s, 1H), 5.25 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.53 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.6, 157.6, 144.3, 139.8, 135.2, 130.5, 128.7, 128.5, 128.5, 123.8, 116.4, 106.2, 94.2, 64.4, 62.0, 56.2, 14.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}O_4N_2$ $[M+H]^+$ 367.1652, found 367.1653.

Ethyl 2-[5-(4-(2,2-dimethylpropanamidephenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18ag) [Scheme 73]. Following to the general procedure, **14ac** (22.3 mg, 0.0960 mmol), *N*-(4-iodophenyl) pivalamide **105ag** (58.2 mg, 0.192 mmol), Herrmann catalyst (9.0 mg, 0.0096 mmol), *n*-Bu_4NI (7.1 mg, 0.019 mmol) and Cs_2CO_3 (62.6 mg, 0.192 mmol) were used. After the mixture was stirred at 80 °C for 14 h, potassium ethyl xanthate (6.2 mg, 0.038 mmol) was added and stirred at 150 °C for 4 h. **18ag** (14.8 mg, 38%) was obtained as a white solid after purification by Biotage Isolera® (hexane/EtOAc) and PTLC ($CHCl_3$/acetone = 20 : 1); Mp: 196-200 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 3H), 7.33-7.28 (m, 7H), 6.30 (d, *J* = 1.6 Hz, 1H), 5.98 (s, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.33 (s, 9H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.8, 168.5, 144.1, 139.8, 138.6, 135.1, 129.9, 128.7, 128.5, 127.2, 126.0, 120.0, 106.3, 64.4, 62.1, 39.7, 27.6, 14.0; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}O_3N_3$ $[M+H]^+$ 406.2125, found 406.2122.

Ethyl 2-(5-(4-morpholinophenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18ah) [Scheme 73]. Following to the general procedure, **14ac** (19.4 mg, 0.0835 mmol), 4-(4-iodophenyl) morpholine **105ah** (48.3 mg, 0.167 mmol), Herrmann catalyst (7.9 mg, 0.0084 mmol), *n*-Bu_4NI (6.2 mg, 0.017 mmol) and Cs_2CO_3 (54.4 mg, 0.167 mmol) were used. After the mixture was stirred at 80 °C for 6 h, potassium ethyl xanthate (5.4 mg, 0.034 mmol) was added and the mixture was stirred at 150 °C for 5 h. **18ah** (12.1 mg, 37%) was obtained as a yellow solid after purification by PTLC (Hexane/acetone = 2 : 1); Mp: 113 °C (decomp.); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.6 Hz, 1H), 7.37-7.34 (m, 4H), 7.26-7.24 (m, 3H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.28 (d, *J* = 1.6 Hz, 1H), 6.03 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.89 (t, *J* = 5.2 Hz, 4H), 3.23 (t, *J* = 5.2 Hz, 4H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.7, 151.3, 144.6, 139.8, 135.3, 130.1, 128.7, 128.5, 128.4, 121.2, 115.1, 105.9, 66.8, 64.4, 62.0, 48.6, 14.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{26}O_3N_3$ $[M+H]^+$ 392.1969, found 392.1969.

Ethyl 2-(5-([1,1'-biphenyl]-4-yl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18ai) [Scheme 73]. Following to the general procedure, **14ac** (19.9 mg, 0.0857 mmol), 4-iodobiphenyl **105ai** (48.0 mg, 0.171 mmol), Herrmann catalyst (8.0 mg, 0.0086 mmol), *n*-Bu_4NI (6.3 mg, 0.017 mmol) and Cs_2CO_3 (55.7 mg, 0.171 mmol) were used. After the mixture was stirred at 80 °C for 12 h, potassium ethyl

xanthate (5.5 mg, 0.034 mmol) was added and the mixture was stirred at 150 °C for 4 h. **18ai** (15.6 mg, 48%) was obtained as a colorless oil after purification by PTLC (hexane/acetone = 2 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69-7.64 (m, 5H), 7.51-7.36 (m, 10H), 6.39 (d, *J* = 1.6 Hz, 1H), 6.10 (s, 1H), 4.25 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.6, 144.3, 141.7, 140.1, 139.9, 135.1, 129.6, 129.2, 128.9, 128.7, 128.5, 128.4, 127.8, 127.4, 127.1, 106.5, 64.6, 62.1, 14.1; HRMS (ESI) *m/z* calcd for $C_{25}H_{23}O_2N_2$ $[M+H]^+$ 383.1754, found 383.1752.

Ethyl 2-(5-(4-fluorophenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18aj) [Scheme 73]. Following to the general procedure, **14ac** (20.1 mg, 0.0865 mmol), 4-fluoro-iodobenzene **105aj** (38.4 mg, 0.173 mmol), Herrmann catalyst (8.1 mg, 0.0087 mmol), *n*-Bu_4NI (6.4 mg, 0.017 mmol) and Cs_2CO_3 (56.4 mg, 0.173 mmol) were used. After the mixture was stirred at 80 °C for 14 h, potassium ethyl xanthate (5.6 mg, 0.035 mmol) was added and the mixture was stirred at 150 °C for 4 h. **18aj** (13.7 mg, 49%) was obtained as a colorless oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.35-7.28 (m, 7H), 7.12 (t, *J* = 8.8 Hz, 2H), 6.30 (s, 1H), 5.96 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.5, 163.0 (d, J_{C-F} = 249.5 Hz), 143.5, 139.8, 135.0, 131.1 (d, $J_{C-C-C-F}$ = 8.7 Hz), 128.6, 128.6, 128.5, 126.4 (d, $J_{C-C-C-C-F}$ = 3.9 Hz), 115.9 (d, J_{C-C-F} = 21.2 Hz), 106.7, 64.6, 62.1, 14.0; ^{19}F-NMR (376 MHz, $CDCl_3$) δ -112.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}O_2N_2F$ $[M+H]^+$ 325.1347, found 325.1346.

Ethyl 2-(5-(4-ethoxycarbonylphenyl)-1*H*-pyrazol-1-yl)-2-phenylacetate (18ak) [Scheme 73]. Following to the general procedure, **14ac** (23.4 mg, 0.101 mmol), ethyl-4-iodobenzoate **105ak** (33.5 mg, 0.202 mmol), Herrmann catalyst (9.4 mg, 0.010 mmol), *n*-Bu_4NI (7.5 mg, 0.020 mmol) and Cs_2CO_3 (65.8 mg, 0.202 mmol) were used. After the mixture was stirred at 80 °C for 21 h, potassium ethyl xanthate (6.5 mg, 0.040 mmol) was added and the mixture was stirred at 150 °C for 3 h. **18ak** (16.3 mg, 43%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.8 Hz, 2H), 7.67 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.35 (s, 5H), 6.39 (d, *J* = 2.0 Hz, 1H), 6.00 (s, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.3, 166.0, 143.6, 140.0, 134.8, 134.7, 130.7, 129.9, 129.1, 128.62, 128.57, 128.4, 107.0, 64.8, 62.2, 61.3, 14.3, 14.0; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}O_4N_2$ $[M+H]^+$ 379.1652, found 379.1652.

Ethyl 2-(5-(4-methylphenyl)-1*H*-pyrazol-1-yl)-2-(4-methoxy)phenylacetate (18ba) [Scheme 73]. Following to the general procedure, **14ad** (25.5 mg, 0.0972 mmol), 4-iodotoluene **105aa** (42.4 mg, 0.194 mmol), Herrmann catalyst (9.1 mg, 0.0097 mmol), *n*-Bu_4NI (7.2 mg, 0.019 mmol) and Cs_2CO_3 (63.2 mg, 0.194 mmol) were used. After the mixture was stirred at 80 °C for 16 h, potassium ethyl xanthate (6.5 mg, 0.039 mmol) was added and the mixture was stirred at 150 °C for 3 h. **18ba** (16.5 mg, 49%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR

(400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.27-7.26 (m, 4H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.30 (s, 1H), 5.97 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 2.43 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.9, 159.5, 144.4, 139.7, 138.8, 130.1, 129.4, 129.1, 127.5, 127.3, 113.8, 106.2, 63.9, 61.9, 55.2, 21.3, 14.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}O_3N_2$ $[M+H]^+$ 351.1703, found 351.1704.

Ethyl 2-(5-(4-methylphenyl)-1*H*-pyrazol-1-yl)-2-(4-ethoxycarbonyl)phenylacetate (18ca) [Scheme 73]. Following to the general procedure, **14db** (32.4 mg, 0.107 mmol), 4-iodotoluene **105aa** (46.4 mg, 0.213 mmol), Herrmann catalyst (10.0 mg, 0.0107 mmol), *n*-Bu_4NI (7.9 mg, 0.0214 mmol) and Cs_2CO_3 (69.4 mg, 0.213 mmol) were used. After the mixture was stirred at 80 °C for 13 h, potassium ethyl xanthate (6.9 mg, 0.0428 mmol) was added and the mixture was stirred at 150 °C for 3 h. **18ca** (9.2 mg, 22%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.63 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.25-7.17 (m, 4H), 6.30 (d, *J* = 2.0 Hz, 1H), 6.03 (s, 1H), 4.38-4.33 (m, 2H), 4.24-4.19 (m, 2H), 2.40 (s, 3H), 1.38-1.35 (m, 3H), 1.21-1.17 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.0, 166.2, 144.9, 140.1, 140.0, 139.1, 130.5, 129.7, 129.5, 129.0, 128.6, 127.2, 106.4, 64.1, 62.2, 61.0, 21.3, 14.3, 14.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{25}O_4N_2$ $[M+H]^+$ 393.1809, found 393.1805.

Ethyl 2-(5-(4-methylphenyl)-1*H*-pyrazol-1-yl)-2-(2-naphthyl)acetate (18da) [Scheme 73]. Following to the general procedure, **14da** (24.9 mg, 0.0882 mmol), 4-iodotoluene **105aa** (38.4 mg, 0.176 mmol), Herrmann catalyst (8.3 mg, 0.0088 mmol), *n*-Bu_4NI (6.5 mg, 0.018 mmol) and Cs_2CO_3 (57.3 mg, 0.176 mmol) were used. After the mixture was stirred at 80 °C for 21 h, potassium ethyl xanthate (5.6 mg, 0.035 mmol) was added and the mixture was stirred at 150 °C for 4 h. **18da** (10.7 mg, 33%) was obtained as a yellow oil after purification by PTLC (hexane/EtOAc = 7 : 3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85-7.78 (m, 3H), 7.73 (s, 1H), 7.66 (d, *J* = 1.4 Hz, 1H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.48-7.46 (m, 2H), 7.25 (d, *J* = 2.8 Hz, 4H), 6.33 (d, *J* = 0.8 Hz, 1H), 6.18 (s, 1H), 4.24 (q, *J* = 6.8 Hz, 2H), 2.41 (s, 3H), 1.23-1.18 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.7, 144.7, 139.9, 138.9, 133.1, 133.0, 132.7, 129.5, 129.1, 128.2, 128.0, 127.6, 126.4, 126.2, 126.2, 106.3, 64.6, 62.1, 21.3, 14.1; One carbon peak could not be detected probably due to overlapping; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}O_2N_2$ $[M+H]^+$ 371.1754, found 371.1757.

Ethyl 2-(4-bromo-5-phenyl-1*H*-pyrazol-1-yl)-2-phenylacetate (107) [Scheme 74]. To a solution of **16at** (15.3 mg, 0.0499 mmol) in CH_2Cl_2 (5.2 mL), NBS (10.6 mg, 0.0600 mmol) was added. The mixture was stirred at 50 °C in a sealed tube for 25 h, and then evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **107** (11.0 mg, 57%) as a white solid; Mp: 82-84 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.51-7.48 (m, 3H), 7.35-7.29 (m, 7H), 5.91 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2, 142.3,

140.4, 134.3, 130.1, 129.6, 128.9, 128.8, 128.8, 128.6, 128.1, 94.4, 65.5, 62.2, 14.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}O_2N_2{}^{79}Br$ $[M+H]^+$ 385.0546, found 385.0546, $C_{19}H_{18}O_2N_2{}^{81}Br$ $[M+H]^+$ 387.0526, found 387.0526.

1-Benzyl-5-phenyl-1*H*-pyrazole (108) [Scheme 74]. To a solution of **16at** (30.0 mg, 0.0979 mmol) in DMSO (980 μL), LiCl (16.6 mg,0.390 mmol) was added. The mixture was stirred at 150 °C for 23 h. Then LiCl (49.9 mg, 1.18 mmol) was added to the mixture and the resulting mixture was stirred for 23 h. Then the mixture was cooled to room temperature and diluted with water, extracted with Et_2O three times, washed with water and brine and dried over $MgSO_4$. Then the residue was filtered and evaporated. The residue was purified by Biotage Isolera® (hexane/EtOAc) to afford pyrazole **108** (13.4 mg, 58%) as a white solid; Mp: 51-57 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 1.6 Hz, 1H), 7.39 (m, 3H), 7.35-7.22 (m, 5H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.36 (d, *J* = 2.0 Hz, 1H), 5.35 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.1, 139.3, 137.6, 130.7, 128.9, 128.6, 128.6, 127.5, 126.8, 106.4, 53.1; One carbon peak could not be detected probably due to overlapping; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}N_2$ $[M+H]^+$ 235.1230, found 235.1225.

2-Phenyl-2-(5-phenyl-1*H*-pyrazol-1-yl)ethan-1-ol (109) [Scheme 74]. To a solution of **16at** (29.5 mg, 0.0963 mmol) in THF (960 μL), $LiAlH_4$ (3.6 mg, 0.095 mmol) was added. The mixture was stirred at 0 °C for 6 h. Then the mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc three times. The collected organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by PTLC (hexane/EtOAc = 7 : 3) to afford alcohol **109** (15.5 mg, 61%) as a yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 1.4 Hz, 1H), 7.38-7.24 (m, 6H), 7.20 (m, 2H), 7.10-7.08 (m, 2H), 6.37 (d, *J* = 1.8 Hz, 1H), 5.44 (dd, *J* = 7.2, 3.6 Hz, 1H), 4.41 (dd, *J* = 12, 7.2 Hz, 1H), 4.11 (dd, *J* = 12, 3.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.9, 139.2, 138.7, 130.2, 129.1, 128.7, 128.6, 128.5, 127.8, 126.6, 106.5, 65.9, 63.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}ON_2$ $[M+H]^+$ 265.1335, found 265.1332.

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