多重結合の活性化を基盤とする高原子効率的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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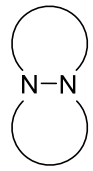
略語表

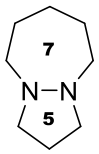
Ac	acetyl
acac	acetylacetonate
ACE	angiotensin-converting enzyme
aq.	aqueous
Ar	aromatic, aryl
brsm	based on recovered starting material
Bn	benzyl
br	broad
Boc	*tert*-butoxycarbonyl
Bu	butyl
cat.	catalyst
ca.	circa
c	cyclo
Cp	cyclopentadienyl
dig	diagonal
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	1,2-dichloroethane
DMF	*N*,*N*-dimethylformamide
d	doublet
ESI	electrospray ionization
Et	ethyl
EBX	ethynylbenziodoxolone
eq	equal
equiv.	equivalent
HRMS	high resolution mass spectrum
IR	infrared
i	iso
Tf	trifluoromethanesulfonyl
M	metal
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
LG	leaving group
L	ligand
MS	mass spectrum
m.p.	melting point

Mes	mesityl
MOM	methoxymethyl
Me	methyl
m	multiplet
NEP	neutral endopeptidase
NHC	*N*-heterocyclic carbene
hexane	*n*-hexane
NIS	*N*-iodosuccinimide
NR	no reaction
ND	not detected
n	normal
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge thermal ellipsoid plot
Cp*	pentamethylcyclopentadiene
Ph	phenyl
pic	picolinate
q	quartet
RCM	ring-closing metathesis
rt	room temperature
SPPL2a	signal peptide peptidase-like 2a
s	singlet
SM	starting material
TBS	*tert*-butyldimethylsilyl
t, *tert*	tertiary
TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
THF	tetrahydrofuran
esp	DuBois-Espino catalyst, α,α,α',α'-tetramethyl-1,3-benzenedipropionato
TMS	trimethylsilyl, tetramethylsilane
TIPS	triisopropylsilyl
t	triplet

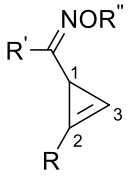
- 各化合物の命名は、原則として Chemical Abstracts の命名法に従ったが、スペクトルデータの記載は、慣用的なものを使用した。
- 本論文中では以下に示すような窒素－窒素結合を介して縮環した化合物を *N*,*N*-縮環化合物と呼称する。例えば右に示す化合物の例では *N*,*N*-5,7-縮環化合物と呼ぶ。

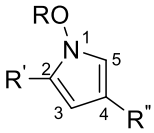


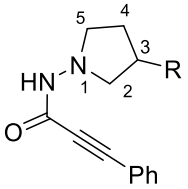
ex.)

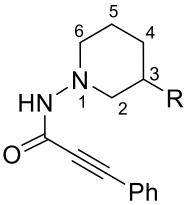


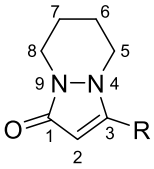
- 本論文中の化合物の Numbering は下記のように統一した

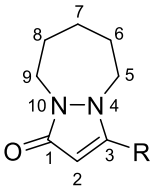


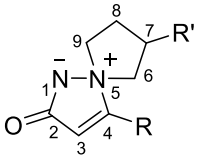


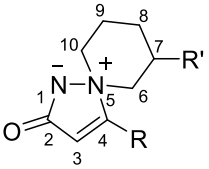












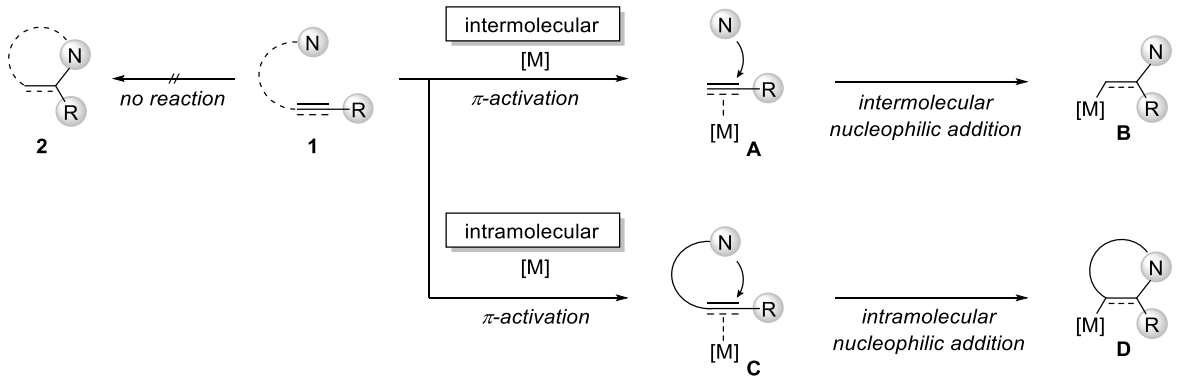
目次

総論

含窒素ヘテロ環化合物はアルカロイド等の天然物として幅広く存在している。アルカロイドは多彩な生物活性を示すことから医薬品や農薬として用いられている化合物が多数存在し、新たな薬品開発のためのシード化合物としても重要である。[1] 優れた薬効が期待されるシード化合物としてのアルカロイドには、複雑な骨格を有しているものが存在する。合成困難であるこれらのアルカロイドは、多工程の合成プロセスに伴う費用や廃棄物の増加という問題を抱えており、より短工程での構築を目的とするアルカロイドの全合成研究や効率的な骨格構築のための合成研究が行われている。

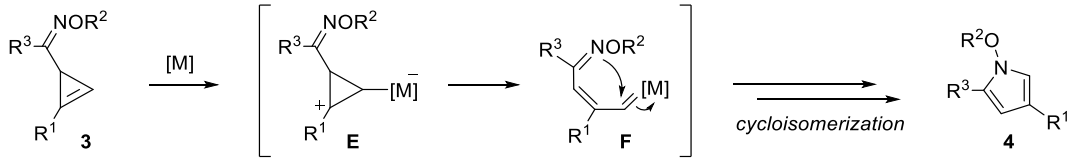
一方で、現代社会において、有用物質をより効率良く生産するために、「化学廃棄物の低減化」に配慮した環境調和型の反応が強く望まれている。環境調和型の反応を考える上で、Trost らによって原子効率という概念が提唱されている。[2] 原子効率は【原子効率 (%) = 目的物の分子量/反応物の分子量 × 100】で表され、効率的な化学合成を目指す上で重要な概念の 1 つとなっている。原子効率が高い反応ほど、生じる廃棄物が少なく環境調和性に優れた反応となる。有機合成化学で使用される反応のうち、転位反応、付加反応および異性化反応等は原子効率の高い反応であるが、脱離反応や置換反応のように反応物から遊離する原子団が存在する反応は原子効率の低い反応である。

このような背景のもと、著者は高い原子効率で複雑な含窒素ヘテロ環を構築する新規合成法を見出すため、遷移金属触媒を用いた多重結合へのπ配位を起点とする窒素求核種との反応に着目した (Scheme 1)。アルケンやアルキンなどの多重結合をもつ化合物はπ結合に起因する高い電子密度を有しており、電子豊富な炭素－炭素多重結合は求核性を有する窒素原子に対して反応性を示さない (**1** → **2**)。しかし、電子密度の低い金属を配位させることで、多重結合部位の求電子性が増加し、窒素求核剤を用いた分子間での求核付加反応が進行するようになる (**A** → **B**)。[3] また、分子内の適切な位置に窒素原子を導入し、π結合の活性化を行えば、閉環反応により含窒素ヘテロ環化合物を構築することが出来る (**C** → **D**)。[4] この反応は通常、温和な条件で反応が進行し、高い原子効率で反応が進行する環境調和型の含窒素ヘテロ環合成法として有用である。



Scheme 1. Transition-metal catalyzed activation of multiple bond for nucleophilic addition.

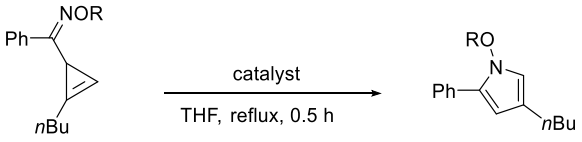
そこで、上記概念を利用した新たな反応開発を行うためシクロプロペンに着目した。シクロプロペンは3員環内に二重結合を有するため高いひずみエネルギーを有しており、[5] 通常困難な炭素－炭素結合の開裂が進行しやすい。[6] そこで、*N*-アルコキシ-1-イミノシクロプロペン**3**に対して遷移金属触媒を用いた環化異性化反応を計画した。すなわち、シクロプロペニルイミンに遷移金属を作用させると、アルケン部位に金属種が付加することでシクロプロパン中間体**E**が生成する。次に、炭素－炭素結合の開裂を伴って金属カルベン中間体**F**が生成した後、窒素原子からの求核付加反応により、多置換ピロール**4**が合成できると考えた (Scheme 2)。



Scheme 2. Transition-metal catalyzed cycloisomerization of cyclopropenylimine.

まず、*N*-ベンジルオキシ-1-イミノシクロプロペン **5a** の *E*/*Z* 異性体混合物を用いて環化異性化反応を検討した。THF 還流条件下、$CuBr_2$ を用いて反応を行うと期待した環化異性化反応が進行し、三置換ピロール **9a** が 19%の収率で得られた (Table 1, entry 1)。また、$CuCl_2$ を用いると 34%に収率が向上した (entry 2)。しかし、その他の金属触媒や Brønsted 酸触媒は本環化異性化反応に有効ではなかった (entries 3 and 4)。次に、オキシムエーテルの酸素原子上の置換基効果に関して検討したところ、*O*-アリルオキシム **6a** および *O*-メチルオキシム **7a** の環化異性化反応は効率的に進行したが、オキシム **8a** からは対応するピロール **12a** は得られなかった (entries 6-8) (第 1 章第 1 節)。

Table 1. Optimization of the reaction conditions for cycloisomerization of cyclopropenylimines.



(*E*/*Z*)-**5a-8a** **9a-12a**

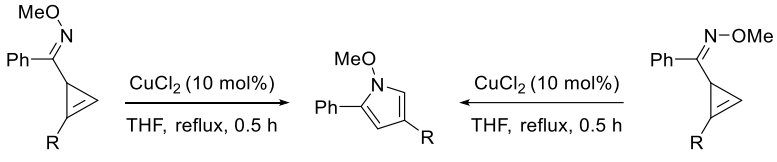
entry	substrate [a]	catalyst (mol%)	product	yield (%)
1	(*E*/*Z*)-**5a**: (R = Bn)	$CuBr_2$ (20)	**9a**	19
2	(*E*/*Z*)-**5a**: (R = Bn)	$CuCl_2$ (20)	**9a**	34
3	(*E*/*Z*)-**5a**: (R = Bn)	$AuCl_3$ (20)	**9a**	ND
4	(*E*/*Z*)-**5a**: (R = Bn)	AcOH (20)	**9a**	NR
5	(*E*/*Z*)-**5a**: (R = Bn)	$CuCl_2$ (10)	**9a**	33
6	(*E*/*Z*)-**6a**: (R = allyl)	$CuCl_2$ (10)	**10a**	60
7	(*E*/*Z*)-**7a**: (R = Me)	$CuCl_2$ (10)	**11a**	60
8	(*E*/*Z*)-**8a**: (R = H)	$CuCl_2$ (10)	**12a**	ND

a) *E*/*Z* ratio of cyclopropenylimines **5a−8a** is 3:1.

続いて、C=N 結合の幾何異性が反応性に与える影響について調べるため、2 位に様々な

アルキル基をもつシクロプロペニルイミン(*E*)-**7a-7d** または(*Z*)-**7a-7d** を用いて環化異性化反応を行った (Table 2)。その結果、いずれの場合も *E* 体の反応では *Z* 体の反応より収率が低下することが明らかになった。特に *tert*-ブチル基のような嵩高い置換基を有する場合、*Z* 体の基質では速やかに原料が消費されたのに対して、*E* 体の基質は 77%の原料が回収された。(entries 7-8)。これらの結果は、窒素原子の非共有電子対とシクロプロペン環が *syn* の位置関係の場合にのみ環化異性化反応が進行していることを示唆している。従って、非共有電子対とシクロプロペン環の位置関係が *anti* である *E* 配置のシクロプロペニルイミンの反応では、環化異性化の過程で *Z* 配置への異性化を経由しているため収率が低下したと考えている。 (第 1 章第 2 節)。

Table 2. Effects of the geometry and substituent at the 2-position of the cyclopropenylimines.

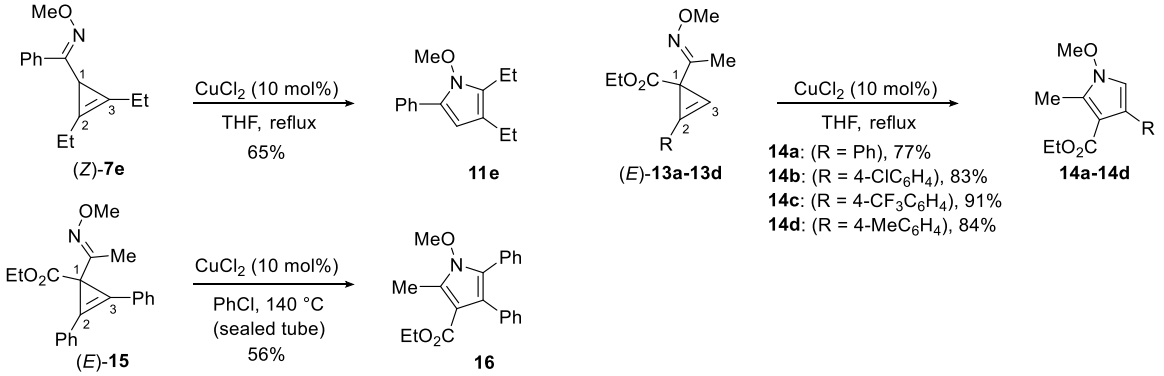


(*Z*)-**7a-7d** **11a-11d** (*E*)-**7a-7d**

entry	R	geometry of C=N	product	yield (%) [a]
1	*n*Bu	*Z*	**11a**	66
2	*n*Bu	*E*	**11a**	58
3	*i*Bu	*Z*	**11b**	85
4	*i*Bu	*E*	**11b**	57
5	c-pentyl	*Z*	**11c**	53
6	c-pentyl	*E*	**11c**	42
7	*t*Bu	*Z*	**11d**	76
8	*t*Bu	*E*	**11d**	10 (77)

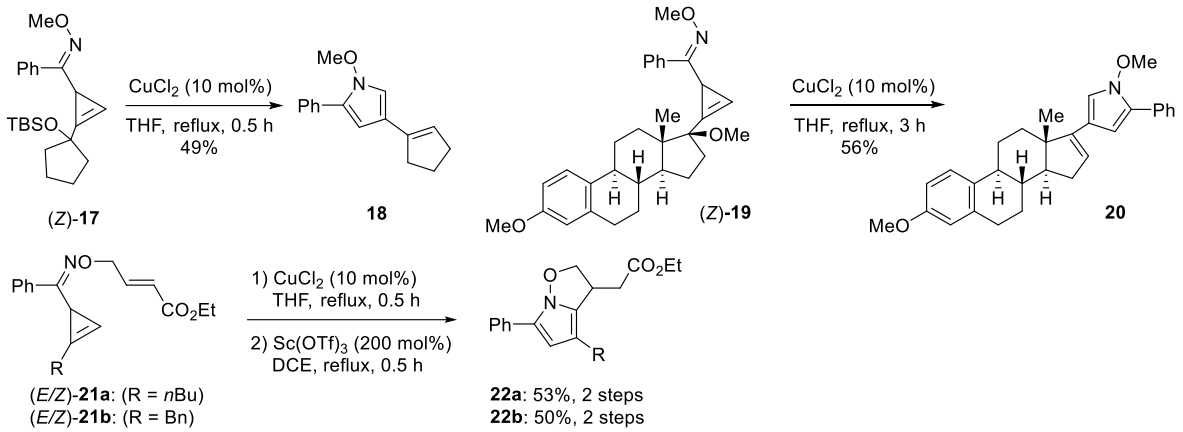
a) Yield in parentheses is for the recovered starting material.

次に、シクロプロペン環上の様々な位置に置換基を有するシクロプロペニルイミンを用いて本反応の基質適用範囲に関する検討を行った (Scheme 3)。シクロプロペニルイミンの 2 位と 3 位にエチル基をもつ(*Z*)-**7e** からは 65%の収率で四置換ピロール **11e** が得られた。次に、1 位と 2 位に置換基をもつシクロプロペン(*E*)-**13** を用いると、単一の四置換ピロールが得られた。さらに、1 位から 3 位の全てに置換基を有するシクロプロペン(*E*)-**15** の場合、より高温条件が必要であったが、未だに効率的な合成報告例の乏しい全置換ピロールが 56%の収率で得られた (第 1 章第 3 節)。[7)]



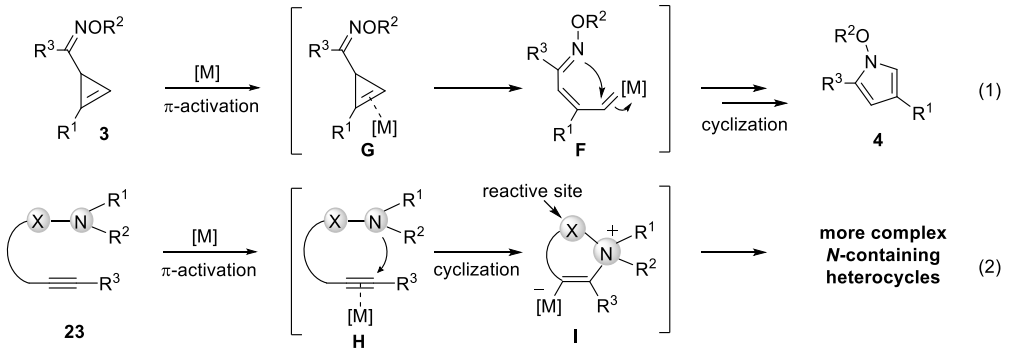
Scheme 3. Synthesis of multisubstituted pyrroles from 1-iminocyclopropenes.

この環化異性化反応の有用性を確認するために、更なる検討を行った (Scheme 4)。まず、シリルオキシ基をもつシクロプロペンの反応では、環化異性化反応に伴いシリルオキシ基の脱離が同時に進行し、シクロペンテン環を有するピロール **18** が 49%の収率で得られた。さらに、ステロイド骨格をもつシクロプロペンでも同様に、環化異性化とメトキシ基の脱離が一挙に進行し、ピロール **20** が得られた。最後に、クロトニル基を有するシクロプロペニルイミン **21** の環化異性化反応の後、更なる環化反応について検討した。ジクロロエタン還流中、$Sc(OTf)_3$ を作用させると環化反応が進行しピロロイソキサゾール **22** が得られた。



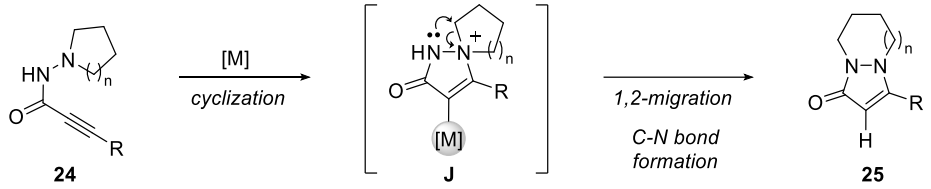
Scheme 4. Cycloisomerization-elimination reaction and synthesis of pyrrolo[1,2-*b*]isoxazoles.

上記の環化異性化反応では、シクロプロペニルイミンのシクロプロペン部位をπ-Lewis酸性の遷移金属触媒で活性化することで、金属カルベン中間体**F**が生成し、続いて窒素原子の求核攻撃により閉環反応が進行することでピロール骨格が得られている (Scheme 5, eq 1)。このアルコキシイミンの窒素原子は求核部位として閉環反応に必要であり、酸素原子はα効果[8] によりイミン窒素の求核性の向上およびイミンの安定化への寄与が考えられる。そこで次にこのような特異な性質を持つ連続ヘテロ原子の反応性を利用し、さらに両原子を環内に組み込むヘテロ環の新規合成法を考案した。すなわち、多重結合をπ-Lewis酸性の遷移金属触媒で活性化し、一方の窒素原子の求核攻撃により、含窒素ヘテロ環を反応中間体**I**として構築した後、その窒素原子と結合したヘテロ原子 (X) が反応点となるように分子設計を行えば、連続反応により比較的単純な基質から複雑な含窒素ヘテロ環が構築できると考えた (eq 2)。



Scheme 5. Our work and working hypothesis for construction of more complex *N*-containig heterocycles.

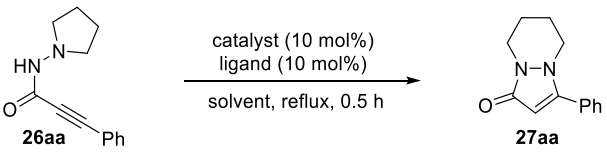
上記概念を基に、アルキンを活性化した後、連続する2つのヘテロ原子の両方を求核部位とする連続反応を計画した。すなわち環状アミンを有するヒドラジドを基質として遷移金属触媒を用いた閉環反応を行えば、スピロアンモニウム中間体**J**に対してアミド窒素からの求核攻撃による1,2-転位反応が進行し、炭素－窒素結合の形成を伴って窒素－窒素結合を介して縮環したヘテロ環が構築できると想定した (Scheme 6)。



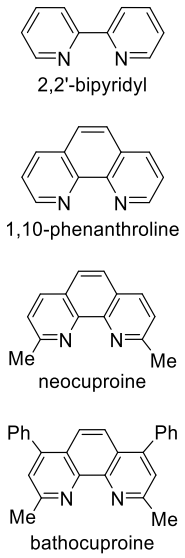
Scheme 6. Sequential cyclization-1,2-migration reaction with C-N bond formation.

はじめに、環状アミンを有するプロピオールアミドの閉環－転位反応の反応条件を検討した (Table 3)。まず、ピロリジン環を有するアルキニルヒドラジド**26aa**を1,2-ジクロロエタン還流条件下、触媒として$CuBr_2$を用いたところ、目的のピラゾロピリダジン**27aa**が21%の収率で得られた (entry 1)。次に、様々な銅触媒および溶媒を検討したところ、クロロベンゼン還流条件下、$CuBr_2$を用いると42%まで収率が向上した (entries 2-6)。更なる収率の向上を期待して、種々の配位子を検討した。2,2'-ビピリジルのように構造の自由度が高い配位子は本反応にあまり効果的ではなかったが、1,10-フェナントロリンのような剛直な構造の配位子を用いると閉環－転位反応が最も効率良く進行し、ピラゾロピリダジン**27aa**が93%の収率で得られた (entries 7-10) (第2章第1節)。

Table 3. Copper-catalyzed sequential cyclization-migration reaction of alkynylhydrazide **26aa**.

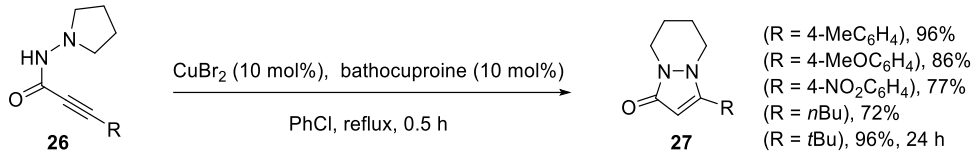


entry	catalyst	ligand	solvent	yield (%)
1	$CuBr_2$	-	DCE	21
2	CuBr	-	DCE	5
3	$Cu(OTf)_2$	-	DCE	trace
4	$CuBr_2$	-	MeCN	20
5	$CuBr_2$	-	EtOH	25
6	$CuBr_2$	-	PhCl	42
7	$CuBr_2$	2,2'-bipyridyl	PhCl	28
8	$CuBr_2$	1,10-phenanthroline	PhCl	68
9	$CuBr_2$	neocuproine	PhCl	64
10	$CuBr_2$	bathocuproine	PhCl	93



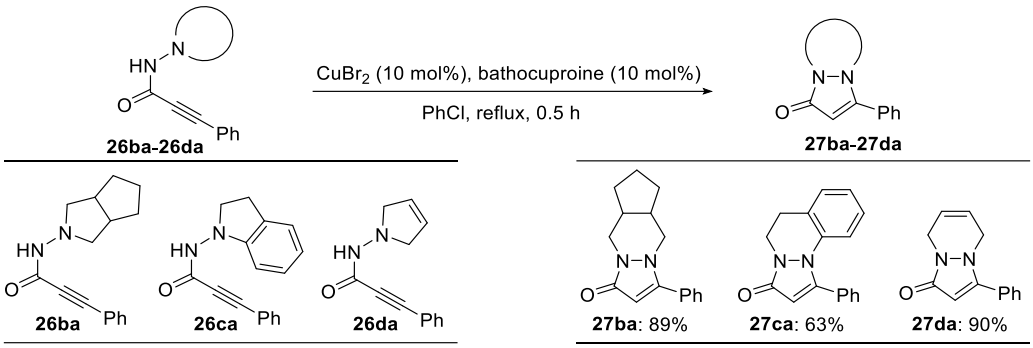
次に、本反応におけるアルキン末端の置換基効果に関して検討した (Scheme 7)。その結果、アルキン末端のベンゼン環上に様々な置換基をもつ基質で反応が進行し、電子供与基

および電子求引基のような置換基の種類にかかわらず、対応するピラゾロピリダジンが良好な収率で得られた。さらに、アルキン末端に *n*-ブチル基を有する基質を用いても本反応は速やかに進行した。また、*tert*-ブチル基のような嵩高い置換基をもつ基質でも、反応時間を延長することで高収率でピラゾロピリダジンが得られることが分かった (第2章第2節)。



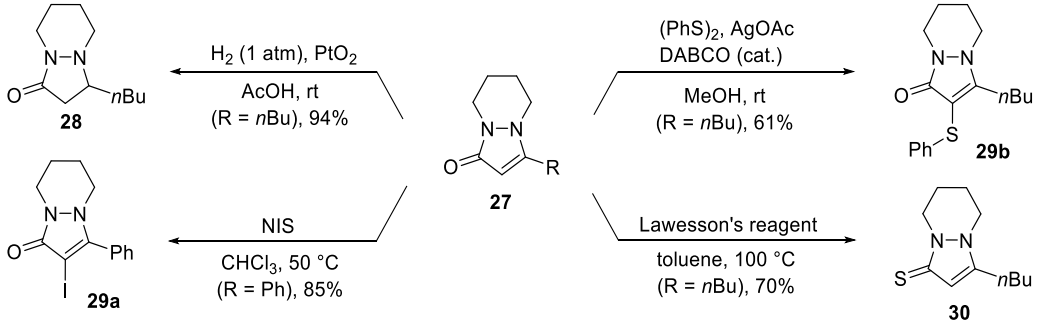
Scheme 7. Substrate scope for terminal alkyne of the alkynylhydrazides.

続いて、環状アミン部位の一般性について検討した (Scheme 8)。環状アミン部位に5員環を有するオクタヒドロシクロペンタピロールまたはインドリンを有する基質からは三環性の*N,N*-縮環型ピラゾロン**27ba**および**27ca**が得られた。また、ピロリジン環内に二重結合をもつ基質を用いても対応するピラゾロピリダジン**27da**が得られた。



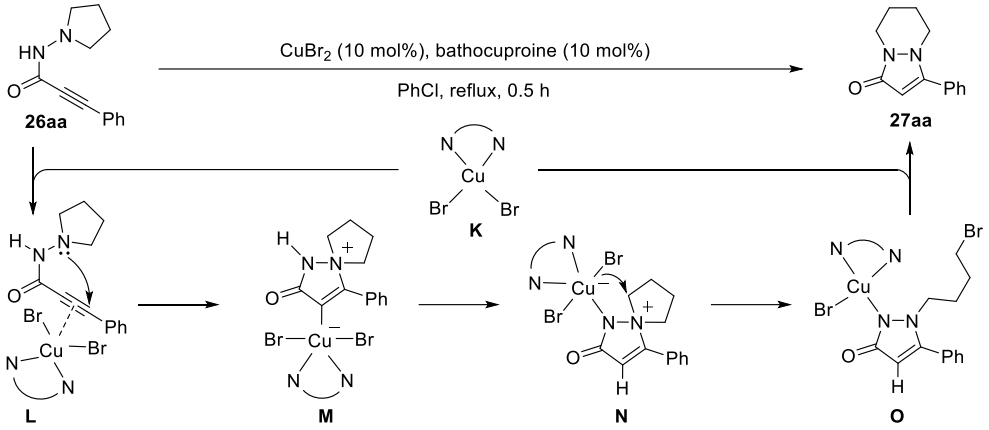
Scheme 8. Substrate scope for cyclic amine moiety of the alkynylhydrazides.

得られたピラゾロピリダジンの有用性を確認する目的で、**27**の官能基変換を行った (Scheme 9)。まず、**27**を水素雰囲気下、PtO_2とともに処理すると、ピラゾロンの二重結合が還元されたピラゾリジノン**28**が得られた。また、ヨウ素化、フェニルチオ化[9] により**29a**および**29b**が得られ、ピラゾロンの2位に置換基を導入することが可能であった。さらに、アミドのカルボニル基の変換としてLawesson試薬を用いて加熱を行うことで、チオピラゾロン**30**が得られた (第2章第2節)。



Scheme 9. Transformation of **27**.

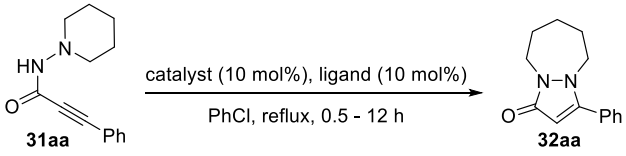
本閉環－転位反応の反応経路は以下のように推定している (Scheme 10)。まず、銅触媒とバソクプロイン複合体 **K** によりアルキニルヒドラジド **26aa** のアルキン部位が活性化されることで 5-*endo-dig* 環化が進行し、スピロアンモニウム中間体 **M** が形成される。続いてアミドプロトンの 1,3-転位により銅アミンイミド **N** が生成する。次にピロリジニウムの窒素原子に隣接する炭素原子に対して銅アミンイミド **N** の臭化物イオンが求核攻撃することで臭化アルキル **O** が生成する。最後に銅アミドと臭化アルキル部位の分子内求核置換反応が進行することで、触媒の再生を伴い *N*,*N*-縮環型ピラゾロン **27aa** が生成したと考えている。(第 2 章第 3 節)。



Scheme 10. Plausible reaction pathway.

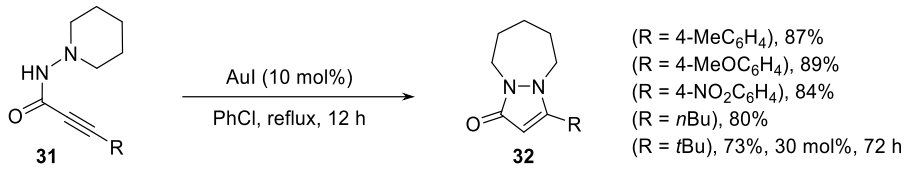
次に、閉環－転位反応がピペリジン環を有するアルキニルヒドラジド**31aa**へ展開できるか検討した。 著者の知る限り*N*,*N*-5,7-縮環化合物の合成に関して系統的な合成研究が行われた例は付加環化反応に限られている。[10] そのため、本反応が基質**31aa**に対して適用可能であれば、*N*,*N*-5,7-縮環化合物の新たな一般的合成法になることが期待される。見出した最適条件で**31aa**を処理したが、ピラゾロジアゼピン**32aa**は中程度の収率でしか得られなかった (Table 4, entry 1)。そこで、**31aa**に対する最適条件を見出すための検討を行った。**31aa**を$AuBr_3$存在下、バソクプロインとともに反応させたところ、収率が若干向上した (entry 2)。金触媒を用いる際の配位子の必要性を明らかにするために、配位子非存在下で反応を行ったところ、収率に大きな影響はなく配位子が必要ないことがわかった (entry 3)。さらに、触媒としてAuIを用いると92%の収率でピラゾロジアゼピン**32aa**が得られた entry 4) (第3章第1節)。

Table 4. Sequential cyclization-migration reaction of alkynylhydrazide **31aa**.



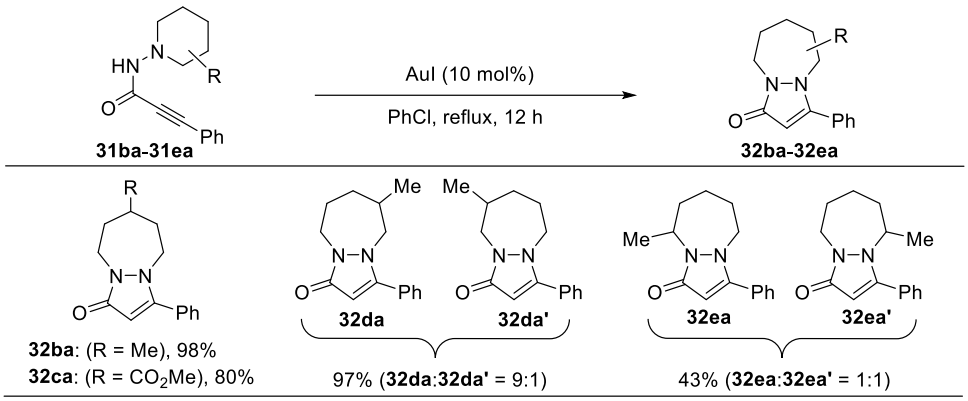
entry	catalyst	ligand	yield (%)
1	$CuBr_2$	bathocuproine	44
2	$AuBr_3$	bathocuproine	53
3	$AuBr_3$	-	52
4	AuI	-	92

ピペリジン環を有するアルキニルヒドラジドのアルキン末端の置換基効果について検討した (Scheme 11)。前述したピロリジン環の基質と同様に、アルキン末端にアリール基およびアルキル基を有するアルキニルヒドラジド**31**から対応するピラゾロジアゼピン**32**が良好な収率で得られた (第3章第2節)。



Scheme 11. Substrate scope for terminal alkyne of the alkynylhydrazides.

続いて、環状アミン部位の一般性について検討した (Scheme 12)。ピペリジン環の4位にメチル基やエステル基を有する基質から収率よくピラゾロジアゼピン**32ba**と**32ca**が得られた。次に、ピペリジンの2位および3位にメチル基を有する基質を用いて反応を行った。その結果、ピペリジン3位にメチル基を有する**31da**からは収率よく目的の化合物が得られたが位置異性体**32da**および**32da'**が9:1の比率で得られた。また、ピペリジン2位にメチル基を有する**31ea**を反応させると、位置異性体**32ea**と**32ea'**が得られたが、位置選択性が1:1に低下した。



Scheme 12. Substrate scope for cyclic amine moiety of the alkynylhydrazides.

以上のように、多重結合の活性化を起点として窒素原子の分子内求核付加反応を介した多置換ピロールおよび縮環型ピラゾロン類の新規合成法の開発研究を行った。その結果、シクロプロペニルイミンを用いた環化異性化反応では全置換ピロールを含む多置換のピロール類を合成できることが分かった。また、環状アミンを有するアルキニルヒドラジドの遷移金属触媒との反応では、閉環反応と連続的な転位反応が進行することで *N*,*N*-縮環型のピラゾロン類が得られることが明らかになった。本反応はいずれも原子効率 100%で複雑な含窒素ヘテロ環を構築することが可能であり、環境調和性に優れた反応である。

本論

第1章　シクロプロペニルイミンの環化異性化反応による多置換ピロール合成法の開発

ピロールが重合したポリピロールは高い導電性を示すことから機能性材料として有用である。[11] また、4 つのピロールが環状に縮合した構造を持つポルフィリンやその誘導体は金属と錯体を形成し、ヘムやクロロフィルとしてヒトの血中の酸素運搬や植物の光合成などの生命活動に関与する。[12, 13] このように特徴的な物理化学的および生化学的性質を示すことからピロールは様々な分野の科学者にとって興味深い含窒素ヘテロ環化合物である。中でも高度に官能基化された多置換ピロールは数多くの医薬品や生物活性物質に含まれる重要な基本構造の 1 つである。例えば、高コレステロール血症治療薬である HMG-CoA 還元酵素阻害剤のアトルバスタチンや、腎細胞がん治療薬であるチロシンキナーゼ阻害剤のスニチニブ、各種がん細胞に対して強い細胞毒性を示す海洋天然物のラメラリン D に含まれている (Figure 1)。これらの興味深い活性を示すことから、これまでに数多くの多置換ピロールの合成研究が行われてきた。

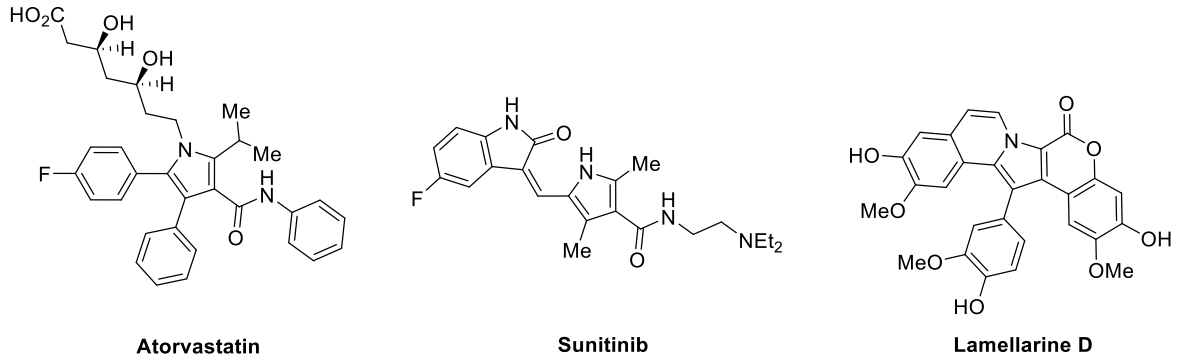
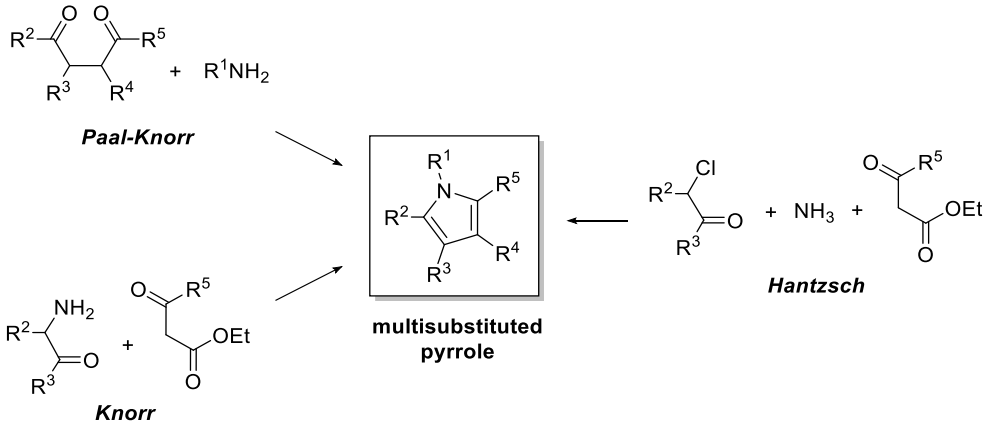


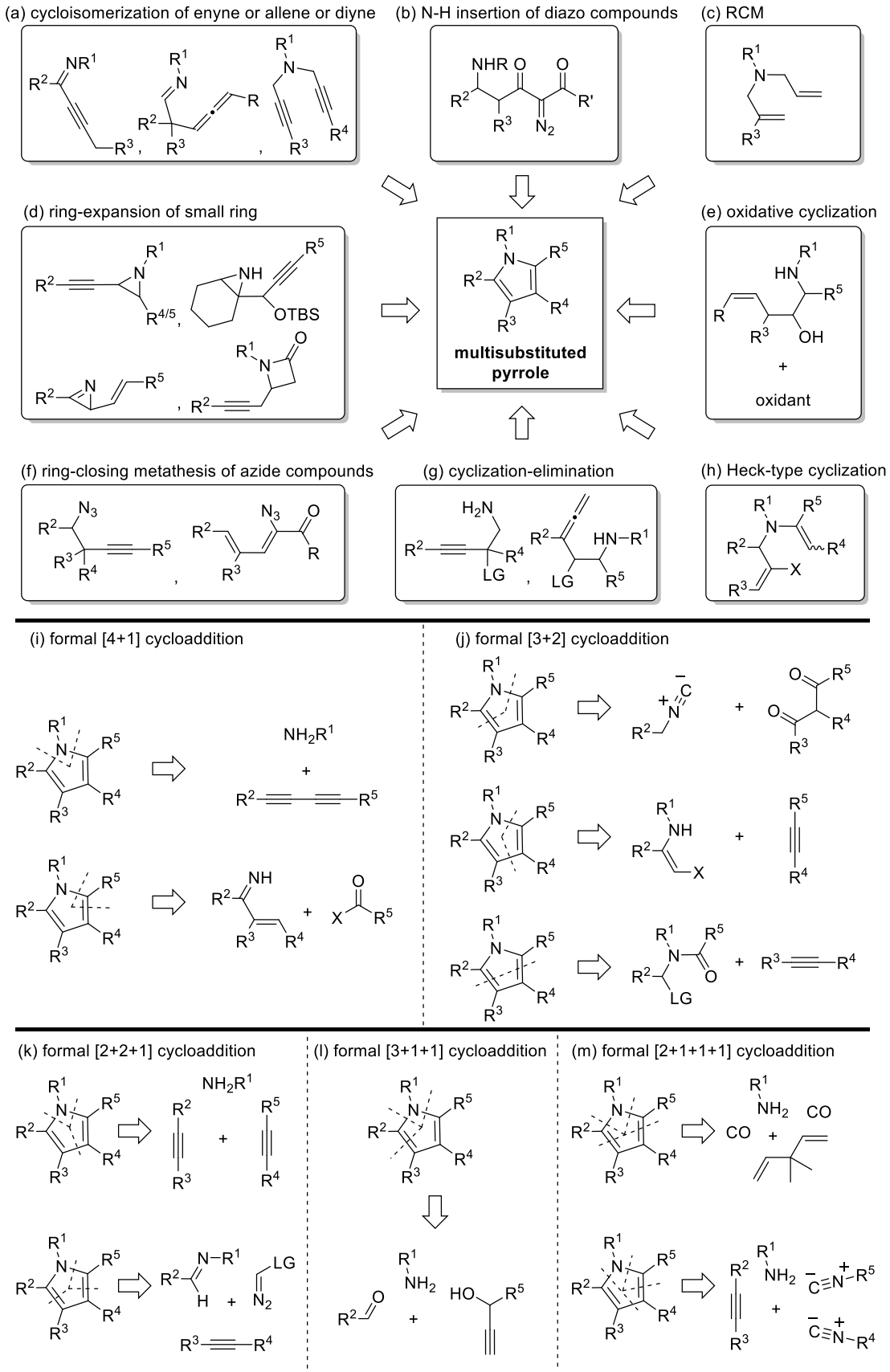
Figure 1. Biologically active compounds bearing multisubstituted pyrrole moiety.

古典的な多置換ピロールの合成法として 1,4-ジケトンと第 1 級アミンの縮合反応である Paal-Knorr 法 [14] 、α-アミノケトンと活性メチレン化合物との縮合反応である Knorr 法 [15] およびα-ハロケトンとβ-ケトエステルにアンモニアまたはアミンを作用させる Hantzsch ピロール合成法 [16] などが知られている (Scheme 13)。これらの縮合反応を促進するためには、高温条件または強酸の使用がしばしば必要であるため、適用できる基質には制限がある。さらに、これらの縮合反応はいずれも 2 分子の水が脱離するため原子効率に改善の余地がある。



Scheme 13. Classic approaches to access multisubstituted pyrroles.

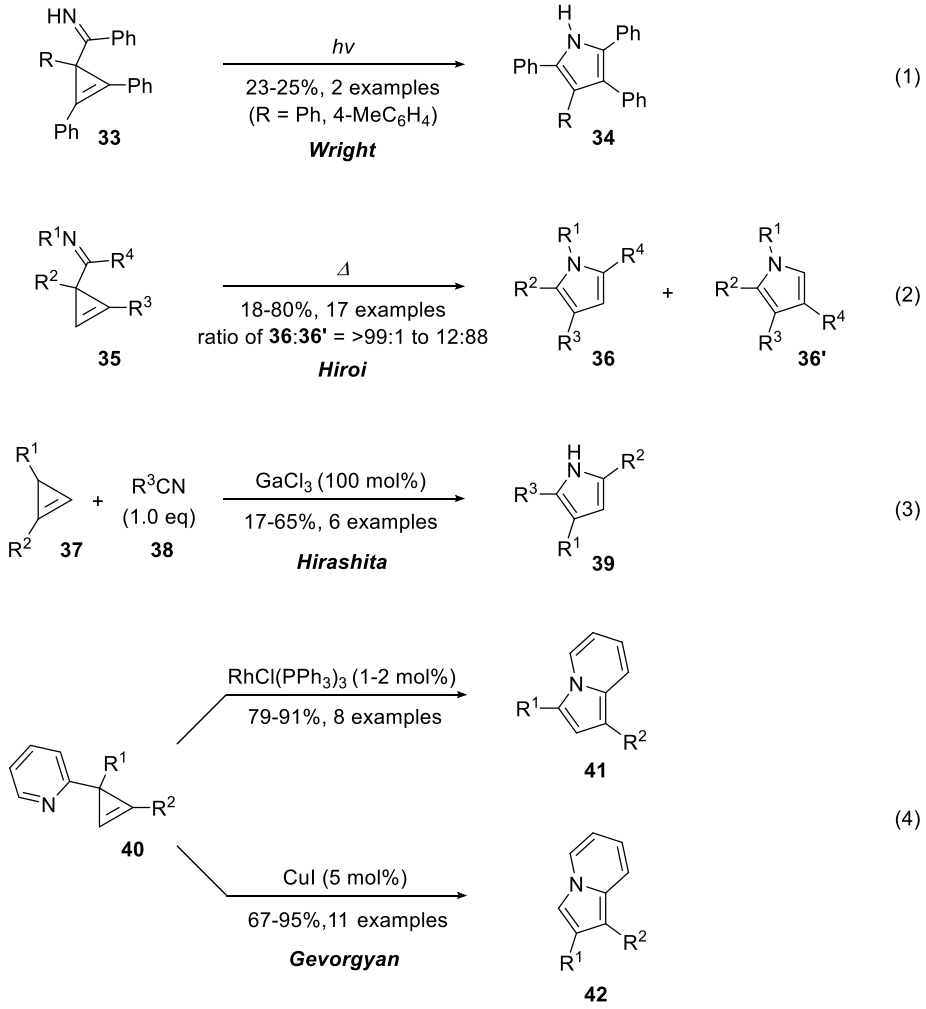
近年、温和な条件下、高い原子効率で含窒素ヘテロ環を構築する最も強力な手法の 1 つとして遷移金属触媒を用いた環化反応が発展してきている。[4] ピロールの合成に関しても様々な反応様式により種々の多置換ピロールの合成法が見いだされている。これらの反応を用いる成分の数に着目し、3 つに分類した (Scheme 14)。1 つ目は 1 成分の分子内反応による多置換ピロール構築法であり、代表的な例として (a) 分子内に炭素－炭素二重結合や三重結合部位を含むアミンまたはイミンの環化異性化反応、[17] (b) ジアゾ化合物を用いた N-H 挿入反応、[18] (c) ジイン化合物の閉環メタセシス反応、[19] (d) アジリジン、アジリン、β-ラクタムなどの含窒素小員環化合物の環拡大反応、[20] (e) 鎖状アミンの酸化的環化反応、[21] (f) アジド化合物の閉環メタセシス、[22] (g) ホモプロパルギルアミンまたはアレニルアミンの付加-脱離反応、[23] (h) ジイン化合物の Heck 型反応などがある。[24] 2 つ目は 2 成分の分子間反応であり、(i) 形式的[4+1]-付加環化反応、[25] (j) 形式的[3+2]-付加環化反応がこれに該当する。[26] 3 つ目は 3 成分以上の形式的な付加環化反応による多成分連結反応であり、これまでに (k) 形式的[2+2+1]-付加環化反応、[27] (l) 形式的[3+1+1]-付加環化反応、[28] (m) 形式的[2+1+1+1]-付加環化反応が報告されている。[29] このように多置換ピロールの構築に関して多数の合成法が開発されているが、大半の報告例において 1 つ以上の問題を抱えていることから (位置選択性、低い原子効率、不十分な収率、長い反応時間、厳しい反応条件、高価または湿気に敏感な触媒の使用、毒性の有機溶媒の使用、複雑な反応操作など)、現在でも、新たな多置換ピロールの合成法の開発が望まれている。



Scheme 14. Transition metal-mediated synthesis of multisubstituted pyrroles.

一方、シクロプロペンは 3 員環内に二重結合を有する炭素環であり、高いひずみエネルギーを有している (54.5 kcal/mol)。[5] 故にシクロプロペン内の炭素－炭素不飽和結合は、通常のアルケン、アレン、アルキンよりも反応性が高く、特異な反応性を示す。シクロプロペンの触媒的な環化異性化反応は、高い原子効率で種々の環状化合物を構築できる反応であり、炭素環 [30] 、含酸素ヘテロ環 [31]、含窒素ヘテロ環 [32] の合成についてはこれまでに多数の報告例があるが、ピロール類の構築の例に関しては 4 例のみであった。

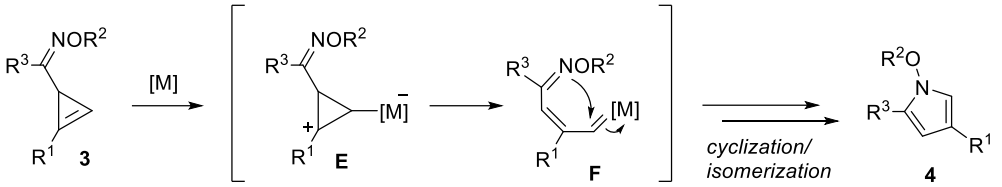
Wright らおよび廣井らのグループはイミノシクロプロペン類の光 [33] および熱 [34] による環化異性化反応により四置換ピロールが得られることを報告している (Scheme 15, eq 1 and 2)。これらは試薬を必要としない環境調和性に優れた反応ではあるが、収率、反応の位置選択性などに改善の余地がある。また、平下らはシクロプロペンに対するニトリルの付加から始まる三置換ピロールの合成法を見出しているが、化学量論量の $GaCl_3$ が必要であることから効率的な多置換ピロールの構築法とは言い難い (eq 3)。[35] また Gevorgyan らは 3-(2-ピリジル)シクロプロペンと Wilkinson 試薬または CuI を用いた環化異性化反応により、



Scheme 15. Synthesis of multisubstituted pyrroles by cycloisomerization of cyclopropenes.

位置選択性に優れた縮環型ピロールの効率的な合成法を見出している (eq 4)。[36] しかし、より多様な多置換ピロールの構築のために汎用性の高い合成法の開発が望まれている。

そこで著者は、高い原子効率かつ位置選択性に優れた多置換ピロール類の合成法の確立を目指して、π-Lewis酸性の遷移金属触媒を用いたシクロプロペニルイミンの環化異性化反応を計画した (Scheme 16)。すなわち、シクロプロペニルイミン**3**に対して遷移金属触媒を用いれば、シクロプロペン内のアルケン部位に遷移金属触媒の付加反応が進行し、シクロプロピルカチオン**E**が生成すると考えられる。続いて、シクロプロペンと同様に高いひずみエネルギーをもつシクロプロパンのひずみの解消を駆動力として、炭素－炭素結合の開裂を伴って金属カルベン中間体**F**が生成する。その後、金属カルベン中間体の求電子性の炭素原子に対して窒素原子の分子内求核付加反応が進行することで、*N*-アルコキシピロール**4**が得られると考えた。加えて、置換様式の異なるシクロプロペン類を用いれば様々な多置換ピロールを高い原子効率で構築できることが想定された。



Scheme 16. Transition-metal catalyzed cycloisomerization of cyclopropenylimine.

第 1 節　反応条件の探索

はじめに、ベンジル基を有するシクロプロペニルイミン **5a** の *E*/*Z* 混合物を用いて環化異性化反応を検討した (Table 5)*[1]。THF 還流下、触媒として $CuBr_2$ を用いて反応を行うと、目的の異性化反応が進行し 1-ベンジルオキシ-4-ブチル-2-フェニルピロール (**9a**) が 19%の収率で得られた (entry 1)。本反応は位置選択的に進行し、位置異性体である 1-ベンジルオキシ-2-ブチル-5-フェニルピロールは生成せず、単一の三置換ピロール **9a** のみが得られた。次に三置換ピロール **9a** の収率向上を目的として、数種のハロゲン化銅を用いて反応を検討したところ、$CuCl_2$ を用いた場合に収率が 34%に向上したが、1 価の銅触媒では目的物は低収率でしか得られなかった (entries 2-4)。続いて異なる金属種として $AgBF_4$ や $AuCl_3$ を用いて環化異性化を試みたが本反応に有効ではなかった (entries 5 and 6)。さらに Brønsted 酸触媒として触媒量の酢酸を試したが、反応は全く進行しなかった (entry 7)。このことから、本反応の進行にはハロゲン化銅が有効であり、$CuCl_2$ が最も良い触媒であることが分かった。また、$CuCl_2$ を 10 mol%に減量して反応を行ったが反応時間の延長や収率の低下は認められなかった (entry 8)。次に反応に有利な配座を取り易くなることを期待して、より高沸点の溶媒を用いて反応を行ったが、三置換ピロール **9a** の収率が低下した (entries 9-11)。また、シクロプロペニルイミンの酸素原子上の置換基効果に関して検討したところ、*O*-アリルオキシム **6a** および *O*-メチルオキシム **7a** の環化異性化反応は効率的に進行したが、オキシム **8a** からは対応するピロール **12a** は得られなかった (entries 12-14)。この結果から、本反応はシクロプロペニルイミンの酸素原子上の置換基の嵩高さに強く影響を受け、嵩の低い置換基ほど収率が向上する傾向が認められた。しかし、最も嵩が低いオキシム **8a** を用いても反応は全く進行しなかった。これは基質が触媒に強く配位することで、触媒が失活したことが原因であると考えている。以上の結果から、本環化異性化反応における最適な条件を、THF 還流下、触媒として 10 mol%の $CuCl_2$ を用いる entry 8 とした。

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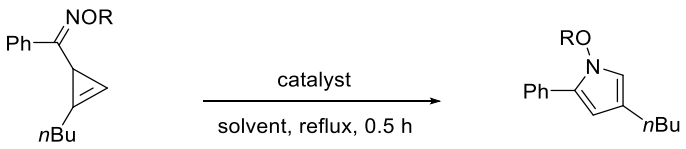
*[1] 本節で用いたシクロプロペニルイミン **5a-8a**, **7b-7d** は、シクロプロペニルケトン **44a-44d** をピリジン存在下、ヒドロキシアミン塩酸塩 **45a-45d** と縮合することで合成した。シクロプロペニルケトン **44a-44d** は触媒量の酢酸ロジウム存在下、アルキンとジアゾアセトフェノン(**43**)とのシクロプロペン化により得られた。なお、詳細については第 4 章第 1 節に記載した。

Table 5. Optimization of cycloisomerization reaction for the synthesis of multisubstituted pyrroles.



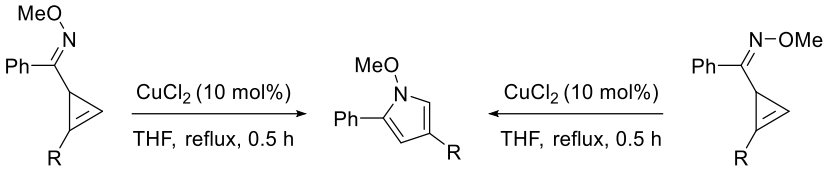
5a-8a **9a-12a**

entry	substrate [a)]	catalyst (mol %)	solvent	product	yield (%)
1	(*E*/*Z*)-**5a**: (R = Bn)	$CuBr_2$ (20)	THF	**9a**	19
2	(*E*/*Z*)-**5a**: (R = Bn)	$CuCl_2$ (20)	THF	**9a**	34
3	(*E*/*Z*)-**5a**: (R = Bn)	CuI (20)	THF	**9a**	3
4	(*E*/*Z*)-**5a**: (R = Bn)	CuBr (20)	THF	**9a**	15
5	(*E*/*Z*)-**5a**: (R = Bn)	$AgBF_4$ (20)	THF	**9a**	ND
6	(*E*/*Z*)-**5a**: (R = Bn)	$AuCl_3$ (20)	THF	**9a**	ND
7	(*E*/*Z*)-**5a**: (R = Bn)	AcOH (20)	THF	**9a**	NR
8	(*E*/*Z*)-**5a**: (R = Bn)	$CuCl_2$ (10)	THF	**9a**	33
9	(*E*/*Z*)-**5a**: (R = Bn)	$CuCl_2$ (10)	PhH	**9a**	20
10	(*E*/*Z*)-**5a**: (R = Bn)	$CuCl_2$ (10)	PhCl	**9a**	5
11	(*E*/*Z*)-**5a**: (R = Bn)	$CuCl_2$ (10)	DCE	**9a**	13
12	(*E*/*Z*)-**6a**: (R = allyl)	$CuCl_2$ (10)	THF	**10a**	60
13	(*E*/*Z*)-**7a**: (R = Me)	$CuCl_2$ (10)	THF	**11a**	60
14	(*E*/*Z*)-**8a**: (R = H)	$CuCl_2$ (10)	THF	**12a**	ND

a) *E*/*Z* ratio of cyclopropenylimines **5a**−**8a** is 3:1.

次に、C=N 結合の幾何異性が反応性に与える影響および、シクロプロペニルイミンの 2 位の置換基効果について検討した (Table 6)。シクロプロペニルイミン(*Z*)-**7a** または(*E*)-**7a** を見出した最適条件で処理すると、*Z* 体の **7a** からは 66%の収率、*E* 体の **7a** からは 58%の収率で三置換ピロール **11a** が得られた。続いて 2 位にイソブチル基、シクロペンチル基、*tert*-ブチル基を有するシクロプロペニルイミン **7b-7d** を用いて環化異性化反応を行った。その結果、いずれの場合も *E* 体のシクロプロペニルイミンを用いた反応では、*Z* 体の反応よりピロールの収率が低下することが明らかになった。特に *tert*-ブチル基のような嵩高い置換基を有する場合では *Z* 体の基質では速やかに原料が消費されたのに対して、*E* 体の基質は 77%の原料が幾何異性を保持したまま *E* 体として回収された。これらの結果は、窒素原子の非共有電子対とシクロプロペン環が *syn* の位置関係の場合にのみ環化異性化反応が進行していることを示唆している。すなわち、非共有電子対とシクロプロペン環の位置関係が *anti* である *E* 体のシクロプロペニルイミンの反応では、環化異性化の過程で *Z* 体への異性化を経由しているため収率が低下したものと考えている。

Table 6. Effects of the geometry and substituent at the 2-position of the cyclopropenylimines.



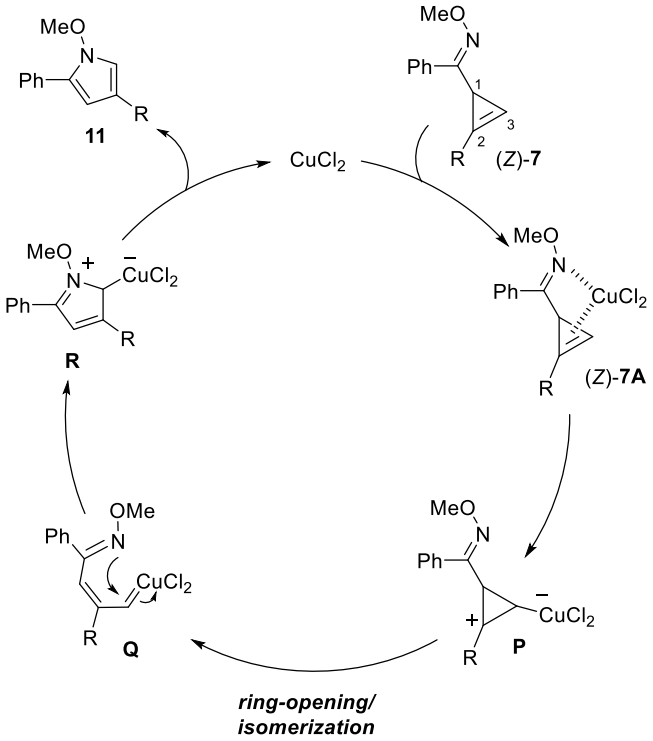
(*Z*)-**7a-7d** **11a-11d** (*E*)-**7a-7d**

entry	R	geometry of C=N	product	yield (%) [a]
1	*n*Bu	*Z*	**11a**	66
2	*n*Bu	*E*	**11a**	58
3	*i*Bu	*Z*	**11b**	85
4	*i*Bu	*E*	**11b**	57
5	c-pentyl	*Z*	**11c**	53
6	c-pentyl	*E*	**11c**	42
7	*t*Bu	*Z*	**11d**	76
8	*t*Bu	*E*	**11d**	10 (77)

a) Yield in parentheses is for the recovered starting material.

第 2 節　反応経路の考察

Z 体のシクロプロペニルイミンの環化異性化反応の推定反応経路を Scheme 17 に示す。まず、シクロプロペニルイミン(*Z*)-**7** の窒素原子とシクロプロペンの炭素－炭素二重結合部位に $CuCl_2$ が配位することで中間体(*Z*)-**7A** が生成する。次に、アルケン部位に $CuCl_2$ が位置選択的に付加することでシクロプロピルカチオン **P** が形成される。[31e, 31f] 次にシクロプロパン環の開環を伴って銅カルベン **Q** が生成する。続いて、イミン窒素がカルベン炭素を求核攻撃することで閉環反応が進行し、ピロリウム中間体 **R** が生成する。最後に触媒が脱離し、芳香族化することでピロール **11** が生成したと考えている。



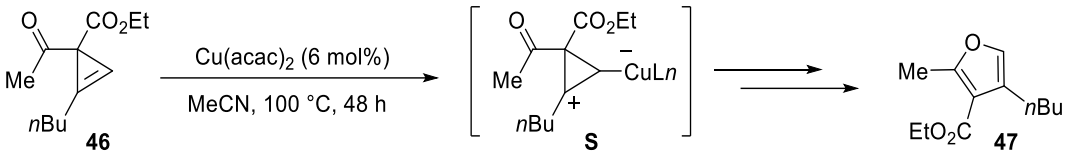
Scheme 17. Plausible reaction pathway.

次に、本反応の詳細について以下の項目について詳しく説明する。

1. シクロプロペニルイミンと $CuCl_2$ の付加反応に関する位置選択性 (**7** → **P**)
2. *E* 体のシクロプロペニルイミンの反応経路
3. シクロプロペニルイミン **7a-7d** の幾何異性による収率の差異に関する考察

1. シクロプロペニルイミンと $CuCl_2$ の付加反応に関する位置選択性

シクロプロペニルイミン **7** のアルケン部位に $CuCl_2$ が付加する際に、シクロプロペニルイミンの 2 位および 3 位に遷移金属が付加する可能性が考えられる。Ma らはシクロプロペニルカルボキシレート **46** を $Cu(acac)_2$ で処理することで、位置選択的に環化異性化反応が進行し、多置換フランが得られることを見出している (Scheme 18)。[31e] すなわち $Cu(acac)_2$ を用いると、シクロプロペン環内のアルケン部位に銅触媒が求電子的に付加することでシクロプロピニルカチオン **S** を経由して 2,3,4-三置換フラン **47** が得られている。シクロプロペニルイミンを用いた環化異性化反応の位置選択性の結果から、上述した反応と同様に、シクロプロペニルイミン **7** のアルケン部位に $CuCl_2$ が求電子的に付加する際、第 2 級のカルボカチオンより安定な第 3 級のカルボカチオンが優先的に生成するためシクロプロペンニルイミンの 3 位に $CuCl_2$ が付加していると考えている。

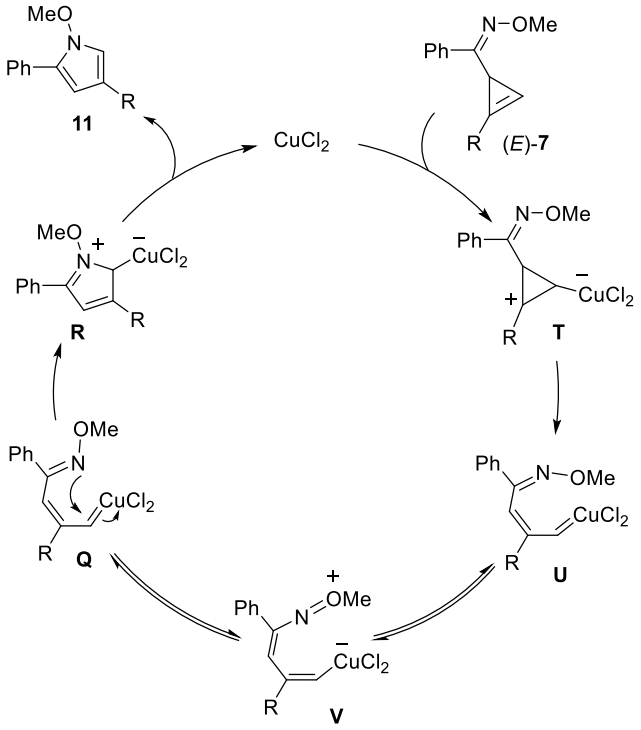


Scheme 18. Catalyst-controlled cycloisomerization reactions of cyclopropenyl carboxylate.

2. *E* 体のシクロプロペニルイミンの反応経路

本環化異性化反応は第 1 章第 1 節で述べた通り、*E* 配置のシクロプロペニルイミンが反応過程で *Z* 配置への異性化を経由して進行していると考えている。また、シクロプロペニルイミン **5a** を THF 還流下、触媒量の酢酸とともに処理した場合、反応が全く進行せず、回収されたシクロプロペニルイミンの *E*/*Z* 異性体混合物の比率に変化がなかった (Table 5, entry 7)。このことから、本環化異性化反応において熱および酸性条件では C=N 結合の異性化反応は進行せず、C=N 結合の異性化には $CuCl_2$ が関与していることが示唆された。なお、一般的なオキシムエーテル類の *E*/*Z* の異性化反応において、熱による異性化反応はほとんど進行しないことが報告されている。[37a] また Lewis 酸を触媒とした異性化においても長い反応時間を要することが知られている。[37b] このことから、シクロプロペニルイミンと $CuCl_2$ による異性化はわずかに進行している可能性はあるが、大部分は開環後に異性化していることが推測された。これらを踏まえ、*E* 体のシクロプロペニルイミンの反応経路を以下のように推定した (Scheme 19)。まず、*E* 体のシクロプロペニルイミン **7** に $CuCl_2$ が付加することでシクロプロピニルカチオン **T** が形成され、シクロプロパン環の開環によりイミン部位が *E* 配置の銅カルベン中間体 **U** が生成する。次にイミン上の酸素原子からの電子の押し出しによりオキソニウム中間体 **V** が形成される。**V** が *Z* 配置の銅カルベン中間体 **Q** に異性化し、**Q** のイミン窒素から銅カルベンの炭素原子への求核付加反応によりピロリニウム中

間体 **R** が生成する。最後に、$CuCl_2$ の脱離と芳香族化が進行することでピロール **11** が得られたと考えている。

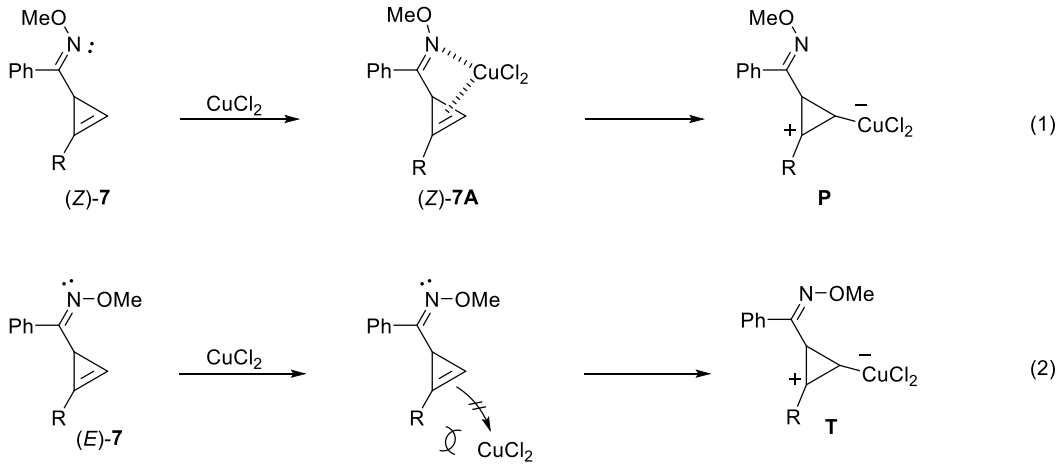


Scheme 19. Plausible mechanism of isomerization of cyclopropenylimine (*E*)-**7**.

3. シクロプロペニルイミン **7a-7d** の幾何異性による収率の差異に関する考察

シクロプロペニルイミン **7a-7d** の反応 (Table 6) における幾何異性による収率の差異は、2 位置換基の立体障害に起因すると考えている。すなわち、本反応の開始段階におけるシクロプロペンのアルケン部位への $CuCl_2$ の配位は、イミンの幾何異性にかかわらず 2 位の置換基によって抵抗を受けるが、*Z* 配置の場合は、イミン窒素の $CuCl_2$ への配位により、(*Z*)-**7A** が形成されることでシクロプロペン環と $CuCl_2$ が反応しやすくなる (Scheme20, eq 1)。そのため、*E* 体に比べて Z 体の反応が効率的に進行し、収率も高くなったと考えている。2 位置換基が第一級または第二級アルキルのように嵩がそれほど大きくない基質 **7a-7c** の反応の場合 (Table 6、entries 1-6) は、イミン窒素の配位による補助を受けなくても、加熱条件により $CuCl_2$ とシクロプロペンのアルケン部位との反応が容易に進行したため、収率に若干の差はあるもののピロール **11a-11c** がまずまずの収率で得られたと考えている。一方、第三級のアルキル基である *tert*-ブチル基をもつシクロプロペニルイミン **7d** では、*E* 体または *Z* 体の環化異性化反応において大幅な反応性の差がみられた。すなわち、(*Z*)-**7d** は速やかに消費されたのに対して、(*E*)-**7d** の場合では 77%の原料が回収された。この結果は、*tert*-ブチル基を有する基質の反応では、アルケン部位と $CuCl_2$ の反応が進行するためには、加熱条件においてもイミン窒素の $CuCl_2$ の配位が重要な役割を担っており、中間体(*Z*)-**7A** を

経なければ、本反応が非常に進行しにくいと考えられる。



Scheme 20. Addition of $CuCl_2$ to cyclopropenylimines (*E*)-**7** or (*Z*)-**7**.

第 3 節　基質一般性に関する検討

様々な置換様式のシクロプロペニルイミン*[2] を用いて環化異性化反応について検討した (Scheme 21)。初めに 1 位と 2 位に置換基を有するシクロプロペニルイミンを用いて環化異性化反応を行った。1 位と 2 位にエチル基を有する(*Z*)-**7e** を用いて反応を行うと、良好に反応が進行し四置換ピロール **11e** が 65%の収率で得られた (eq 1)。続いて、1 位と 2 位の置換基が異なるシクロプロペニルイミン(*Z*)-**7f** を用いて検討を行うと、**11f** とその位置異性体 **11f'**がそれぞれ 47%と 21%の収率で得られた (eq 2)。これら 2 つの生成物は分取薄層クロマトグラフィーにより容易に分離可能であった。位置異性体混合物が得られた原因として、$CuCl_2$ がシクロプロペンのアルケン部位に付加する際に、生成するカルボカチオンの安定性に十分な差がなく、シクロプロペニルイミンの 2 位または 3 位に $CuCl_2$ の付加反応が進行することで位置異性体が得られたと考えている。位置異性体の生成比に差が生じた原因としては、アルキルカチオンに比べてより安定なベンジルカチオンの生成が優先したためと考えている。次に、1 位と 3 位に置換基を有するシクロプロペニルイミン(*E*)-**13** を基質として反応を検討した (eq 3)。シクロプロペニルイミンの 2 位に無置換のベンゼン環を有する **13a** を用いた場合、1 位から 4 位が置換された四置換ピロール **14a** が 77%の収率で得られた。さらに、ベンゼン環上に様々な置換基を有する **13b-13h** を用いても反応が進行し 75-91%の収率で対応する四置換ピロール **14b-14h** が得られることが明らかになった。最後に、未だに効率的な合成報告例の乏しい全置換ピロールの構築を試みた (eq 4)。[7] 1 位から 3 位に置換基を有するシクロプロペニルイミン(*E*)-**15** を用いて反応を行った。ここでは立体障害のために高い熱エネルギーが必要であることが予想されたため、クロロベンゼン中 140 ℃で反応を行うと、1 位から 5 位すべてに置換基を有する全置換ピロール **16** が 56%の収率で得られた。

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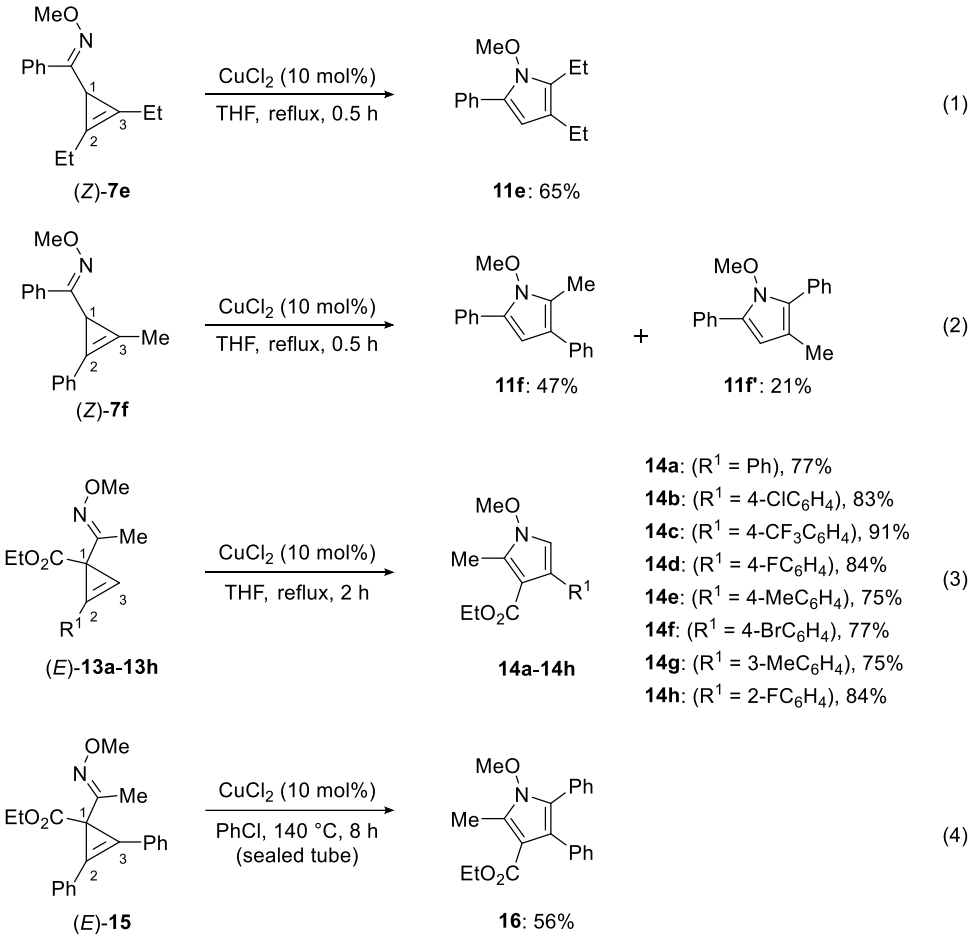
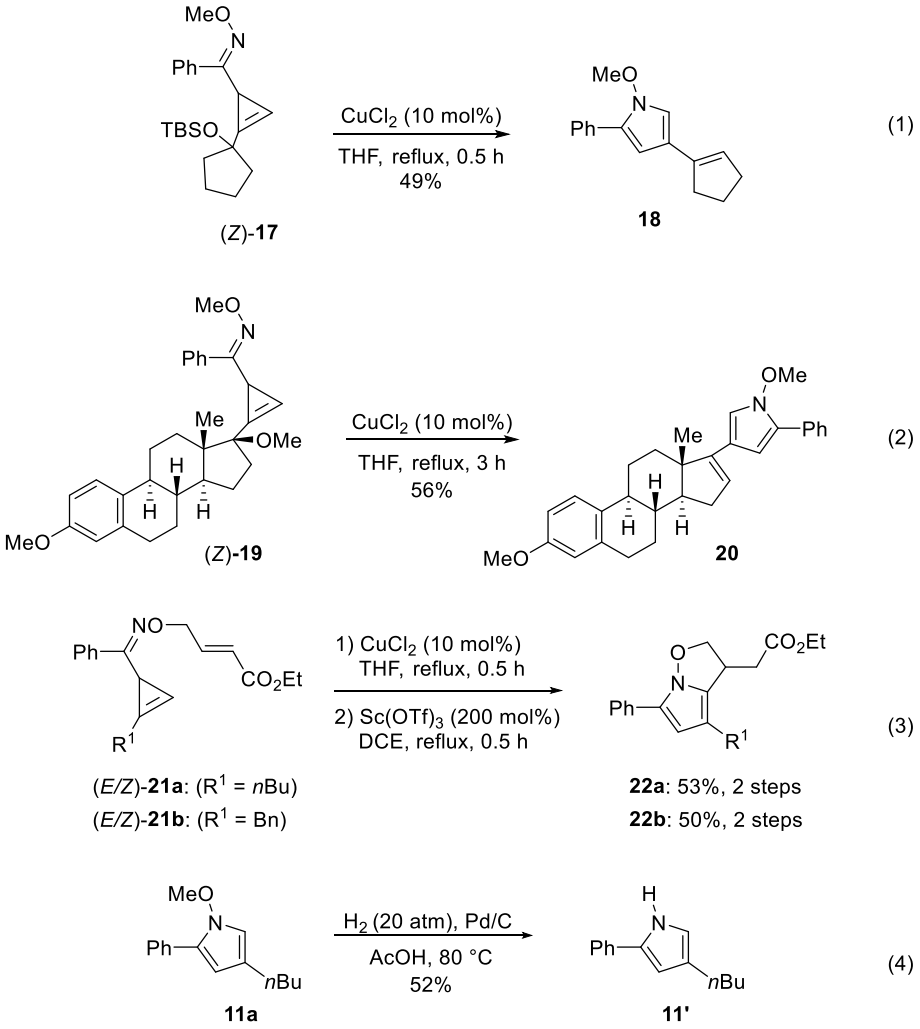
*[2] 本節で用いたシクロプロペニルイミン **7e**, **7f**, **13a-13h**, **15**, **17**, **19** はシクロプロペニルケトン **44e**, **44f**, **48**, **49**, **51a-51h**, **52** をピリジン存在下、ヒドロキシアミン塩酸塩 **45c** と縮合することで合成した。シクロプロペニルケトン **44e**, **44f**, **48**, **49**, **51a-51h**, **52** はロジウム触媒存在下、アルキンとジアゾアセトフェノン(**43**)またはジアゾアセト酢酸エチル(**50**)とのシクロプロペン化により得られた。また、**52** は **51a** とヨードベンゼンとのカップリング反応により合成した。これらの詳細については第 4 章第 2 節に記載した。



Scheme 21. Synthesis of multisubstituted pyrroles from 1-iminocyclopropenes.

さらに本環化異性化反応の有用性を確認する目的でシクロプロペニルイミンの 2'位に酸素官能基をもつ基質の環化異性化反応または*N*-アルコキシピロールを用いた環化反応を行った (Scheme 22)。シクロペンタン環の 2'位にシリルオキシ基を有するシクロプロペニルイミン(*Z*)-**17** を $CuCl_2$ で処理すると、環化異性化とそれに続くシリルオキシ基の脱離により、シクロペンテン環を有するピロール **18** が得られた (eq 1)。続いて、シクロプロペニルイミンの 2 位にステロイド骨格を有する(*Z*)-**19** を反応させたところステロイド骨格を有する三置換ピロール **20** が 56%の収率で得られた (eq 2)。この結果は、本環化異性化がほかの複雑な分子にも適用でき、高い官能基耐性をもつことを示唆している。さらに、クロトニル基を有するシクロプロペニルイミン **21a**, **21b** を環化異性化することで得られると考えられる、*N*-アルコキシピロールの更なる環化反応について検討した (eq 3)。シクロプロペニルイミン **21a**, **21b** に環化異性化反応を行った後、ジクロロエタン還流下、$Sc(OTf)_3$ を用いると分子内環化反応が進行し、ピロロイソキサゾール **22a**, **22b** が 2 工程収率 53%, 50%で得られた。また、ピロール窒素原子上のアルコキシ基は、パラジウム/炭素を用いた接触還元により除去することが可能であり、窒素上に置換基を持たないピロール **11'**への変換も可能であった (eq 4)。

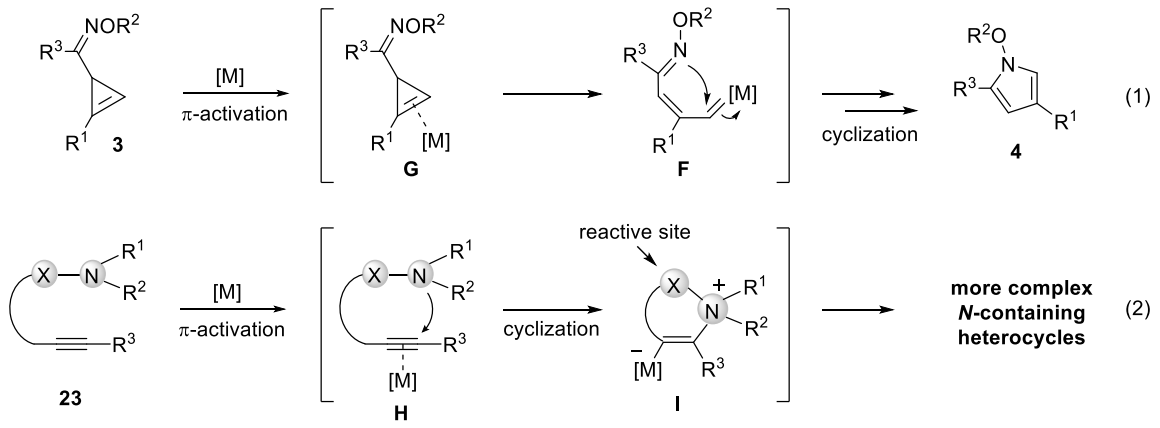


Scheme 22. Cycloisomerization-elimination reaction, synthesis of pyrrolo[1,2-*b*]isoxazoles and reduction of pyrrole.

以上のように著者は、*N*-アルコキシシクロプロペニルイミンと $CuCl_2$ を用いた環化異性化反応による多置換ピロールの合成法を開発した。本環化異性化反応の特徴は、(1) 安価な触媒の使用、(2) 簡便な反応操作、(3) 短い反応時間、(4) 比較的温和な反応条件、(5) 100%の原子効率、(6) 中程度から高収率で全置換ピロールを含む多置換ピロールを位置選択的に構築できる点である。また、これまでにシクロプロペン類の環化異性化による合成報告例のないステロイド骨格を有するピロールおよび全置換ピロールを構築することが可能であり、汎用性に優れた手法である。

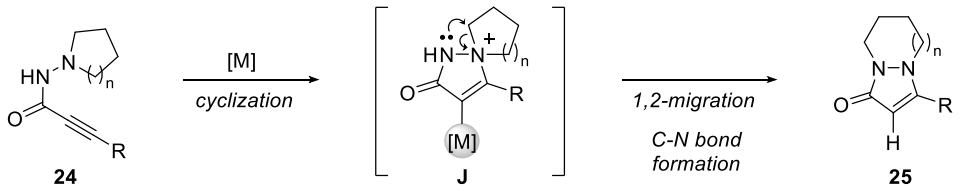
第2章　*N*-ピロリジニルアルキニルヒドラジドの連続的閉環－転位反応の開発

前章で*N*-アルコキシシクロプロペニルイミンと遷移金属触媒を用いた環化異性化反応による多置換ピロールの合成法の開発について述べた。この反応では、シクロプロペニルイミンのシクロプロペン部位をπ-Lewis酸性の遷移金属触媒で活性化することで、金属カルベン中間体**F**が生成し、続いて窒素原子の求核攻撃により閉環反応が進行することでピロール骨格が得られている (Scheme 23, eq 1)。このアルコキシイミンの窒素原子は求核部位として閉環反応に必要であり、酸素原子はα効果[8] によりイミン窒素の求核性の向上およびイミンの安定化への寄与が考えられる。そこで次にこのような特異な性質を持つ連続ヘテロ原子の反応性を利用し、さらに両原子を環内に組み込むヘテロ環の新規合成法を考案した。すなわち、多重結合をπ-Lewis酸性の遷移金属触媒で活性化し、一方の窒素原子の求核攻撃により、含窒素ヘテロ環を反応中間体**I**として構築した後、その窒素原子と結合したヘテロ原子 (X) が反応点となるように分子設計を行えば、連続反応により比較的単純な基質から複雑な含窒素ヘテロ環が構築できると考えた (eq 2)。



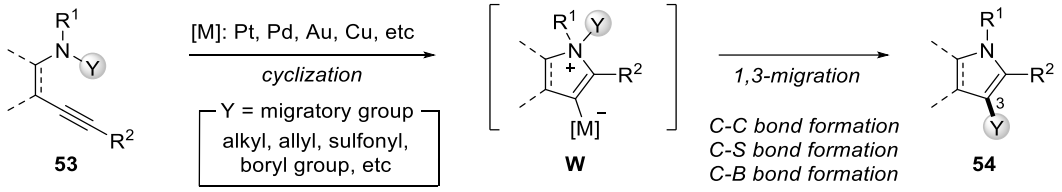
Scheme 23. Our work and working hypothesis for construction of more complex *N*-containig heterocycles.

上記概念を基に、アルキンを活性化した後、連続する2つのヘテロ原子の両方を求核部位とする連続反応を計画した。すなわち環状アミンを有するアルキニルヒドラジドを基質として遷移金属触媒を用いた閉環反応を行えば、スピロアンモニウム中間体**J**に対してアミド窒素からの求核攻撃による1,2-転位反応が進行し、炭素－窒素結合の形成を伴って*N*,*N*-縮環型のピラゾロン類が構築できると想定した (Scheme 24)。



Scheme 24. Sequential cyclization-1,2-migration reaction with C-N bond formation.

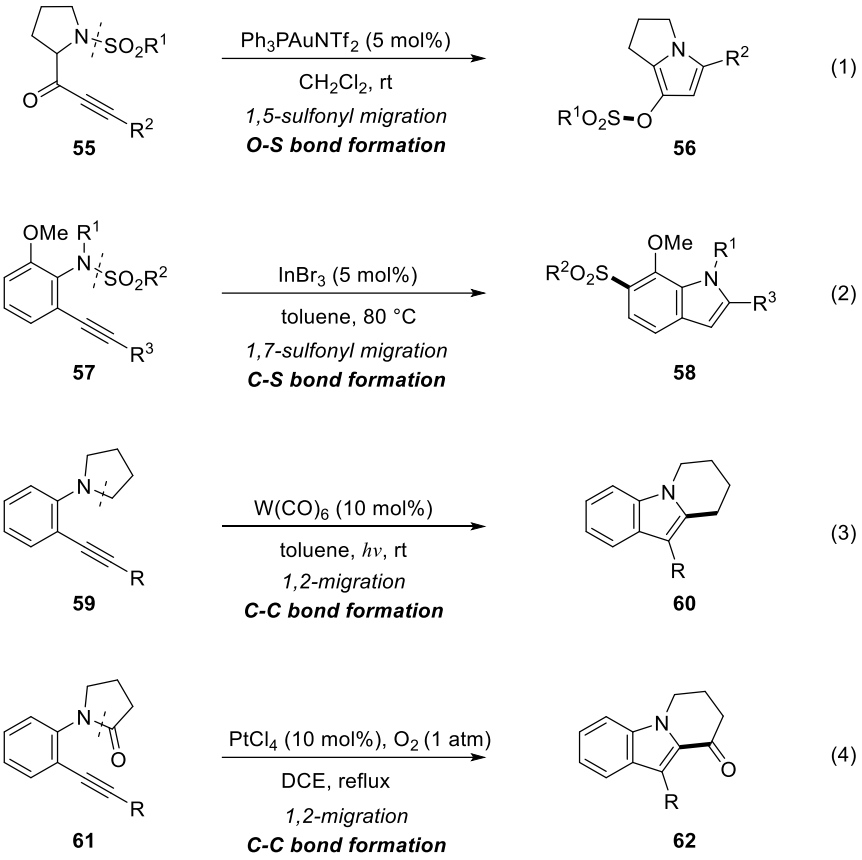
これまでに報告されているアルキンへの窒素原子の求核付加を起点とする閉環－転位反応を利用した含窒素ヘテロ環の合成法について概説する。アルキンへの窒素原子の求核攻撃の後に転位反応が進行する例は、そのほとんどが 1,3-転位反応である (Scheme 25)。すなわち、窒素原子上に転位基 Y を有するアルキニルアミン **53** を種々の遷移金属触媒で処理することで窒素原子からの求核付加反応が進行し、ビニルメタル中間体 **W** が形成される。続いて窒素原子上に存在する転位基の 1,3-転位反応が進行することで 3 位に置換基が導入された含窒素ヘテロ環 **54** が得られる。この 1,3-転位反応の例では、含窒素ヘテロ環の 3 位に新たに形成される結合は、炭素－炭素結合、炭素－硫黄結合、炭素－ホウ素結合の形成が知られている。[38-40)]



Scheme 25. Transition-metal-catalyzed sequential cyclization-1,3-migration reaction.

豊富な閉環－1,3-転位反応を用いた含窒素ヘテロ環化合物の構築例とは対照的に、その他の転位様式で進行する含窒素ヘテロ環構築例は以下に示す例に限られている。Blanc らはピロリジン環を有するイノン **55** を触媒量の $Ph_3PAuNTf_2$ で処理すると閉環－1,5-スルホニル転位反応が進行し、ピロールの 3 位にスルホニルオキシ基を有する **56** が得られることを報告している (Scheme 26, eq 1)。[41)] また、山本らは *o*-アルキニルスルホニルアニリン **57** を 5 mol%の $InBr_3$ で処理することで、閉環と 1,7-スルホニル転位反応が進行し、インドールの 6 位にスルホニル基が導入される手法を見出している (eq 2)。[42)] さらに、岩澤らおよび Zhang らにより、*o*-アルキニルフェニルピロリジン誘導体や *o*-アルキニルフェニルラクタム誘導体をπ-Lewis 酸触媒と反応することで、閉環－1,2-転位反応が進行し、三環性のインドール誘導体へと変換されることが報告されている (eq 3 and 4)。[43)] これらの閉環－転位反応は含窒素ヘテロ環の構築と置換基の導入を高い原子効率で実現出来る有用な反応である。しかし、現状では閉環反応の後に、1,3-転位以外の転位様式で進行する反応例が少なく、構築できる含窒素ヘテロ環の多様性が少ないことが課題である。岩澤らおよび Zhang らのグループによる閉環－1,2-転位反応の例はあるが、これらはいずれも転位反応により炭素－炭素結

合が形成される反応である。今回計画する連続反応のように、アルキンに対する窒素原子の求核攻撃により閉環した後、1,2-転位が進行する反応例において、炭素－窒素結合の形成を伴う転位反応は報告されていない。従って、本閉環－転位反応は窒素－窒素結合で縮環したヘテロ環の新規合成法になり得ると考え本研究に着手した。

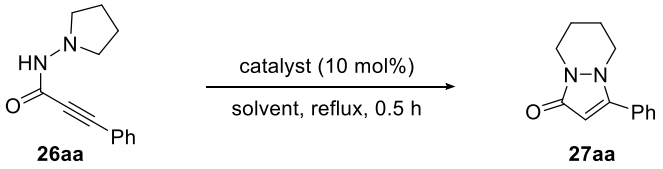


Scheme 26. Transition-metal-catalyzed sequential cyclization-migration reaction.

第１節　反応条件の探索

初めに、ピロリジン環を有するアルキニルヒドラジド **26aa** を基質として閉環－転位反応を様々な条件で検討した (Table 7) *[3]。ジクロロエタン還流下、触媒として $CuBr_2$ を 10 mol% 用いて反応を行うと、所望の閉環－転位反応が進行し、ピラゾロピリダジン **27aa** が 21%の収率で得られた (entry 1)。次に CuBr, $Cu(OTf)_2$ および $CuCl_2$ を用いて反応を行ったが、本閉環－転位反応はほとんど進行しなかった (entries 2-4)。続いて種々の溶媒について還流条件下で検討したところ、ジクロロエタンと同程度の沸点を有するアセトニトリルやエタノールを用いた場合、ピラゾロピリダジン **27aa** の収率はほとんど変わらなかった (entries 5 and 6)。一方、より沸点の高い溶媒として、クロロベンゼンを用いた際に、収率は 42%まで向上した (entry 7)。これらの結果から、本閉環－転位反応は種々の溶媒から受ける影響は小さく、高い熱エネルギーに依存して反応が進行することが示唆された。次に、アルキンと高い親和性を示す金触媒を用いて反応を試みたが、$CuBr_2$ を使用した場合の収率を上回ることはできなかった (entries 8-10)。

Table 7. Optimization of catalysts for cyclization-migration reaction.



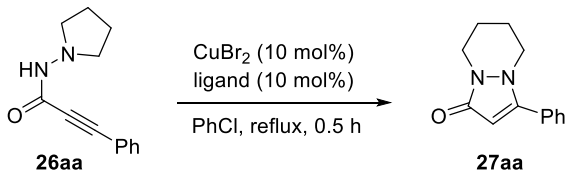
26aa **27aa**

entry	catalyst	solvent / b.p. (°C)	yield (%)
1	$CuBr_2$	DCE / 83	21
2	CuBr	DCE / 83	5
3	$Cu(OTf)_2$	DCE / 83	0
4	$CuCl_2$	DCE / 83	0
5	$CuBr_2$	MeCN / 82	20
6	$CuBr_2$	EtOH / 78	25
7	$CuBr_2$	PhCl / 132	42
8	$AuBr_3$	PhCl / 132	23
9	$PicAuCl_2$	PhCl / 132	7
10	$(PPh_3)AuCl$	PhCl / 132	35

*[3] なお、本章で用いたアルキニルヒドラジド **26** の合成に関してはプロピオール酸 **63** と 1-アミノピロリジン類 **64** との縮合反応により合成しており、詳細については第 4 章第 3-4 節に記載した。

そこで更なる収率の向上を目的として、種々の配位子を用いて反応を検討した (Table 8)。配位子に 2,2'-ビピリジル **L1** を用いたところ収率が 28%に低下したが、1,10-フェナントロリン **L2** では 68%まで収率が向上した (entries 1 and 2)。このことから、**L1** のように構造の自由度が高い配位子は本反応にあまり効果的ではなく、**L2** のように剛直な構造の配位子が適していることが示唆された。そこで、フェナントロリン系の配位子を更に検討した (entries 3-5)。その結果、バソクプロイン (**L5**) を使用すると収率が 93%に向上した。次に、より温和な条件での反応を検討した。クロロベンゼン中、反応温度を 100 ℃まで低下させると、収率が 71%に低下した (entry 6)。また、$CuBr_2$ およびバソクプロインの触媒量を 5 mol%に減量すると、収率が 76%に低下した。以上の結果より、クロロベンゼン還流下、$CuBr_2$ およびバソクプロインを 10 mol%用いる entry 5 を本反応の最適条件とした。

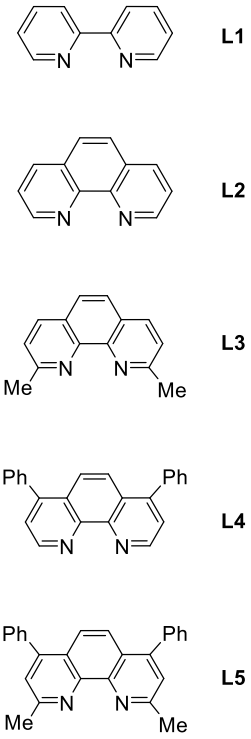
Table 8. Screening of ligands for cyclization-migration reaction.



26aa **27aa**

entry	ligand	yield (%)
1	2,2'-bipyridyl (**L1**)	28
2	1,10-phenanthroline (**L2**)	68
3	neocuproine (**L3**)	64
4	bathophenanthroline (**L4**)	70
5	bathocuproine (**L5**)	93
6[a)]	bathocuproine (**L5**)	71
7[b)]	bathocuproine (**L5**)	76

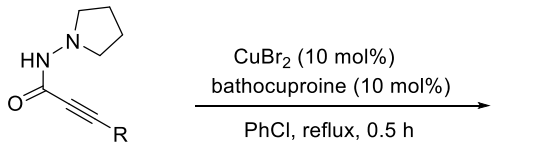
a) The reaction was carried out at 100 °C.
b) The reaction was carried out using 5 mol% of $CuBr_2$ and **L5.**



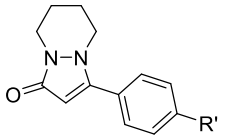
第２節　基質一般性に関する検討

アルキニルヒドラジド **26ab-26at**, **26ba-26ea** を用いて閉環－転位反応の基質一般性について検討した (Table 9)。初めに、アルキン末端に置換したベンゼン環のパラ位に様々な置換基を有するアルキニルヒドラジド **26ab-26ak** を用いて反応を行った。その結果、いずれの基質でも反応が進行し、ピラゾロピリダジン **27ab-27ak** が良好な収率で得られた (68%-96%)。また、ベンゼン環のパラ位に臭素原子をもつピラゾロピリダジン **27af** については単結晶 X 線構造解析によってその構造を確認した。続いて、ベンゼン環のオルト位またはメタ位にメチル基を有するアルキニルヒドラジドからも高い収率でピラゾロン **27al-27an** が得られた(71%-94%)。また、アルキン末端に 1-ナフチル基または 1,3-ベンゾジオキソール構造をもつ基質を用いても反応は問題なく進行した (**27ao**, **27ap**: 76%, 79%)。次に、アルキン末端にアルキル基を有する基質を用いて反応を行った。*n*-ブチル基やシクロヘキシル基のように第1級または第2級アルキル基を有する基質から良好な収率でピラゾロン **27aq**, **27ar** が得られた (72, 94%)。さらに、立体障害の大きな *tert*-ブチル基を有する基質でも、反応時間を延長することで高収率でピラゾロン **27as** が得られた (96%)。銅触媒と反応する可能性のあるイソプロペニル基をもつアルキニルヒドラジド **26at** も、76%の収率でピラゾロン **27at** へと変換された。以上の結果より、本閉環－転位反応はアルキン末端の電子状態や立体効果の影響をあまり受けないことが明らかになった。続いて、環状アミン部位の基質一般性について検討するため、アルキニルヒドラジド **26ba-26da** を用いて本反応を行った。環状アミン部位として、オクタヒドロシクロペンタ[*c*]ピロールまたはインドリンを有する基質からは対応する三環性のピラゾロン **27b** または **27c** がそれぞれ 89%、63%の収率で得られた。また、ピロリジン環内に炭素－炭素二重結合をもつアルキニルヒドラジド **26da** に対しても本閉環－転位反応が適用可能であった。ピロリジン環の 3 位に *N*-Boc 基を有するアルキニルヒドラジド **26ea** を反応させると、位置選択的に反応が進行し、ピラゾロピリダジン **27ea** が 80%の収率で得られた。この反応の位置選択性については第 2 章第 3 節で説明する。

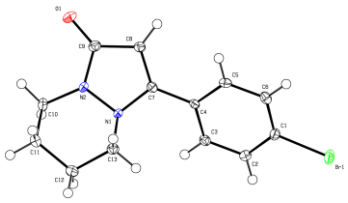
Table 9. Substrate scope for terminal alkyne and cyclic amine moiety of the alkynylhydrazides.



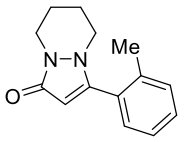
26ab-26at, **26ba-26ea** **27ab-27at**, **27ba-27ea**



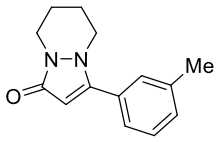
27ab: (R' = Me), 96%
27ac: (R' = OMe), 86%
27ad: (R' = Ph), 83%
27ae: (R' = F), 92%
27af: (R' = Br), 94%
27ag: (R' = CO_2Me), 68%
27ah: (R' = CN), 78%
27ai: (R' = NO_2), 77%
27aj: (R' = CF_3), 83%
27ak: (R' = OMOM), 74%



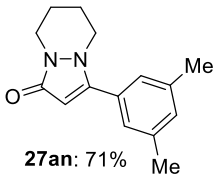
ORTEP of **27af**



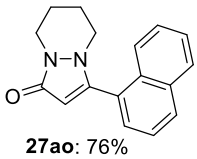
27al: 94%



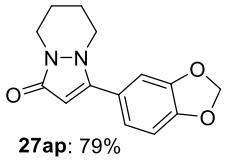
27am: 86%



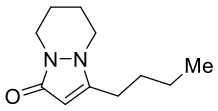
27an: 71%



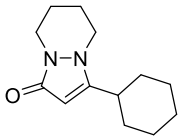
27ao: 76%



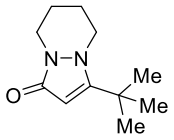
27ap: 79%



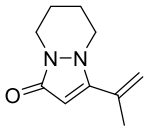
27aq: 72%



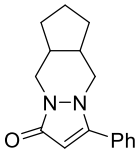
27ar: 94%



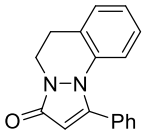
27as: 96%



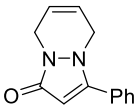
27at: 76%



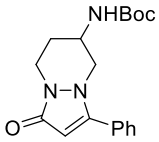
27ba: 89%



27ca: 63%

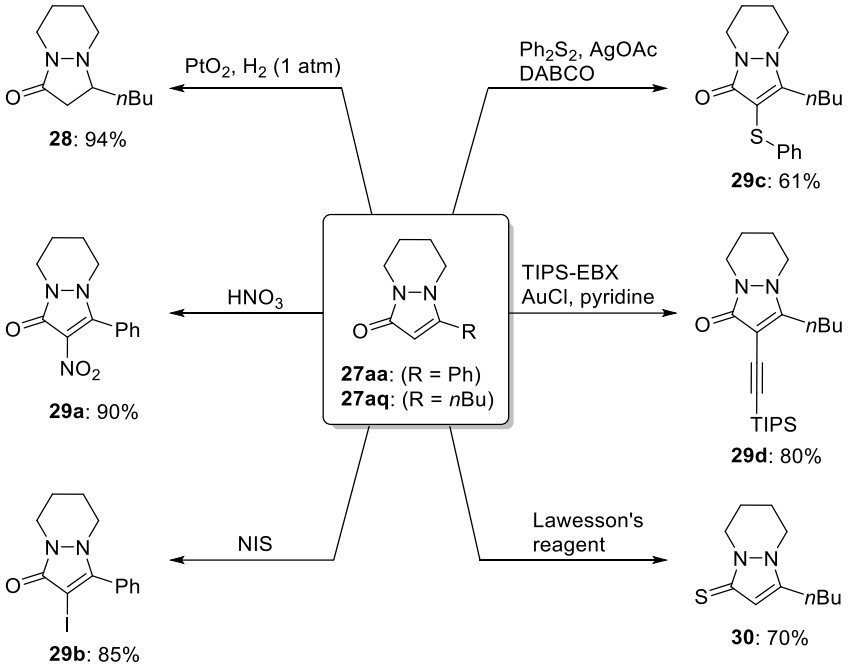


27da: 90%



27ea: 80%

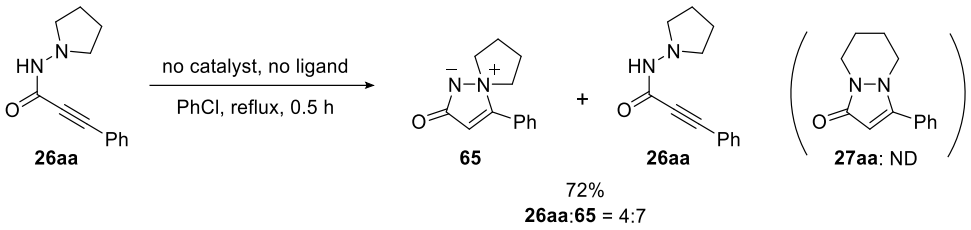
本反応で得られたピラゾロピリダジンの有用性を確認する目的で、ピラゾロピリダジン **27aa** または **27aq** の官能基変換を行った (Scheme 27)。ピラゾロピリダジン **27aq** を水素雰囲気下、酸化白金で処理するとピラゾロン環内の炭素－炭素二重結合が還元され、ピラゾリジノン **28** が 94%の収率で得られた。続いて、ピラゾロピリダジンの 2 位に様々な置換基の導入を試みた。その結果、ニトロ基、[44] ヨード基、フェニルチオ基、[9] アルキニル基 [45] の導入に成功した (**29a-29d**: 61-90%)。また、アミドカルボニル基の変換として、Lawesson 試薬を用いて加熱することでチオピラゾロン **30** が 70%の収率で得られた。



Scheme 27. Transformation of **27aa** or **27aq**.

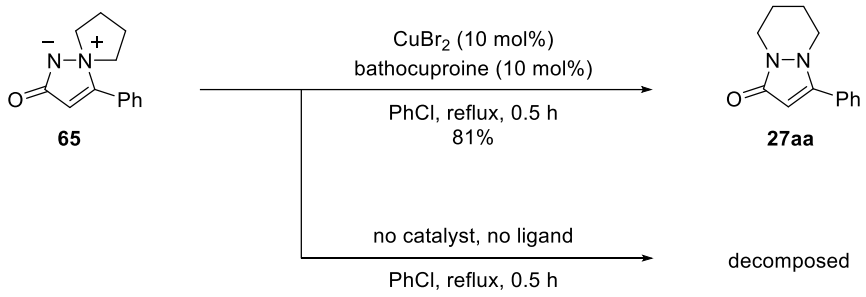
第 3 節　反応経路の考察

本閉環－転位反応の反応経路を推定するため対照実験を行った。初めに、本反応における $CuBr_2$ およびバソクプロインの必要性を明らかにするため、アルキニルヒドラジド **26aa** を $CuBr_2$ およびバソクプロイン非存在下、クロロベンゼン還流条件で 30 分撹拌すると、ピラゾロピリダジン **27aa** は全く得られず、スピロアミンイミド **65** と原料が 4:7 の比で得られた (Scheme 28)。この結果から、加熱のみでも環化反応は進行するが、触媒により閉環および転位の段階が促進されていることが示唆された。



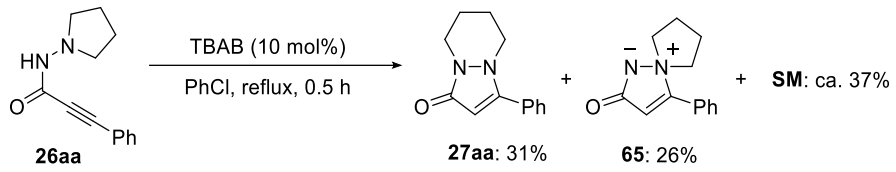
Scheme 28. Cyclization-migration reaction of hydrazide **26aa** without $CuBr_2$ and bathocuproine.

次に、スピロアミンイミド **65** をクロロベンゼン還流下、$CuBr_2$ およびバソクプロインとともに処理したところ、ピラゾロピリダジン **27aa** が 81%の収率で得られた (Scheme 29)。この結果から、スピロアミンイミド **65** が反応中間体であることが示唆された。一方、スピロアミンイミ **65** を触媒および配位子非存在下で処理したところ、基質が分解した。従って、本反応で用いる触媒はスピロアミンイミドの環拡大に寄与していることが明らかになった。



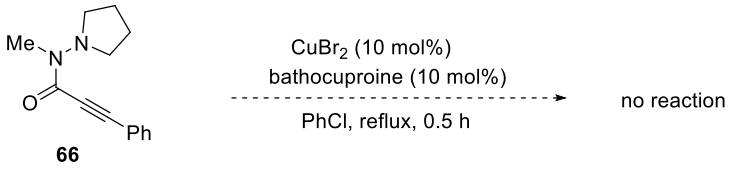
Scheme 29. Cyclization-migration reaction of aminimide **65**.

本反応における臭化物イオンの関与の有無を調べるために、触媒量の TBAB を用いて閉環－転位反応を検討した。その結果、ピラゾロピリダジン **27aa** が 31%、アミンイミド **65** が 26%、アルキニルヒドラジド **26aa** が 37%の収率で得られた (Scheme 30)。本検討で **27aa** が得られたことから、臭化物イオンが転位反応に寄与していると考えられる。



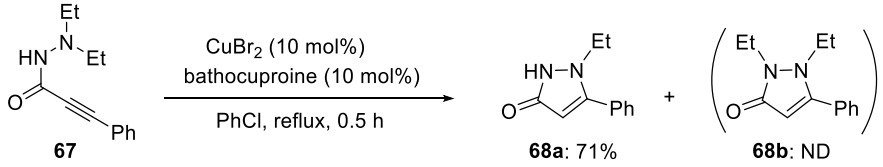
Scheme 30. TBAB-catalyzed cyclization-migration reaction of alkynylhydrazide **26aa**.

続いて、アミド窒素上の水素原子がメチル基で置換された *N*-メチルアルキニルヒドラジド **66** を最適条件で処理したが、反応は全く進行しなかった (Scheme 31)。これは、本反応にアミドプロトンが関与していることを示唆している。



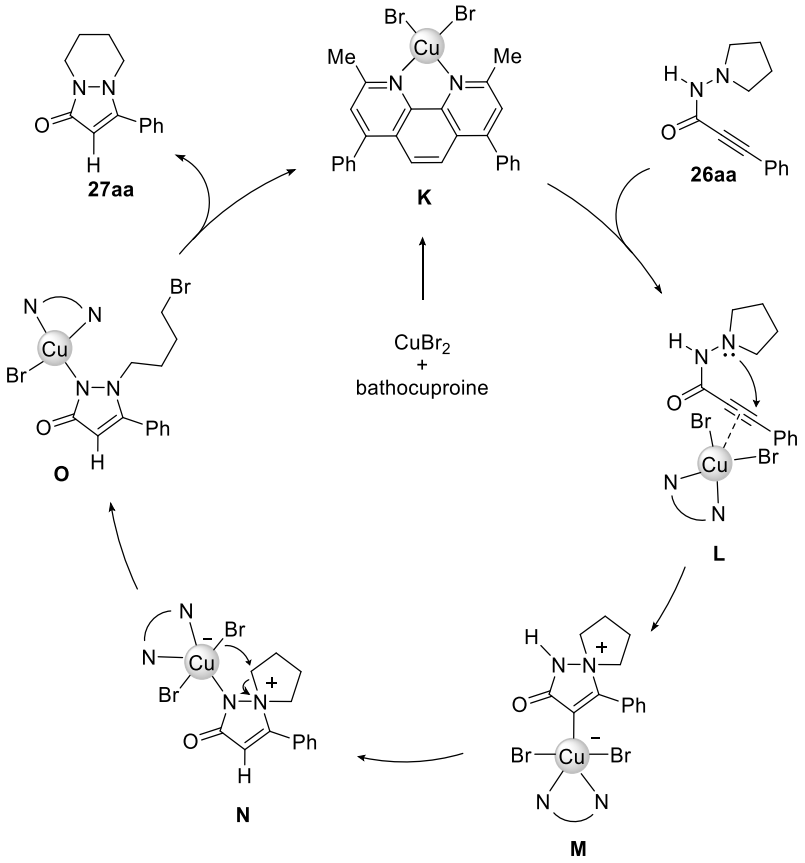
Scheme 31. Cyclization-migration reaction of *N*-methylalkynylhydrazide **66**.

本反応に環状構造が必要であるか確認する目的で、非環状のアルキニルヒドラジド **67** を用いて最適条件下、閉環－転位反応について検討した (Scheme 32)。その結果、エチル基が 1 つ脱離したピラゾロン **68a** は得られたが、転位体 **68b** は得られなかった。この結果から、転位反応が進行するために環状構造が必要であることが分かった。また、ピラゾロン **68a** はアミンイミド中間体からエチル基が脱離して生成したと考えている。



Scheme 32. Cyclization-migration reaction of acyclic hydrazide **67**.

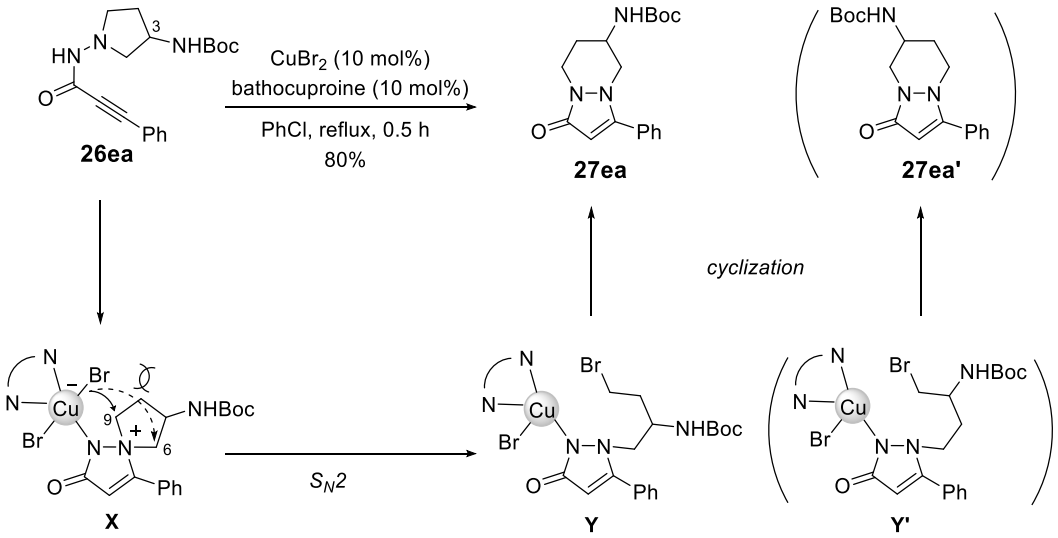
以上の考察を基に、本反応の推定反応経路を Scheme 33 に示す。本反応はまず、銅触媒とバソクプロイン複合体 **K** によりアルキニルヒドラジド **26aa** のアルキン部位が活性化されることで 5-*endo-dig* 環化反応が進行し、スピロアンモニウム中間体 **M** が形成される。続いてアミドプロトンの 1,3-転位により銅アミンイミド **N** が生成する。次にピロリジニウムの窒素原子に隣接する炭素原子に対して銅アミンイミド **N** の臭化物イオンが求核攻撃することで臭化アルキル **O** が生成する。最後に銅アミドと臭化アルキル部位の分子内求核置換反応が進行することで、触媒の再生を伴いピラゾロピリダジン **27aa** が生成したと考えている。なお、**O** に相当する中間体が得られていないことから、臭化アルキル **O** の生成を経ずに、**N** のピロリジニウム部位の炭素－アミド窒素結合の開裂、炭素－臭素結合の形成、アミド窒素－銅結合の開裂、アミン窒素－炭素結合の形成および炭素－臭素結合の開裂が協奏的に進行することで、**27aa** へと変換される可能性も考えられる。



Scheme 33. Plausible reaction pathway.

続いて、本反応における配位子の効果について考察した。まず、フェナントロリン系の配位子が収率の向上に寄与した理由について考察する。1,10-フェナントロリンは弱いσドナー性の配位子として働くことが知られている。[46] そのため、1,10-フェナントロリン配位子が $CuBr_2$ と複合体を形成し、銅の電子密度が増加すると、ブロモ基の求核性が向上する。その結果、ピロリジニウムへの臭化物イオンの付加反応が促進され収率が向上したと考えている。しかし、2,2'-ビピリジルはフェナントロリンよりも強いσドナー性の配位子として働くが、本閉環転位反応には効果的ではなかった。詳細な原因については明らかではないが、考えられる理由の 1 つとして、ピリジンの 2 位の結合が単結合であり、1,10-フェナントロリンに比べて配座の固定されていない自由度の高い配位子であるため、高温条件で銅との複合体を形成しにくかったためと考えている。電子的な要因に加えて、嵩高い配位子であるバソクプロインは立体的な効果により中間体の安定性に寄与したと考えている。前述した通り、5 員環アミンイミド中間体 **65** は熱安定性が低いことが示唆されている (Scheme 29)。この熱による分解経路については明らかではないが、反応温度の上昇に伴い 5 員環アミド同士や夾雑物との分子間反応が分解経路に含まれていると推則している。そのため、嵩高い配位子と銅の複合体が中間体に配位することで、分子間反応による分解経路が抑制された結果、収率が向上したと考えている。

推定した反応機構を基に、第 2 章第 2 節で述べたピロリジン環の 3 位に *N*-Boc 基を有するアルキニルヒドラジド **26ea** を基質とする反応の位置選択性について考察する (Scheme 34)。アルキニルヒドラジド **26ea** が $CuBr_2$ とバソクプロイン複合体により環化し、銅触媒の 1,3-転位反応が進行することで銅アミンイミド **X** が形成される。この銅アミンイミドから臭化物イオンがアミンイミドの 6 位または 9 位を求核攻撃することで、銅アミド **Y** または **Y'**を経由して、位置異性体 **27ea** および **27ea'**が生成する可能性が考えられる。このアミンイミドの 6 位の炭素原子に臭化物イオンが接近すると、*N*-Boc 基との立体反発が生じるため、9 位に優先的に求核攻撃することで、ピラゾロン **27ea** のみが得られたと考えている。



Scheme 34. Regioselectivity of alkynylhydrazide **26ea** for cyclization-migraion reaction.

以上のように著者は、環状アミンを有するアルキニルヒドラジドと $CuBr_2$ およびバソクプロインを用いることで、閉環－1,3-転位－形式的 1,2-転位反応が連続する、ピラゾロピリダジン環の合成法を開発した。本閉環－転位反応は、1 工程で 2 つの炭素－窒素結合および 1 つの炭素－水素結合を一挙に形成し、比較的単純なアルキニルヒドラジドからピラゾロピリダジンを構築できる。また、アルキンへの窒素原子の求核攻撃の後に 1,2-転位反応が進行する反応において、転位の段階で炭素－窒素結合が形成される初めての例である。本反応は操作が簡便で短時間で反応が進行し、原子効率 100%で多様なピラゾロピリダジンが構築できる効率的な手法である。

第 3 章　*N*-ピペリジニルアルキニルヒドラジドの閉環－転位反応によるピラゾロジアゼピン合成法の開発

5員環と7員環が窒素－窒素結合を介して縮環した骨格は、寄生虫トリパノソーマに対する細胞毒性、[47] ACEおよびNEP阻害活性[48] 等をもつ化合物に含まれている (Figure 2)。さらに、急性骨髄性白血病および多発性骨髄腫の異種移植モデルにおいて抗腫瘍活性を示したCB-6644[49] や、抗原提示細胞の増殖と機能に重要な役割を果たすSPPL2aの活性を阻害するSPL-707[50] にもこの骨格が含まれており、近年では新たな抗がん剤および自己免疫疾患治療薬のターゲット分子となることが期待されている。その他にも、オキサジアゼピン環とピラゾロン環が窒素－窒素結合で縮環した骨格を有するピノキサデンおよびそれに類する化合物は除草剤として働くことが知られている。[51] このことから、5員環と7員環が窒素－窒素結合を介して縮環した骨格を有する化合物は、潜在的に医薬品および農薬のシード化合物となる可能性を秘めている。

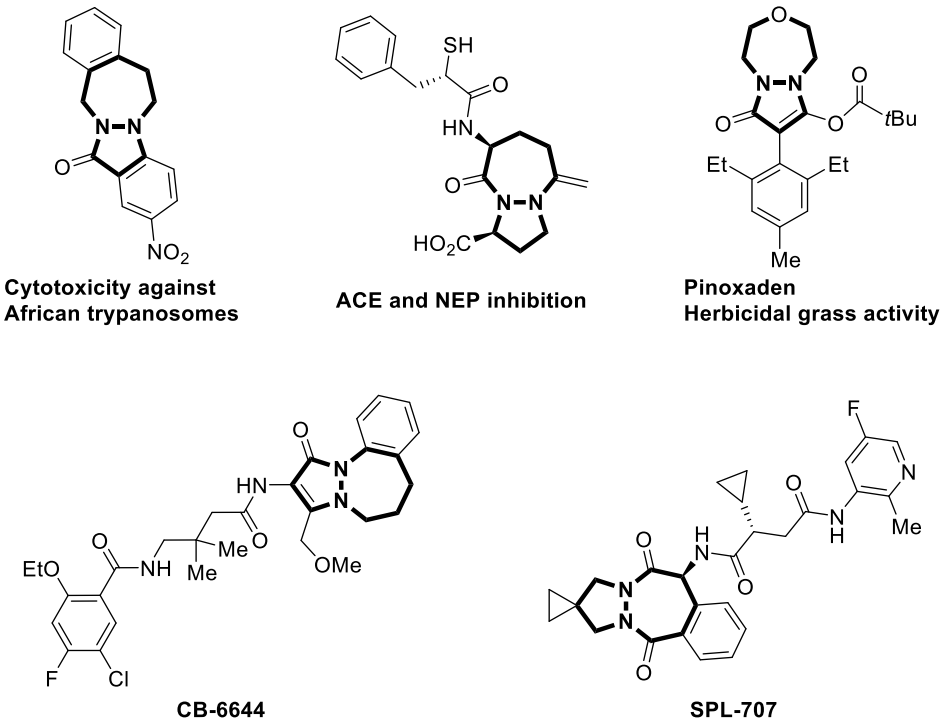
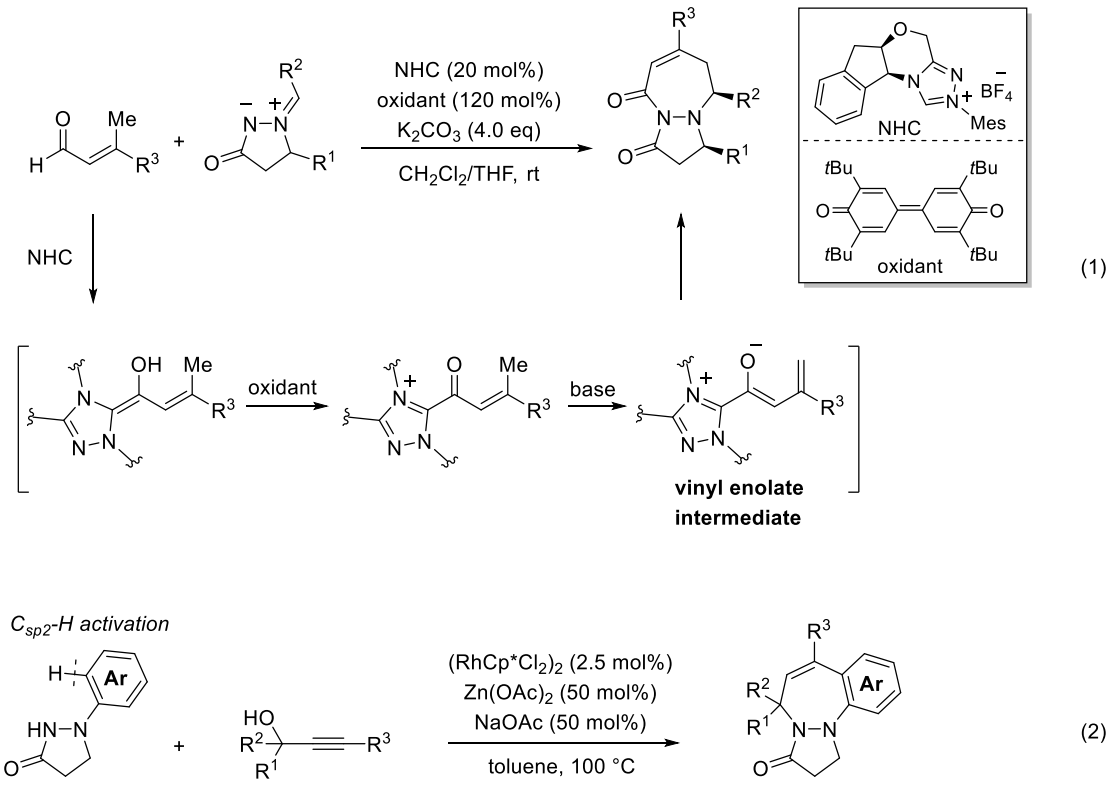


Figure 2. Representative bioactive molecules with a *N*,*N*-5,7-fused skeleton.

しかし、種々の反応により*N*,*N*-5,7-縮環化合物を合成している例は数例報告されているが、[52] 著者の知る限り、これまでに*N*,*N*-5,7-縮環化合物の合成に関して系統的な合成研究が行われた例は付加環化反応に限られている。[10] この付加環化反応について2種類の反応が知られている。1つはアゾメチンイミンを1,3-双極子とする反応であり、もう1つは、ロジウム触媒を用いたC-H活性化を介した反応である。前者の例として、Chiらはα, β-不飽和アルデヒ

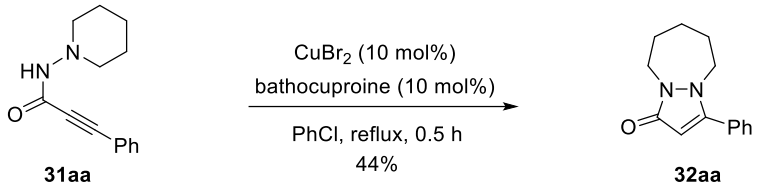
ドにNHC触媒、酸化剤および塩基を用いて発生させたビニルエノラート中間体を1,4-双極子としてアゾメチンイミンと反応させることで*N,N*-5,7-縮環化合物が得られることを見出している (Scheme 35, eq 1)。[10a] 本手法は容易に基質を合成できるため、多様な*N,N*-5,7-縮環化合物の構築法として期待できる。しかし、共役アルデヒドとして適用できる基質はβ位にアリール基またはアルケニル基をもつものに限られている。また、その他の付加環化反応の例としてはベンゾトリアゼピンまたはベンゾオキサジアゼピンを含む三環性化合物の合成に限られている。[10b-10e] もう一方のロジウム触媒を用いたC-H活性化反応を介した付加環化反応例として、Fanらは1-アリール-3-ピラゾリジノンをロジウム触媒で処理すると、アリール基のオルトC_{sp2}-H結合が活性化されることでプロパルギルアルコールとの[4+3]-付加環化反応が進行し、ベンゾジアゼピンと縮環したピラゾリジノンが得られることを報告している (eq 2)。[10g] この反応に代表されるように、これまでに報告されているC-H活性化による*N,N*-5,7-縮環化合物の合成法は、1-アリール-3-ピラゾリジノンのC_{sp2}-H活性化反応のみであり、[10f-10g] 生成物がベンゾジアゼピン骨格を有する化合物に限定されている。このような背景から、多様な*N,N*-5,7-縮環化合物を合成するための新たな合成法の開発が求められている。



Scheme 35. Synthesis of *N,N*-5,7-fused skeleton by [4+3]-cycloaddition.

前章で示したように、ピロリジン環を有するアルキニルヒドラジドの$CuBr_2$とバソクプロインによる閉環－転位反応では、5員環と7員環が窒素－窒素結合を介して縮環したピラゾロピリダジンが得られた。そこで、本反応をピロリジン環より炭素数の1つ多いピペリジン

環を有するアルキニルヒドラジドへ拡張すれば、5員環と7員環が縮環した多様なピラゾロジアゼピン環が容易に構築できると期待した。本反応の実現可能性を調べるため、ピペリジン環を有するアルキニルヒドラジド**31aa**を10 mol%の$CuBr_2$とバソクプロインとともにクロロベンゼン還流下で反応させた (Scheme 36)。その結果、ピラゾロジアゼピン**32aa**は得られたが、中程度の収率に留まった。そこで、本基質に対する更なる反応条件の探索を行うことで、ピラゾロジアゼピン環の新たな合成法を確立することを目指した。



31aa **32aa**

Scheme 36. Cyclization-migration reaction of alkynylhydrazide **31aa** with $CuBr_2$ and bathocuproine.

第１節　反応条件の探索

ピペリジン環を有するアルキニルヒドラジド **31aa** を基質として、閉環－転位反応を様々な条件で検討した (Table 10) *[4]。まず、比較のために、ピペリジン環を有するアルキニルヒドラジド **31aa** を 10 mol%の $CuBr_2$ とバソクプロインとともにクロロベンゼン還流下で反応させた条件を entry 1 として記載した。続いて $CuBr_2$ と同族の中心金属で臭素原子をもつ $AuBr_3$ を触媒に用いて反応を試みた。クロロベンゼン還流下、$AuBr_3$ およびバソクプロイン存在下で反応を行うと、所望の閉環－転位反応が進行し、ピラゾロジアゼピン **32aa** が 53%の収率で得られた (entry 2)。次に、金触媒を用いる際に、配位子が機能しているか確認する目的で、配位子非存在下で $AuBr_3$ を反応させた (entry 3)。その結果、配位子存在下と非存在下の条件で収率に有意な差がなかったことから、金触媒にバソクプロインが配位しないことが示唆された。そこで、配位子非存在下でいくつかの金触媒に関して検討した。$AuCl_3$、AuCl および $PicAuCl_2$ を触媒に用いて反応させたが、本閉環－転位反応はほとんど進行しなかった (entries 4-6)。一方、AuI を用いて反応を行うとピラゾロジアゼピン **32aa** が 92%の収率で得られた (entry 7)。また、異なるハロゲン化金属種として CoI_2、CuI および $PtCl_2$ について検討したところ、CoI_2 は AuI と同程度の収率でピラゾロジアゼピンを与えたが、CuI および $PtCl_2$ を用いても目的の化合物は全く得られなかった (entries 8-10)。続いて、種々の溶媒について還流条件下で検討したところ、1-ペンタノールはクロロベンゼンを用いた場合と同程度の収率でピラゾロジアゼピン **32aa** を与えた (entry 11)。一方で、アセトニトリルまたは 1,4-ジオキサンを溶媒に用いた際には、環化反応が進行したスピロアミンイミド **70** は得られたが、転位体のピラゾロジアゼピンは、ほとんど得られなかった (entries 12 and 13)。この結果から、環化反応より転位反応の段階においてより高い反応温度が必要であることが示唆された。さらに、触媒量について検討した (entry 14)。クロロベンゼン還流下、5 mol%の AuI で処理すると反応時間の延長と収率の低下が認められた。最後に、本反応における AuI の役割を明らかにするため、アルキニルヒドラジド **31aa** を AuI 非存在下、クロロベンゼン還流条件で 12 時間撹拌すると、原料が 15%、ピラゾロピリダジン **32aa** が 8%、スピロアミンイミド **70** が 72%の収率で得られた (entry 15)。AuI 非存在下では原料回収されたことから、AuI がπ-Lewis 酸性の遷移金属触媒として環化の促進に寄与していることが明らかになった。加えて、転位前駆体となるアミンイミド **70** が主生成物として得られたことから、AuI は転位反応の促進に大きく寄与していることが示唆された。以上の結果から、本閉環－転位反応における最適な条件を、クロロベンゼン還流下、10 mol%の AuI を触媒として用いる entry 7 を本反応の最適条件とした。

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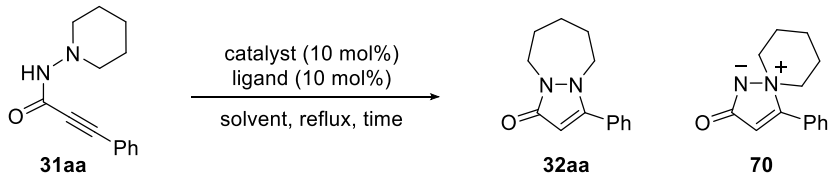
*[4] なお、本章で用いたアルキニルヒドラジド **31** の合成に関してはプロピオール酸 **63** と 1-アミノピペリジン類 **69** との縮合反応により合成しており、詳細については第 4 章第 6-7 節に記載した。

Table 10. Optimization of cyclization-migration reaction.



31aa **32aa** **70**

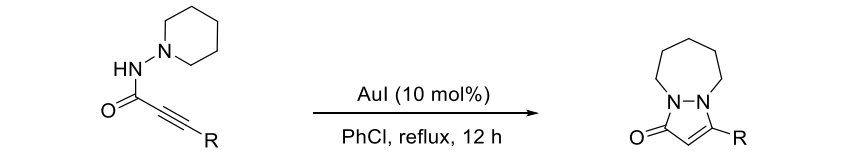
entry	catalyst	ligand	solvent / b.p. (°C)	time (h)	yield (%)
1	$CuBr_2$	bathocuproine	PhCl / 132	0.5	**32aa**: 42
2	$AuBr_3$	bathocuproine	PhCl / 132	1	**32aa**: 53
3	$AuBr_3$	-	PhCl / 132	1	**32aa**: 52
4	$AuCl_3$	-	PhCl / 132	3	ND
5	AuCl	-	PhCl / 132	4	trace
6	$PicAuCl_2$	-	PhCl / 132	1.5	ND
7	AuI	-	PhCl / 132	12	**32aa**: 92
8	CoI_2	-	PhCl / 132	12	**32aa**: 87
9	CuI	-	PhCl / 132	1.5	**32aa**: ND
10	$PtCl_2$	-	PhCl / 132	0.5	**32aa**: ND
11	AuI	-	1-pentanol / 138	12	**32aa**: 89
12	AuI	-	MeCN / 82	12	**32aa**: 4, **70**: 88
13	AuI	-	1,4-dioxane / 101	12	**70**: 50
14[a)]	AuI	-	PhCl / 132	20	**32aa**: 76
15	-	-	PhCl / 132	12	**31aa**: 15, **32aa**: 8, **70**: 72

a) AuI (5 mol%) was used.

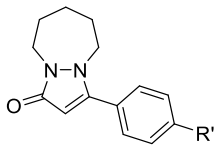
第 2 節　基質一般性に関する検討

アルキニルヒドラジドの閉環－転位反応の基質一般性について検討した (Table 11)。初めに、アルキン末端に置換したベンゼン環のパラ位に様々な置換基を有するアルキニルヒドラジド **31ab-31aj** を用いて反応を行った。その結果、いずれの基質でも反応が進行し、ピラゾロピリダジン **32ab-32aj** が良好な収率で得られた (78%-92%)。また、ベンゼン環のオルト位またはメタ位にメチル基を有するアルキニルヒドラジドからも高い収率でピラゾロン **32al-32an** が得られた (75%-90%)。また、アルキン末端に 1-ナフチル基または 1,3-ベンゾジオキソール構造をもつ基質を用いても反応は問題なく進行した (79%, 93%)。次に、アルキン末端にアルキル基を有する基質を用いて反応を行った。*n*-ブチル基を有する基質からは 80%の収率でピラゾロン **32aq** が得られた。さらに、立体障害の大きな *tert*-ブチル基を有する基質でも、触媒量を 30 mol%に増量し、反応時間を延長することで 73%の収率でピラゾロン **32as** が得られた。これらの結果から本閉環－転位反応は、第 2 章で述べた閉環－転位反応と同様に、アルキン末端の電子状態や立体効果の影響をあまり受けないことが明らかになった。

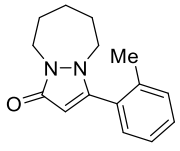
Table 11. Synthesis of pyrazolodiazepines **32ab-32aj**, **32al-32aq**, **32as**.



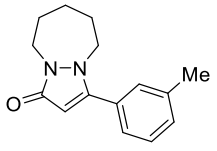
31ab-31ak, **31al-31aq, 31as**　　**32ab-32aj**, **32al-32aq**, **32as**



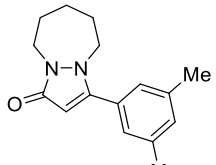
32ab: (R' = Me), 87%
32ac: (R' = OMe), 89%
32ad: (R' = Ph), 85%, 15 h
32ae: (R' = F), 89%
32af: (R' = Br), 82%
32ag: (R' = CO_2Me), 92%
32ah: (R' = CN), 85%
32ai: (R' = NO_2), 84%
32aj: (R' = CF_3), 78%



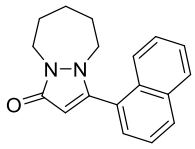
32al: 75%



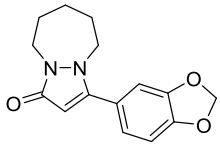
32am: 90%



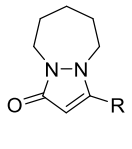
32an: 83%, 18 h



32ao: 79%



32ap: 93%

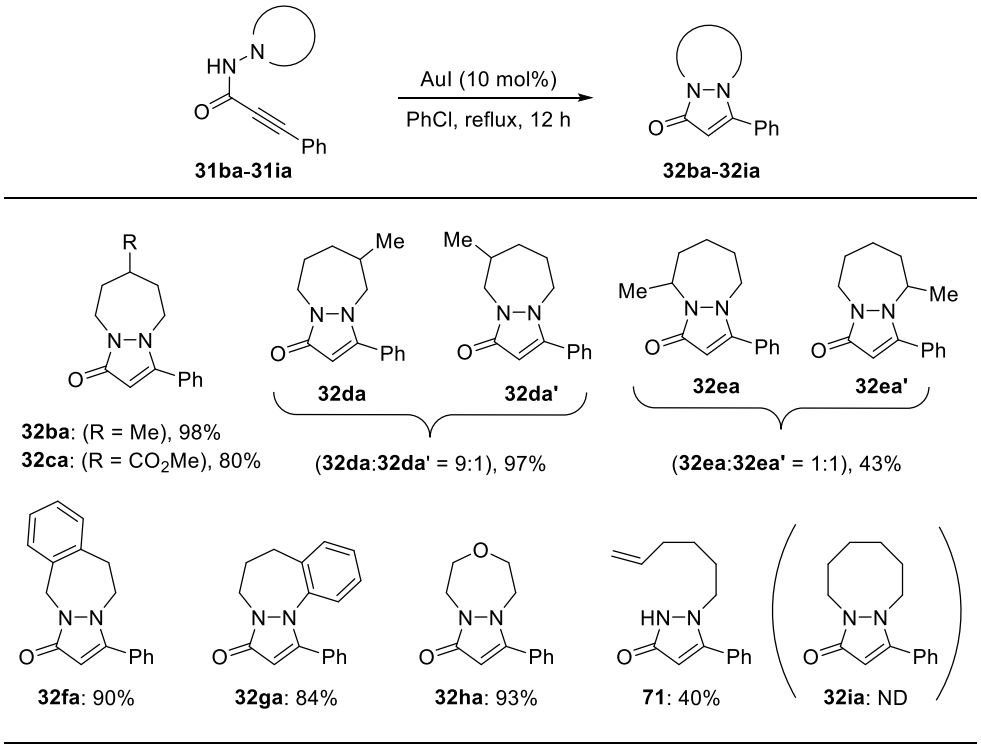


32aq: (R = *n*Bu), 80%
32as: (R = *t*Bu), 73%, 72 h[a)]

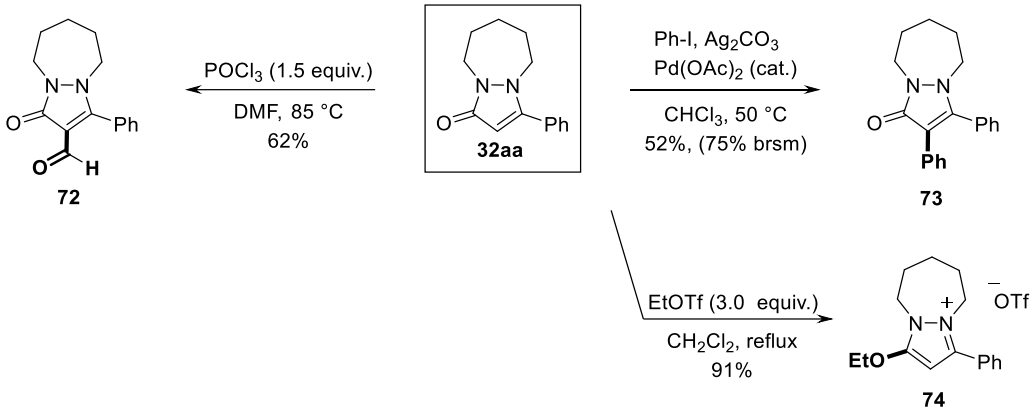
a) The reaction was carried out 30 mol% of AuI.

続いて、環状アミン部位の基質一般性について検討するため、アルキニルヒドラジド **31ba-31ia** を用いて本反応を行った (Table 12)。ピペリジン環の 4 位にメチル基またはエステル基を有するアルキニルヒドラジド **31ba**, **31ca** を用いたところ、収率よく目的のピラゾロジアゼピン **32ba**, **32ca** が得られた (80%, 98%)。次にピペリジン環の 3 位にメチル基を有する基質からは対応するピラゾロジアゼピンの位置異性体 **32da** および **32da'**の混合物が収率 97%、9:1 の比率で得られた。また、ピペリジン環の 2 位にメチル基を有する基質からも対応するピラゾロジアゼピン **32ea** および **32ea'**は得られたが、位置異性体の比率は 1:1 に低下した。これらの反応の位置選択性については第 3 章第 3 節で説明する。続いて、テトラヒドロキノリンまたはテトラヒドロイソキノリンを環状アミン部位にもつ基質からは三環性のピラゾロン **32fa** および **32ga** が得られた (90%, 84%)。さらに、モルホリン環を有する基質はオキサジアゼピン骨格を有するピラゾロン **32ha** を 93%の収率で与えた。より環員数の大きいアゼパン環を有するアルキニルヒドラジドを最適条件で処理したところ、期待した 8 員環と縮環したピラゾロン **32ia** は得られず、末端アルケンを有するピラゾロン **71** が 40%の収率で得られた。

Table 12. Synthesis of pyrazolodiazepines **32ba-32ia**.



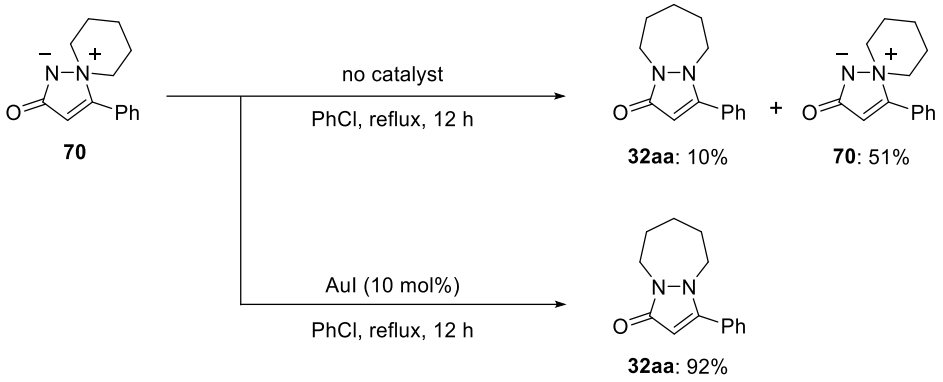
本反応で得られたピラゾロジアゼピンの有用性を確認する目的で、ピラゾロジアゼピン **32aa** の官能基変換を行った (Scheme 37)。ピラゾロジアゼピン **32aa** を基質として Vilsmeier 反応の条件に付すことで、[53] ピラゾロジアゼピンの 2 位にホルミル基が導入された **72** が 62%の収率で得られた。さらに、ピラゾロジアゼピンをクロロホルム中、ヨードベンゼン、Ag_2CO_3 および $Pd(OAc)_2$ で処理することでフェニル基が導入されたピラゾロジアゼピン **73** が 52%の収率で得られた。[54] また、ピラゾロジアゼピン **32aa** をジクロロメタン還流下、エチルトリフラートとともに加熱することで良好な収率でピラゾリニウム **74** へと変換された。[55]



Scheme 37. Transformation of **32aa**.

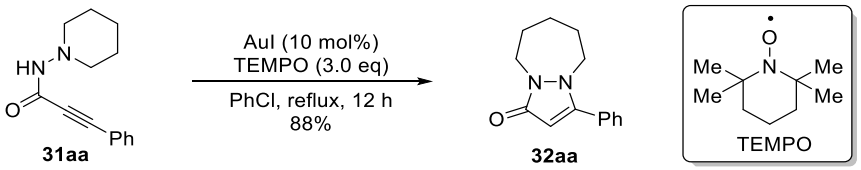
第 3 節　反応経路の考察

本閉環－転位反応の反応経路を推定するため対照実験を行った。初めに、スピロアミンイミド **70** を触媒非存在下で処理したところ、ピラゾロジアゼピン **32aa** が 10%の収率で得られ、スピロアミンイミドが 51%回収された (Scheme 38)。また、スピロアミンイミド **70** をクロロベンゼン還流下、AuI で処理したところ、ピラゾロピリダジン **32aa** が 92%の収率で得られた。これらの結果から、スピロアミンイミド **70** が反応中間体であることが示唆された。また、触媒非存在下で得られたピラゾロジアゼピン **32aa** に関しては、アミンイミド **70** からの Stevens 型転位反応を介してピラゾロジアゼピンが生成したと考えている。[56)]



Scheme 38. Migration reaction of aminimide **70**.

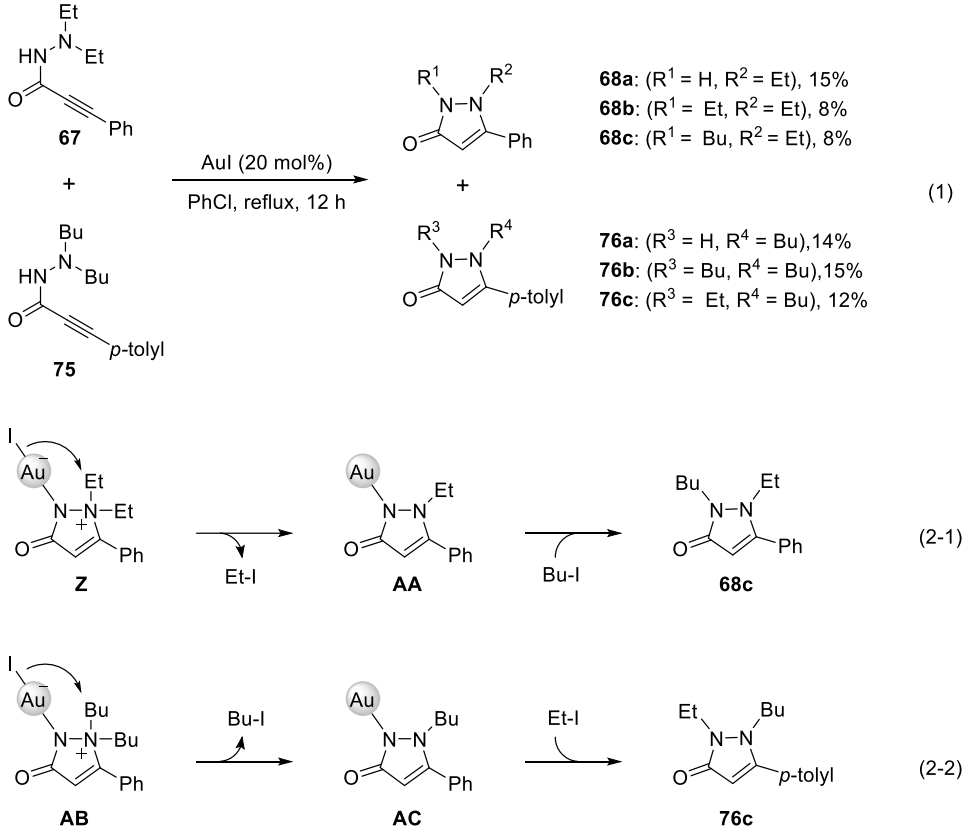
本反応がラジカル機構を介して進行しているかを調べるため、アルキニルヒドラジド **31aa** を 10 mol%の AuI と過剰量の 2,2,6,6-テトラメチルピペリジン 1-オキシル (TEMPO) で処理した (Scheme 39)。その結果、TEMPO 非存在下と同程度の収率でピラゾロジアゼピン **31aa** が得られ、本反応にはラジカルが関与していないことが示唆された。



Scheme 39. Cyclization-migration reaction with TEMPO.

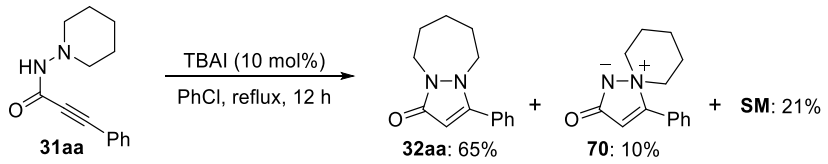
次に、非環状のアルキニルヒドラジド **67** および **75** を用いて交差実験を行った。物質量が等しい **67** および **75** を最適条件で処理したところ、交差成績体 **68c** および **76c** が得られた (Scheme 40, eq 1)。この結果について、これら交差成績体 **68c**, **76c** は、アミンイミド中間体 **Z**, **AB** のアンモニウム窒素上のアルキル基がヨウ化物イオンの求核攻撃を受けることで脱離し、ヨウ化アルキルが生成した後、金アミド中間体 **AA** または **AC** のアミド窒素とヨ

ウ化アルキルによる分子間求核置換反応が進行することで生成したと考えている (eq 2-1 and 2-2)。



Scheme 40. Crossover experiment of alkynylhydrazides **67** and **75**.

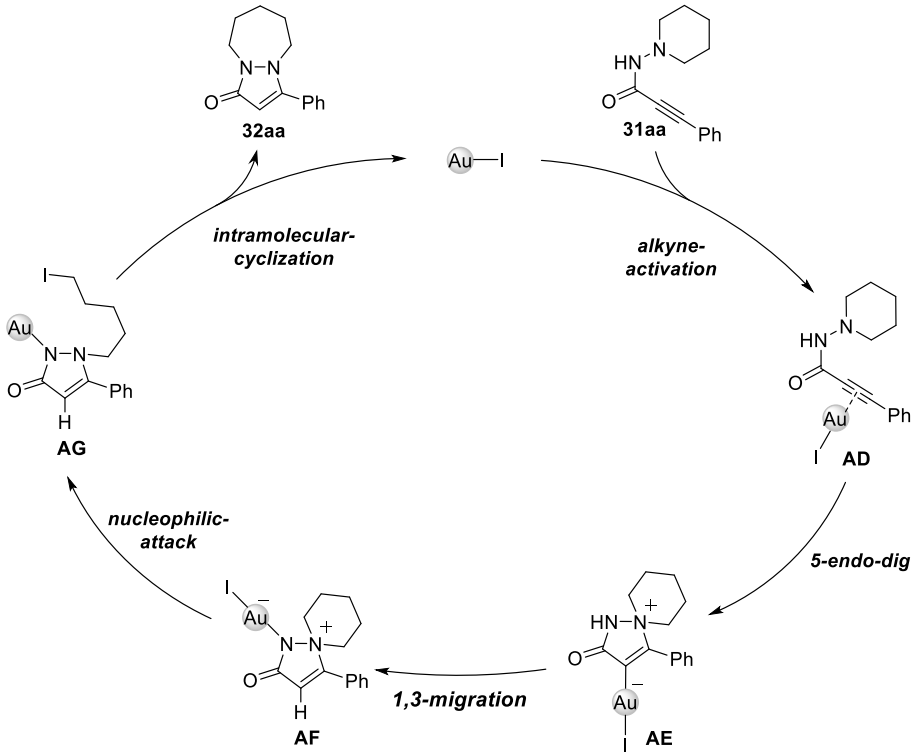
本反応におけるヨウ化物イオンの関与の有無を調べるために、触媒量の TBAI を用いて閉環－転位反応について検討した。その結果、ピラゾロピリダジン **32aa** が 65%、アミンイミド **70** が 10%、アルキニルヒドラジド **31aa** が 21%の収率で得られた (Scheme 41)。本検討で **32aa** が主生成物として得られたことから、ヨウ化物イオンが転位反応に寄与していると考えられる。



Scheme 41. TBAI-catalyzed cyclization-migration reaction of alkynylhydrazide **31aa**.

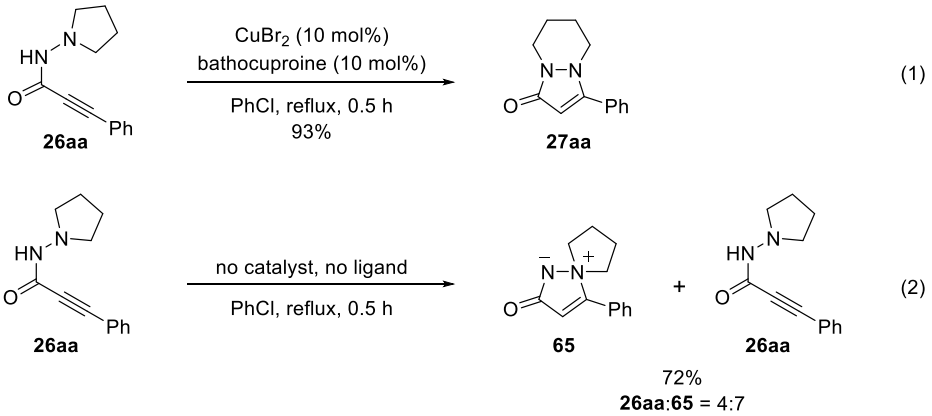
以上の考察を基に、本反応の推定反応経路を Scheme 42 に示す。本反応はまず、AuI によりプロピオールアミド **31aa** のアルキン部位が活性化されることで 5-*endo*-*dig* 環化反応が進行し、スピロアンモニウム中間体 **AE** が形成される。続いてアミドプロトンの 1,3-転位により金アミンイミド **AF** が生成する。次にピペリジニウムの窒素原子に隣接する炭素原子

に対して金アミンイミド **AF** のヨウ化物イオンが求核攻撃することでヨウ化アルキル **AG** が生成する。最後に金アミドとヨウ化アルキル部位の分子内求核置換反応が進行することで、AuI の再生を伴いピラゾロジアゼピン **32aa** が生成したと考えている。



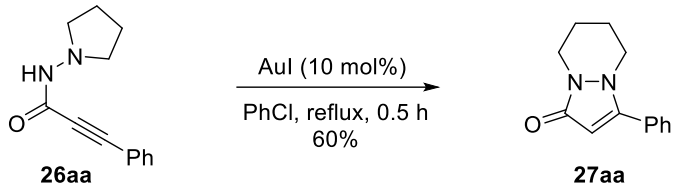
Scheme 42. Plausible reaction pathway.

ここで、第 2 章で述べたピロリジン環を有するアルキニルヒドラジドと第 3 章で見出したピペリジン環を有するアルキニルヒドラジドの閉環－1,2-転位反応で最適な触媒系が異なった理由について考察する。まず、閉環反応について述べる。ピロリジン環を有するアルキニルヒドラジド **26aa** を最適条件または加熱のみの条件に付した場合を比較すると同じ反応時間で原料消費に差があることから $CuBr_2$/バソクプロイン複合体が閉環反応の速度を向上させていることが示唆される (Scheme 43, eq 1 and 2)。また、比較のために **26aa** を



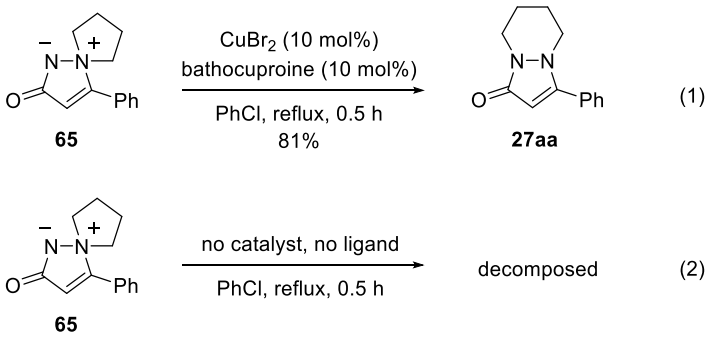
Scheme 43. Cyclization-migration reaction of hydrazide **26aa** with or without $CuBr_2$/bathocuproine.

AuI で処理したが、原料が完全に消費されピラゾロピリダジン **27aa** が得られたことから AuI も $CuBr_2$/バソクプロインと同様に閉環反応を促進していることが明らかになった (Scheme 44)。しかし、現状ではどちらの触媒の方が閉環反応をより効率的に促進しているかは不明である。



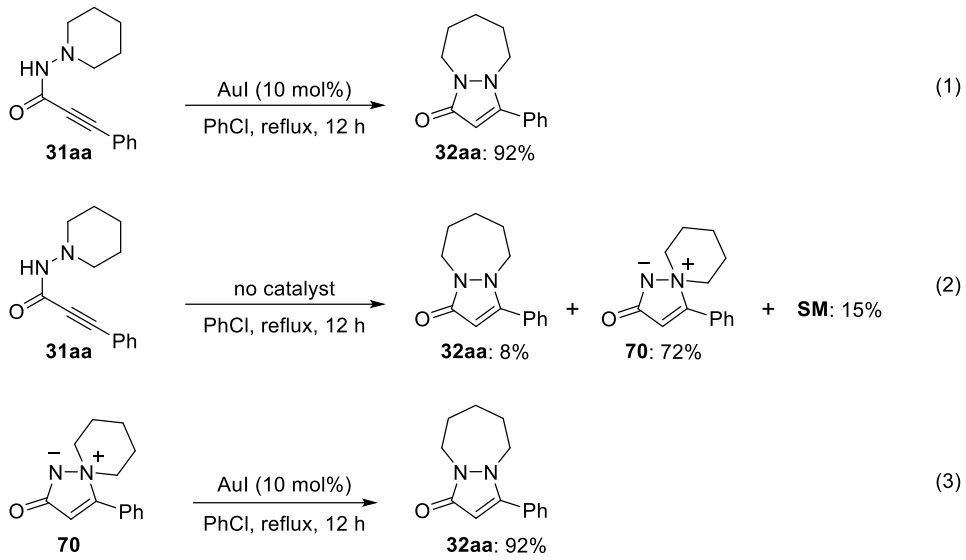
Scheme 44. Cyclization-migration reaction of hydrazide **26aa** with AuI.

また、5 員環アミンイミド **65** を $CuBr_2$ およびバソクプロインで処理することでピラゾロピリダジン **27aa** が 81%の収率で得られているが、Scheme 43, eq 1 で示した **26aa** の反応よりも収率は低下している。この原因は、Scheme 45, eq 2 の実験結果からアミンイミド **65** が熱に対して不安定なためと考えている。したがって、アミンイミド **65** の不安定性に起因する収率の低下を考慮すると、ヒドラジド **26aa** の閉環－転位反応とアミンイミド **65** の転位反応 (Scheme 45, eq 1) は、同程度の収率でピラゾロピリダジン **27aa** を与えていると考えられる。すなわち、閉環反応の段階は、本反応全体の収率にはほとんど影響せず、ほぼ定量的に進行していると考えている (Scheme 43, eq 1 and Scheme 45, eq 1)。



Scheme 45. 1,2-Migration reaction of aminimide **65** with or without $CuBr_2$/bathocuproine.

ピペリジン環を有するアルキニルヒドラジド **31aa** の閉環反応においても、ピロリジン環を有するヒドラジド **26aa** と同様に考えると、AuI により閉環反応が促進されている (Scheme 45, eq 1 and 2)。加えて、ヒドラジド **31aa** を AuI で処理した場合も環化体であるアミンイミド **70** を AuI で処理した場合にも収率の差がないことから、閉環反応がほぼ定量的に進行していると推測している (Scheme 46, eq 1 and 3)。



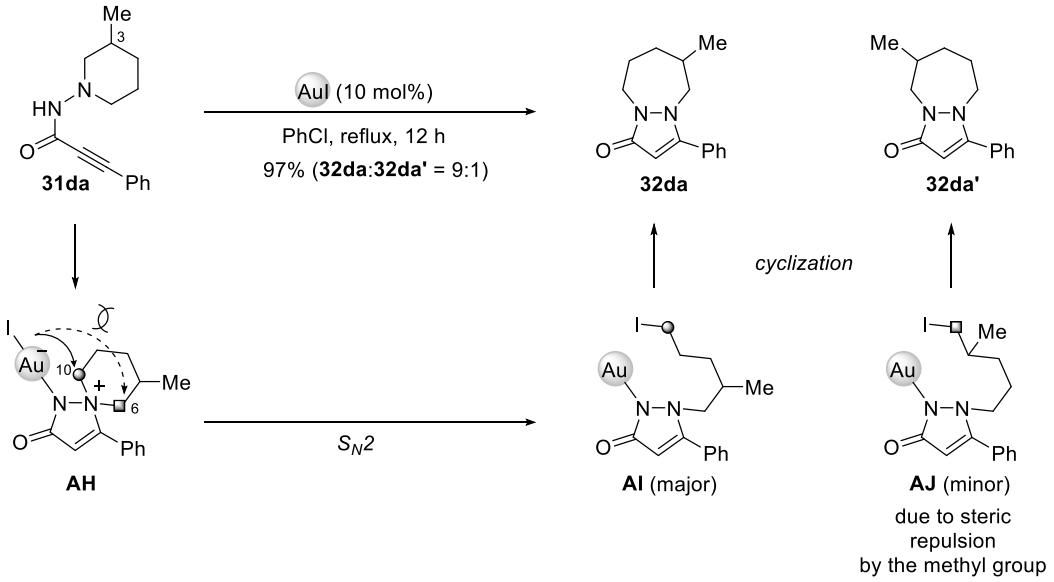
Scheme 46. Cyclization-migration reaction of hydrazide **31aa** with or without AuI and 1,2-migration reaction of aminimide **70** with AuI.

閉環反応において $CuBr_2$/バソクプロイン複合体も AuI を用いても閉環反応はほぼ定量的に進行していると考えている。これらを踏まえて、ピペリジンを有するヒドラジド **31aa** を AuI で処理した際に、収率向上につながったのは転位反応が促進されたからと考えている。

続いて、転位反応について考察する。この 1,2-転位反応は (1) ハロゲンの求核付加の段階と (2) 銅または金アミドとハロゲン化アルキルとの分子内求核置換反応による環化の段階に分けることが出来る。一般的に非プロトン性溶媒中におけるハロゲン化物イオンの反応性を比較すると、臭化物イオンはヨウ化物イオンよりも求核性が高く、ヨウ化物イオンは臭化物イオンより脱離能が高い。この反応性の違いから考えると、ピペリジン環を有するヒドラジド **31aa** の 1,2-転位において AuI が良かった理由は、アルキニルヒドラジド **31aa** の閉環反応にヨウ素の高い脱離能が必要であったからと考えられる。すなわち **31aa** の分子内求核置換反応は 7 員環形成反応であるため、6 員環形成に比べて反応しにくく、[57] $CuBr_2$ を用いた場合に生成する臭化アルキル中間体では反応性が十分でないと考えられる。一方、ピロリジン環をもつヒドラジド **26aa** は 6 員環形成が容易であるため、臭化アルキル中間体でも反応性が十分であったと考えている。これに加えて第 2 章第 3 節で述べたように、ピロリジン環を有するヒドラジド **26aa** の閉環－転位反応にはバソクプロインの嵩高さによる分解経路の抑制が収率の向上につながったため、$CuBr_2$ とバソクプロインが最適な触媒であったと推測している。しかし、Table 10, entry 9 でピペリジン環を有するアルキニルヒドラジド **31aa** に CuI を作用させても目的物が得られなかったことから金属種の違いが本反応に及ぼす影響については明確ではなく、反応機構の更なる検討に関しては今後の課題である。

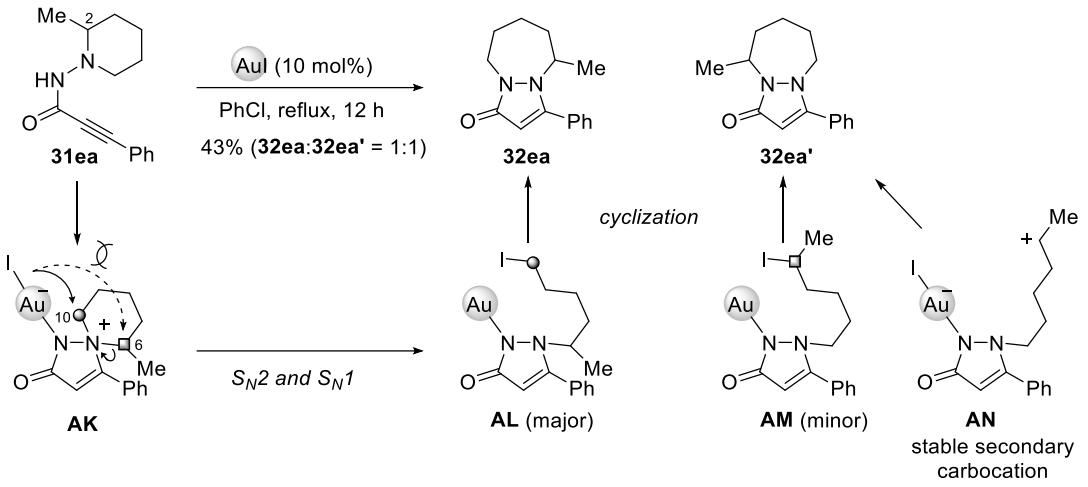
次に推定した反応機構を基に、第 3 章第 2 節で述べたピペリジン環の 3 位または 2 位にメチル基を有するアルキニルヒドラジド **31da** または **31ea** を基質とする閉環－転位反応の

位置選択性について考察する。まず、ピペリジン環の 3 位にメチル基を有するアルキニルヒドラジド **31da** が AuI により環化し、ヨウ化金の 1,3-転位反応が進行することで金アミンイミド **AH** が形成される (Scheme 47)。この金アミンイミドからヨウ化物イオンがアミンイミドの 10 位または 6 位を求核攻撃することで、金アミド **AI** または **AJ** を経由して、位置異性体 **32da** および **32da'**が生成する可能性が考えられる。ここで、アミンイミドの 6 位の炭素原子にヨウ化物イオンが接近すると、メチル基との立体反発が生じるため、10 位に優先的に求核攻撃が進行することでピラゾロン **32da** が主生成物として得られたと考えている。



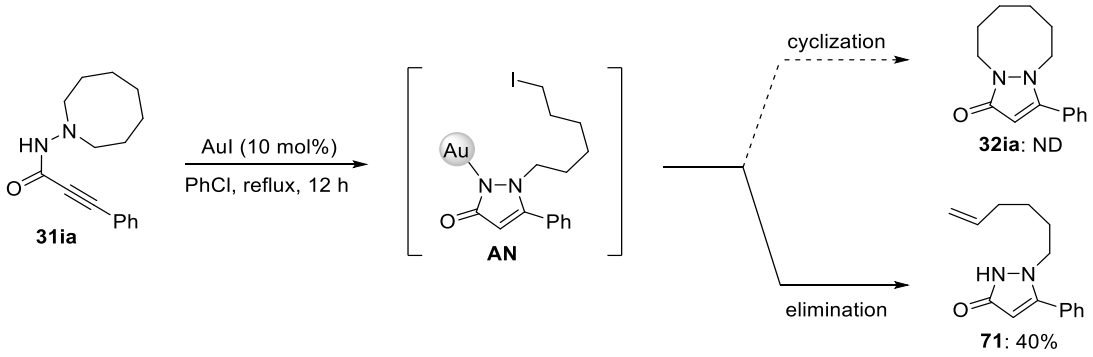
Scheme 47 egioselectivity of alkynylhydrazide **31da** for cyclization-migraion reaction.

続いて、ピペリジン環の 2 位にメチル基を有するアルキニルヒドラジドを用いた反応の位置選択性が低下した理由を考察する。アルキニルヒドラジド **31ea** を AuI で処理すると、環化と 1,3-転位反応が進行し、金アミンイミド **AK** が形成される。上述した反応機構と同様であれば、ヨウ化物イオンがアミンイミドの 10 位または 6 位を求核攻撃することで、金アミド **AL** または **AM** を経由して、位置異性体 **32ea**, **32ea'**が生成する可能性が考えられる (Scheme 48)。ここでヨウ化物イオンの求核攻撃の際に、アミンイミドの 6 位の炭素原子にヨウ化物イオンが接近すると、メチル基との立体反発が生じるため、10 位に優先的に求核攻撃が進行することでピラゾロン **32ea** が生成すると考えられる。しかし、6 位で置換反応が進行する場合は S_N1 反応も考慮する必要がある。すなわち 6 位のメチル基によるカルボカチオンの安定化のため開環体 **AN** が生成し、環化することで **32ea'**が生成する機構も考えられる。このカルボカチオンを介して環化する経路が存在するため **32ea'**の生成の割合が増加し、結果として位置選択性が低下したと考えている。



Scheme 48. Regioselectivity of alkynylhydrazide **31ea** for cyclization-migraion reaction.

最後に、アルキニルヒドラジド **31ia** から生じた、末端アルケンを有するピラゾロン **71** の生成について考察する。これは、環状アミン部位の環員数の増大に伴い分子内求核置換反応が進行しにくくなったことが原因と考えられる。すなわち、反応過程で生成したヨウ化アルキル **AO** が分子内のアミド窒素からの求核攻撃を受けるよりも脱離反応が優先的に進行した結果、末端アルケンを有するピラゾロン **71** が生成したと考えている (Scheme 49)。



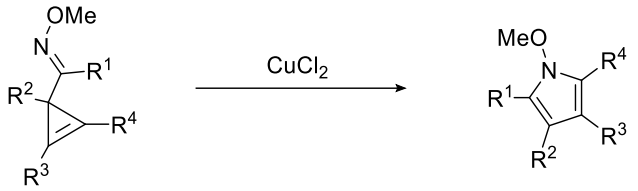
Scheme 49. Competition between cyclization and elimination.

以上のように著者は、第 2 章で見出したピロリジン環を有するアルキニルヒドラジドの閉環-1,2-転位反応を基に、ピロリジン環より 1 炭素増炭したピペリジン環を有するアルキニルヒドラジドについて再度反応条件を探索することで、基質適用範囲を拡張することに成功した。本研究は *N*,*N*-5,7-縮環化合物の合成に関する系統的な合成研究として、分子内反応による唯一の例であり、合成例の少ない二環性の *N*,*N*-5,7-縮環化合物に関して様々な化合物を合成することが可能である。また、本手法は簡便な反応操作で、比較的単純なアルキニルヒドラジドから高収率かつ高い原子効率で多様なピラゾロジアゼピン環を構築できる手法である。

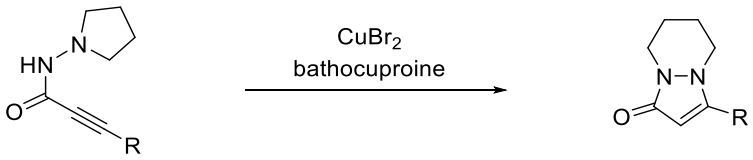
結論

著者は多重結合の活性化を基盤として、含窒素ヘテロ環の合成を高い原子効率で実現するため、新規合成法の開発研究を行った。その結果、多置換ピロール、ピラゾロピリダジン類およびピラゾロジアゼピン類の新規合成法の開発に成功した。

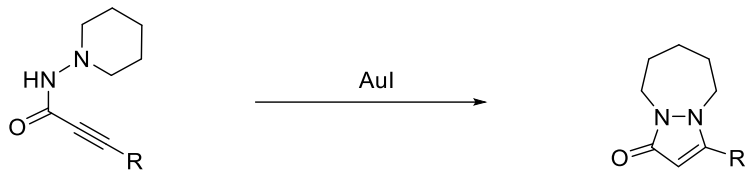
① *N*-アルコキシシクロプロペニルイミンに対し $CuCl_2$ を作用させると、環化異性化反応が進行し、様々な置換様式の *N*-アルコキシピロールが原子効率 100%で得られることを見出した。



② ピロリジン環を有するアルキニルヒドラジドに $CuBr_2$ とバソクプロインを作用させることで、閉環－1,3-転位－形式的 1,2-転位反応が連続的に進行し、原子効率 100%でピラゾロピリダジン類が得られることを見出した。



③ ピペリジン環を有するアルキニルヒドラジドの閉環－1,3-転位－形式的 1,2-転位反応を検討し、AuI を用いる *N*,*N*-5,7-縮環化合物の一般的合成法を確立することに成功した。本手法は原子効率 100%で多様なピラゾロジアゼピンの構築が可能である。



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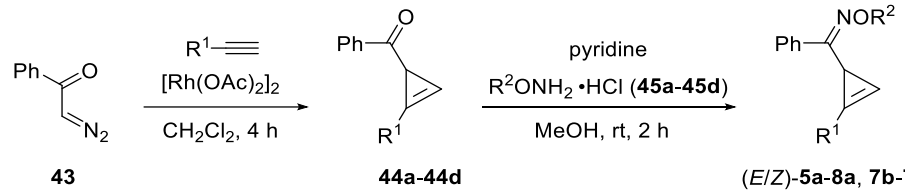
^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz, 400 MHz JNM-ECZ400S, a Varian VNS AS 500 MHz or a Varian VNS AS 600 MHz operating at 300 MHz/75 MHz, 500 MHz/125 MHz, or 600 MHz/150 MHz for ^{1}H and ^{13}C acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance or TMS as the internal standard. 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 Biotage Automated Liquid Chromatography System Isorera One using Biotage SNAP KP-Sil 50g silica gel 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}). HPLC analyses were carried out on a SHIMADZU LC-20AT pump and SPD-20A UV/V is detector or JASCO PU-4180 RHPLC pump and UV-4075 UV/Vis detector. Optical rotations were measured on a JASCO DIP-370 degital polarimeter. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted.

Table S1. Preparation of cyclopropenylimine **5a-8a**, **7b-7d**. [32e, 58)]



43 **44a-44d** (*E*/*Z*)-**5a-8a**, **7b-7d**

cyclopropenylketone	cyclopropenylimine
44a: (R^1 = *n*Bu), 88% **44b**: (R^1 = *i*Bu), 52% **44c**: (R^1 = *c*-pentyl), 80% **44d**: (R^1 = *t*Bu), 33%	**5a**: (R^1 = *n*Bu, R^2 = Bn), 87% **6a**: (R^1 = *n*Bu, R^2 = allyl), 69% **7a**: (R^1 = *n*Bu, R^2 = Me), 74% **8a**: (R^1 = *n*Bu, R^2 = H), 65% **7b**: (R^1 = *i*Bu, R^2 = Me), 80% **7c**: (R^1 = *c*-pentyl, R^2 = Me), 79% **7d**: (R^1 = *t*Bu, R^2 = Me), 88%

General procedure A: preparation of cyclopropenylketones 44a-44d [Table S1]. To the appropriate alkyne (1.5-5.0 equiv.) and $[Rh(OAc)_2]_2$ (0.005 equiv.) in CH_2Cl_2 (*c* = 0.67 M) was added, by means of a syringe pump, ethyl diazoacetate **43** (1.0 equiv.) in CH_2Cl_2 (*c* = 2.0 M) over 4 h at rt. After the addition, stirring was continued for 3 h. Then, the reaction mixture was filtered through a small column of silica gel, which was washed with $CHCl_3$ to remove the catalyst. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography (Hexane/EtOAc) to afford cyclopropenylketone **44**.

(2-Butyl-2-cyclopropen-1-yl)phenylmethanone (44a). Prepared according to **general procedure A** from 1-hexyne (3.9 mL, 34.2 mmol) and diazoacetate **43** (1.0 g, 6.84 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 50:1). **44a** was obtained as a colorless oil (1211 mg, 6.05 mol, 88%). **IR (neat):** 1669 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09-7.85 (m, 2H), 7.59-7.34 (m, 3H), 6.30 (s, 1H), 3.19 (s, 1H), 2.58 (s, 2H), 1.60-1.52 (m, 2H), 1.37 (sext, *J* = 7.2 Hz, 2H), 0.89 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 204.1, 138.4, 132.4, 128.4, 128.0, 114.7, 92.8, 28.9, 24.8, 24.5, 22.2, 13.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}O$: 201.1274, found 201.1275.

[2-(2-Methylpropyl)-2-cyclopropen-1-yl]phenylmethanone (44b). Prepared according to **general procedure A** from 4-methyl-1-pentyne (846 mg, 10.3 mmol) and diazoacetate **43** (1.0 g, 6.84 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 20:1). **44b** was obtained as a colorless oil (725 mg, 3.62 mmol, 52%). **IR (neat):** 1669 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.14-7.84 (m, 2H),

7.63-7.36 (m, 3H), 6.36 (s, 1H), 3.21 (s, 1H), 2.54-2.29 (2H), 2.00-1.90 (m, 1H), 0.98 (t, J = 6.4 Hz, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 172.5, 141.1, 128.4, 128.3, 126.0, 69.1, 42.9, 34.4, 30.7, 27.4; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{14}H_{17}O$: 201.1274, found: 201.1174.

(2-Cyclopentyl-2-cyclopropen-1-yl)phenylmethanone (44c). Prepared according to **general procedure A** from cyclopentyl acetylene (1.74 g, 18.5 mmol) and diazoacetate **43** (1.80 g, 12.3 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 10:1). **44c** was obtained as a colorless oil (2.10 g, 9.89 mmol, 80%). **IR (neat):** 1668 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.08-7.98 (m, 2H), 7.58-7.41 (m, 3H), 6.25 (s, 1H), 3.23 (s, 1H), 3.13-2.94 (m, 1H), 2.00-1.79 (m, 1H), 1.80-1.41 (m, 8H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 204.0, 138.6, 132.3, 128.4, 118.4, 91.2, 35.7, 31.1, 30.9, 25.3, 24.8; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{15}H_{17}O$: 213.1274, found: 213.1273.

[2-(1,1-Dimethylethyl)-2-cyclopropen-1-yl]phenylmethanone (44d). Prepared according to **general procedure A** from 3,3-dimethyl-1-butyne (1.50 g, 18.0 mmol) and diazoacetate **43** (1.70 g, 12.0 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 10:1). **44d** was obtained as a colorless oil (0.80 g, 3.99 mol, 33%). **IR (neat):** 1666 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.25-7.80 (m, 2H), 7.69-7.31 (m, 3H), 6.21 (s, 1H), 3.24 (s, 1H), 1.18 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 203.9, 138.5, 132.3, 128.4, 128.0, 122.7, 89.8, 31.7, 28.0, 24.8; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{14}H_{17}O$: 201.1274, found: 201.1175.

General procedure B: preparation of cyclopropenylimines 5a-8a, 7b-7d [Table S1]. To a solution of cyclopropenylketone **44** (1.0 equiv.) in MeOH and pyridine (10:1, 0.135 M) was added *O*-alkoxyamine hydrochloride **45** (2.0 equiv. or 10.0 equiv.) under Ar atmosphere at 0 °C. After being stirred for 2 h at rt, the reaction mixture was diluted with aq. 1 M HCl and extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel to give a cyclopropenylimine **5-8**.

(*E*/*Z*)-(2-Butyl-2-cyclopropen-1-yl)phenylmethanone *O*-(phenylmethyl)oxime (*E*/*Z*)-5a. Following **general procedure B**, cyclopropenylketone **44a** (2.27 g, 11.3 mmol) and *O*-benzylhydroxylamine hydrochloride **45a** (3.62 g, 22.7 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 3.00 g of **5a** (9.83 mmol, 87%) as a colorless oil as 3:1 mixture of *E/Z* isomers. **IR (neat):** 3060, 3022, 2866, 1693 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$)** for (*Z*)-**5a**: δ 7.43-7.12 (m, 10H), 6.42 (br s, 1H), 5.05 (s, 2H), 2.47 (s, 1H), 2.35 (br t, J = 7.2 Hz, 2H), 1.46-1.37 (m, 2H), 1.29-1.18 (m, 2H), 0.82 (br t, J = 7.2 Hz, 3H); **^{1}H NMR (300 MHz, $CDCl_3$)** for (*E*)-**5a**: δ 7.43-7.12 (m, 10H), 6.42 (br s, 1H), 5.19 (s, 2H), 2.88 (s, 1H), 2.35 (br t, J = 7.2 Hz, 2H), 1.46-1.37 (m, 2H), 1.291.18 (m, 2H), 0.82 (br t, J = 7.2 Hz, 3H); **^{13}C NMR (75 MHz,**

$CDCl_3$) for (*Z*)-**5a**: δ 163.2, 138.4, 133.3, 127.91, 127.69, 127.61, 127.5, 127.1, 120.4, 98.6, 75.5, 29.0, 28.8, 25.6, 23.1. **^{13}C NMR (75 MHz, $CDCl_3$)** for (*E*)-**5a**: δ 164.2, 138.1, 134.9, 128.1, 128.03, 127.98, 127.85, 127.4, 119.4, 98.0, 76.0, 28.8, 25.9, 22.3; (overlapped signals) δ 127.79 (2C), 17.5 (2C); **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{24}NO$: 306.1852, found: 306.1853.

(*E*/*Z*)-(2-Butyl-2-cyclopropen-1-yl)phenylmethanone *O*-(2-propen-1-yl)oxime (*E*/*Z*)-6a. Following **general procedure B**, cyclopropenylketone **44a** (1.08 g, 5.39 mmol) and *O*-allylhydroxylamine hydrochloride **45a** (1.53 g, 10.8 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 950 mg of **6a** (3.71 mmol, 69%) as a colorless oil as 3:1 mixture of *E/Z* isomers. **IR (neat):** 3082, 3060, 3023, 2859 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$)** for (*Z*)-**6a**: δ 7.35-7.12 (m, 5H), 6.44-6.42 (m, 1H), 6.13-5.88 (m, 1H), 5.38-5.10 (m, 2H), 4.65 (dt, *J* = 5.4, 1.5 Hz, 2H), 2.88 (d, *J* = 1.8 Hz, 1H), 2.39 (dt, *J* = 7.2, 1.8 Hz, 2H), 1.51- 1.41 (m, 2H), 1.33-1.19 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); **^{1}H NMR (300 MHz, $CDCl_3$)** for (*E*)-**5a**: δ 7.35-7.12 (m, 5H), 6.44-6.42 (m, 1H), 6.13-5.88 (m, 1H), 5.38-5.10 (m, 2H), 4.51 (dt, *J* = 5.4, 1.5 Hz, 2H), 2.49 (d, *J* = 1.8 Hz, 1H), 2.38 (dt, *J* = 7.2, 1.8 Hz, 2H), 1.51-1.41 (m, 2H), 1.33-1.19 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)** for (*Z*)-**5a**: δ 163.2, 134.9, 133.5, 127.96, 127.92, 127.8, 120.6, 116.6, 98.7, 74.5, 28.8, 25.4, 23.0; **^{13}C NMR (75 MHz, $CDCl_3$)** for (*E*)-**5a**: δ 164.4, 135.2, 134.7, 128.3, 128.2, 127.98, 119.5, 117.0, 98.1, 74.9, 28.6, 25.7, 22.1; (overlapped signals) δ 17.2 (2C), 13.7 (2C); **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{22}NO$: 256.1696, found: 256.1694.

(2-Butyl-2-cyclopropen-1-yl)phenylmethanone *O*-methyloxime (*E*/*Z*)-7a. Following **general procedure B**, cyclopropenylketone **44a** (140 mg, 0.699 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (117 mg, 1.40 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 50:1) gave 119 mg of **7a** (0.518 mmol, 74%) as a 3:1 mixture of *E*/*Z* isomers. Further purification for separation of geometric isomers by medium-pressure column chromatography (Hexane/Et_2O/EtOAc = 200:2:1) gave (*Z*)-**7a** and (*E*)-**7a**; (*Z*)-**7a**: colorless oil. **IR (neat):** 3083, 3024, 2873, 1676 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.37-7.23 (m, 3H), 7.13-7.08 (m, 2H), 6.44 (q, *J* = 1.5 Hz, 1H), 3.79 (s, 3H), 2.49 (d, *J* = 1.8 Hz, 1H), 2.38 (dt, *J* = 7.2, 1.2 Hz, 2H), 1.51-1.41 (m, 2H), 1.33-1.20 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.8, 133.2, 127.8, 127.7, 127.6, 120.5, 98.5, 61.7, 29.0, 25.6, 23.2, 22.3, 13.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1538; (*E*)-7**a**: colorless oil. **IR (neat):** 3056, 3026, 2871, 1690 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.31-7.30 (5H, m), 6.44 (q, *J* = 1.5 Hz, 1H), 3.96 (s, 3H), 2.85 (d, *J* = 1.5 Hz, 1H), 2.38 (dt, *J* = 7.2, 1.2 Hz, 2H), 1.51-1.41 (m, 2H), 1.30-1.21 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.3, 135.1, 128.3, 128.2, 128.0, 119.5, 98.1, 61.8, 28.6, 25.7, 22.1, 17.1, 13.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1538.

(*E*/*Z*)-(2-Butyl-2-cyclopropen-1-yl)phenylmethanone oxime (*E*/*Z*)-8a. Following **general procedure B**, cyclopropenylketone **44a** (400 mg, 2.00 mmol) and hydroxylamine hydrochloride **45d** (278 mg, 4.0 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 5:1) gave 155 mg of **8a** (280 mg, 1.30 mmol, 65%) as a colorless oil as 3:1 mixture of *E*/*Z* isomers. **IR (neat):** 3056, 3026, 2871; **^{1}H NMR (400 MHz, $CDCl_3$)** for (*Z*)-**8a**: δ 9.83-8.86 (br, 1H), 7.41-7.16 (m, 5H), 6.50 (q, *J* = 1.6 Hz, 1H), 2.48 (d, *J* = 2.0 Hz, 1H), 2.46-2.32 (m, 2H), 1.60-1.38 (m, 2H), 1.36-1.10 (m, 2H), 0.87 (t, *J* = 7.6 Hz, 3H); **^{1}H NMR (400 MHz, $CDCl_3$)** for (*E*)-**8a**: δ 9.83-8.86 (br, 1H), 7.41-7.16 (m, 5H), 6.45 (q, *J* = 1.5 Hz, 1H), 2.93 (d, 2.0 Hz, 1H), 2.46-2.32 (m, 2H), 1.60-1.38 (m, 2H), 1.36-1.10 (m, 2H), 0.84 (t, *J* = 2.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** for (*Z*)-**8a**: δ 163.2, 133.1, 127.9, 120.7, 98.2, 28.8, 25.3, 22.7, 22.2, 13.7; **^{13}C NMR (101 MHz, $CDCl_3$)** for (*E*)-**8a**: δ 163.3, 133.2, 128.05, 120.8, 98.4, 29.0, 25.4, 22.8, 22.3, 13.9; (overlapped signals) δ 128.3 (2C), 128.1 (2C); **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{18}ON$: 216.1383, found: 216.1385.

[2-(2-Methylpropyl)-2-cyclopropen-1-yl]phenylmethanone *O*-methyloxime (*E*/*Z*)-7b. Following **general procedure B**, cyclopropenylketone **44b** (290 mg, 1.45 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (242 mg, 2.90 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 50:1) gave 226 mg of **7b** (1.16. mmol, 80%) as a 3:1 mixture of *E*/*Z* isomers. Further purification for separation of geometric isomers by medium-pressure column chromatography (Hexane/Et_2O/EtOAc = 200:2:1) gave (*Z*)-**7b** and (*E*)-**7b**; (*Z*)-**7b**: colorless oil. **IR (neat):** 3083, 3024, 2873, 1676 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.35-7.22 (m, 3H), 7.11-7.07 (m, 2H), 6.46 (q, *J* = 1.5 Hz, 1H), 3.79 (s, 3H), 2.48 (d, *J* = 1.8 Hz, 1H), 2.28-2.24 (m, 2H), 1.90-1.76 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.8, 133.2, 127.8, 127.7, 127.6, 119.6, 99.0, 61.6, 34.9, 27.0, 23.0, 22.6, 22.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1538; (*E*)-**7b**: colorless oil. **IR (neat):** 3060, 3026, 2871, 1690 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.30-7.24 (m, 5H), 6.44 (q, *J* = 1.5 Hz, 1H), 3.93 (s, 3H), 2.84 (d, *J* = 1.8 Hz, 1H), 2.28-2.24 (m, 2H), 1.83 (m, 1H), 0.86 (d, *J* = 1.5 Hz, 3H), 0.84 (d, *J* = 1.5 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.8, 134.8, 128.0, 127.9, 127.7, 118.4, 98.5, 61.7, 35.1, 26.9, 22.5, 22.4, 17.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1537.

(2-Cyclopentyl-2-cyclopropen-1-yl)phenylmethanone *O*-methyloxime (*E*/*Z*)-7c. Following **general procedure B**, cyclopropenylketone **44c** (1.78 g, 8.38 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (1.40 g, 16.8 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 40:1) gave 1.60 g of **7c** (6.63 mmol, 79%) as a 3:1 mixture of *E*/*Z* isomers. Further purification for separation of geometric isomers by medium-pressure column chromatography (Hexane/Et_2O/EtOAc = 200:2:1) gave (*Z*)-**7c** and (*E*)-**7c**; (*Z*)-**7c**: colorless oil. **IR (neat):** 3057, 3043,

2868, 1676 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.35-7.23 (m, 3H), 7.15-7.12 (m, 2H), 6.38 (t, *J* = 1.5 Hz, 1H), 3.79 (s, 3H), 2.91-2.81 (m, 1H), 2.53 (d, *J* = 1.8 Hz, 1H), 1.80-1.71 (m, 2H), 1.56-1.47 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.6, 132.9, 127.9, 127.8, 127.6, 124.0, 96.9, 61.6, 36.2, 31.0, 31.0, 25.3, 23.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{20}NO$: 242.1539, found: 242.1539; (*E*)-**7c**: colorless oil. **IR (neat):** 3057, 3024, 2869, 1690 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.33-7.27 (m, 5H), 6.36 (q, *J* = 0.9 Hz, 1H), 3.96 (s, 3H), 2.91 (d, *J* = 1.8 Hz, 1H), 2.90-2.82 (m, 1H), 1.78-1.69 (m, 2H), 1.57-1.47 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.4, 134.8, 128.3, 128.2, 127.9, 122.5, 96.4, 61.7, 36.1, 30.50, 30.48, 25.1, 17.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{20}NO$: 242.1540, found: 242.1540.

[2-(1,1-Dimethylethyl)-2-cyclopropen-1-yl]phenylmethanone *O*-methyloxime (*E*/*Z*)-7d. Following **general procedure B**, cyclopropenylketone **44d** (100 mg, 0.499 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (83.0 mg, 0.999 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 50:1) gave 106 mg of **7d** (0.439 mmol, 88%) as a 3:1 mixture of *E*/*Z* isomers. Further purification for separation of geometric isomers by medium-pressure column chromatography (Hexane/Et_2O/EtOAc = 200:2:1) gave (*Z*)-**7d** and (*E*)-**7d**; (*Z*)-**7d**: colorless oil. **IR (neat):** 3060, 3025, 2866, 1680 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.35-7.22 (m, 3H), 7.16-7.12 (m, 2H), 6.35 (d, *J* = 1.5 Hz, 1H), 3.79 (s, 3H), 2.57 (d, *J* = 1.8 Hz, 1H), 1.04 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.3, 132.6, 128.2, 128.0, 127.9, 127.5, 95.5, 61.6, 31.4, 28.2, 23.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1540; (*E*)-**7d**: colorless oil. **IR (neat):** 3056, 3026, 2871, 1690 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.32-7.26 (m, 5H), 6.30 (d, *J* = 1.8 Hz, 1H), 3.97 (s, 3H), 2.92 (d, *J* = 2.1 Hz, 1H), 1.04 (9H, s); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.4, 134.6, 128.5, 128.2, 127.9, 126.3, 94.6, 61.7, 31.1, 27.5, 17.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1540, found: 230.15.

[Table 5, entry 1]. To a solution of cyclopropenylimine **5a** (30.0 mg, 0.098 mmol) in THF (5.0 mL) were added $CuBr_2$ (4.5 mg, 0.019 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **9a** (5.7 mg, 19%).

1-Benzyloxy-4-butyl-2-phenyl-1*H*-pyrrole (9a). IR (neat): 3065, 2853, 1602, 1510 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.65 (d, *J* = 7.8 Hz, 2H), 7.37-7.20 (m, 8H), 6.53 (s, 1H), 6.05 (s, 1H), 4.80 (s, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.57-1.48 (m, 2H), 1.35 (sext, *J* = 7.2 Hz, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 134.0, 131.4, 129.6, 128.9, 128.43, 128.39, 128.1, 126.5, 126.3, 120.3, 115.3, 104.3, 81.2, 33.0, 26.8, 22.4, 14.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{24}NO$: 306.1852, found: 306.1847.

[Table 5, entry 2]. To a solution of cyclopropenylimine **5a** (30.0 mg, 0.098 mmol) in THF (5.0 mL) were added $CuCl_2$ (2.6 mg, 0.019 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **9a** (10.1 mg, 34%).

[Table 5, entry 3]. To a solution of cyclopropenylimine **5a** (30.0 mg, 0.098 mmol) in THF (5.0 mL) were added CuI (1.89 mg, 0.019 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **9a** (1.0 mg, 3%).

[Table 5, entry 4]. To a solution of cyclopropenylimine **5a** (33.5 mg, 0.11 mmol) in THF (5.0 mL) were added CuBr (3.16 mg, 0.022 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **9a** (5.2 mg, 15%).

[Table 5, entry 8]. To a solution of cyclopropenylimine **7a** (30.0 mg, 0.098 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.3 mg, 0.0098 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **9a** (9.8 mg, 33%).

[Table 5, entry 9]. To a solution of cyclopropenylimine **5a** (30.0 mg, 0.098 mmol) in benzene (5.0 mL) were added $CuCl_2$ (1.3 mg, 0.0098 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **9a** (5.9 mg, 20%).

[Table 5, entry 10]. To a solution of cyclopropenylimine **5a** (30.0 mg, 0.102 mmol) in chlorobenzene (5.0 mL) were added $CuCl_2$ (2.6 mg, 0.0102 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **9a** (1.5 mg, 5%).

[Table 5, entry 11]. To a solution of cyclopropenylimine **5a** (50.0 mg, 0.163 mmol) in DCE (8.2 mL)

were added $CuCl_2$ (4.4 mg, 0.0328 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **9a** (6.3 mg, 13%).

[Table 5, entry 12]. To a solution of cyclopropenylimine **6a** (30.0 mg, 0.12 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.6 mg, 0.012 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **10a** (18.4 mg, 60%).

4-Butyl-2-phenyl-1-(2-propenyloxy)-1*H*-pyrrole (10a). IR (neat): 3069, 2853, 1604, 1510 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.66-7.64 (m, 2H), 7.38-7.32 (m, 2H), 7.24-7.19 (m, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 5.95-5.82 (m, 1H), 5.28-5.21 (m, 2H), 4.36 (dt, *J* = 6.6, 1.2 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.61-1.51 (m, 2H), 1.38 (sext, *J* = 7.2 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 131.0, 128.2, 126.1, 126.0, 120.6, 114.0, 104.1, 66.4, 33.2, 27.0, 22.7, 14.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{22}NO$: 256.1696, found: 256.1697.

[Table 5, entry 13]. To a solution of cyclopropenylimine **7a** (93.5 mg, 0.41 mmol) in THF (16.0 mL) were added $CuCl_2$ (5.5 mg, 0.041 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **11a** (56.2 mg, 60%).

4-Butyl-1-methoxy-2-phenyl-1*H*-pyrrole (11a). IR (neat): 3069, 2853, 1604, 1510 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.65-7.61 (m, 2H), 7.37-7.31 (m, 2H), 7.23-7.17 (m, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 3.76 (s, 3H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.61- 1.51 (m, 2H), 1.38 (sext, *J* = 7.2 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 131.0, 128.2, 126.1, 126.0, 120.6, 114.0, 104.1, 66.4, 33.2, 27.0, 22.7, 14.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1534.

[Table 6, entry 1]. To a solution of cyclopropenylimine (*Z*)-**7a** (30.0 mg, 0.13 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.8 mg, 0.013 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **11a** (19.8 mg, 66%).

[Table 6, entry 2]. To a solution of cyclopropenylimine (*E*)-**7a** (30.0 mg, 0.13 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.8 mg, 0.013 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **11a** (17.2 mg, 58%).

[Table 6, entry 3]. To a solution of cyclopropenylimine (*Z*)-**7b** (30.0 mg, 0.13 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.8 mg, 0.013 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **11b** (25.4 mg, 85%).

Methoxy-4-(2-methylpropyl)-2-phenyl-1*H*-pyrrole (11b). IR (neat): 3065, 2871, 1602, 1510 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.67-7.64 (m, 2H), 7.39-7.33 (m, 2H), 7.25-7.19 (m, 1H), 6.65 (d, J = 2.1 Hz, 1H), 6.06 (d, J = 2.1 Hz, 1H), 3.77 (s, 3H), 2.30 (d, J = 6.9 Hz, 2H), 1.78 (m, 1H), 0.93 (d, J = 6.9 Hz, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 131.2, 128.4, 127.6, 126.3, 126.2, 119.5, 114.9, 105.0, 66.4, 36.7, 29.7, 22.5; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1539.

[Table 6, entry 4]. To a solution of cyclopropenylimine (*E*)-**7b** (30.0 mg, 0.13 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.8 mg, 0.013 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **11b** (17.1 mg, 57%).

[Table 6, entry 5]. To a solution of cyclopropenylimine (*Z*)-**7c** (30.0 mg, 0.13 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.8 mg, 0.013 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **11c** (15.8 mg, 53%).

4-Cyclopentyl-1-methoxy-2-phenyl-1*H*-pyrrole (11c). IR (neat): 3068, 2871, 1604, 1512 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.67-7.64 (m, 2H), 7.39-7.33 (m, 2H), 7.25-7.20 (m, 1H), 6.69 (dd, J = 2.4, 0.9 Hz, 1H), 6.11 (d, J = 2.4 Hz, 1H), 3.78 (s, 3H), 2.94-2.83 (m, 1H), 2.05-1.96 (m, 2H), 1.81-1.47 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 131.0, 128.2, 127.5, 126.1, 126.0, 124.9, 113.2, 103.0, 66.4, 38.4, 34.4, 25.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{20}NO$: 242.1539, found: 242.1536.

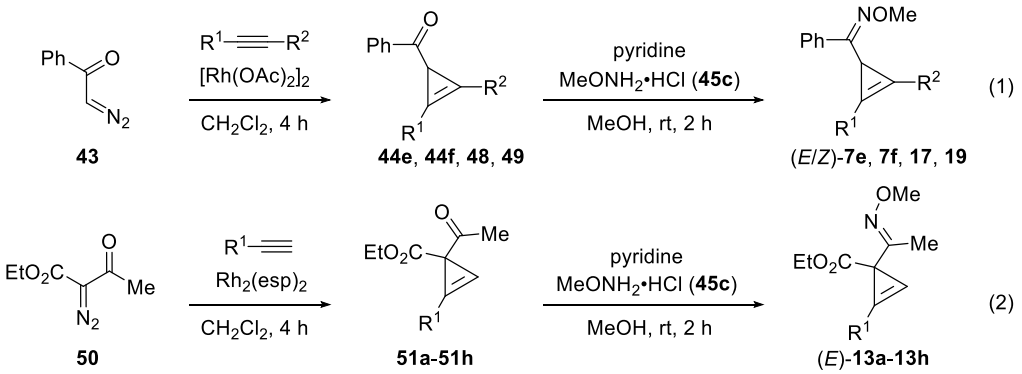
[Table 6, entry 6]. To a solution of cyclopropenylimine (*Z*)-**7c** (30.0 mg, 0.13 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.8 mg, 0.013 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **11c** (12.5 mg, 42%).

[Table 6, entry 7]. To a solution of cyclopropenylimine (*Z*)-**7d** (30.0 mg, 0.13 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.8 mg, 0.013 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **11d** (23.4 mg, 76%).

4-(1,1-Dimethylethyl)-1-methoxy-2-phenyl-1*H*-pyrrole (11d). IR (neat): 3065, 2866, 1602, 1510 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.64 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.23-7.18 (m, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 3.78 (s, 3H), 1.26 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 131.5, 131.3, 128.4, 127.5, 126.3, 126.2, 112.2, 101.8, 66.3, 31.6, 30.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1534.

[Table 6, entry 8]. To a solution of cyclopropenylimine (*E*)-**7d** (30.0 mg, 0.13 mmol) in THF (5.0 mL) were added $CuCl_2$ (1.8 mg, 0.013 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 10:1) to afford *N*-alkoxypyrrole **11d** (3.0 mg, 10%) and recovered starting material (*E*)-**7d** (23.2 mg, 77%).

Table S2. Preparation of cyclopropenylimines. [32e, 58)]



cyclopropenylketone	cyclopropenylimine
cyclopropenylketone derived from **43**	cyclopropenylimine derived from **44e**, **44f**, **48**, **49**
44e: (R^1 = Et, R^2 = Et), 31% **44f**: (R^1 = Ph, R^2 = Me), 34% **48**: (R^1 = TBSO, R^2 = H), 63% **49**: (R^1 = Me, OMe, R^2 = H), 44%	**7e**: (R^1 = Et, R^2 = Et), 76% **7f**: (R^1 = Ph, R^2 = Me), 76% **17**: (R^1 = TBSO, R^2 = H), 70% **19**: (R^1 = Me, OMe, R^2 = H), 84%
cyclopropenylketone derived from **50**	cyclopropenylimine derived from **51a-51h**
51a: (R^1 = Ph), 30% **51b**: (R^1 = 4-ClC_6H_4), 36% **51c**: (R^1 = 4-$CF_3C_6H_4$), 13% **51d**: (R^1 = 4-FC_6H_4), 12% **51e**: (R^1 = 4-MeC_6H_4), 46% **51f**: (R^1 = 4-BrC_6H_4), 29% **51g**: (R^1 = 3-MeC_6H_4), 35% **51h**: (R^1 = 2-FC_6H_4), 25%	**13a**: (R^1 = Ph), 65% **13b**: (R^1 = 4-ClC_6H_4), 69% **13c**: (R^1 = 4-$CF_3C_6H_4$), 73% **13d**: (R^1 = 4-FC_6H_4), 32% **13e**: (R^1 = 4-MeC_6H_4), 60% **13f**: (R^1 = 4-BrC_6H_4), 52% **13g**: (R^1 = 3-MeC_6H_4), 78% **13h**: (R^1 = 2-FC_6H_4), 62%

General procedure C: preparation of cyclopropenylketones 44e, 44f, 48, 49 [Table S2, eq 1]. To the appropriate alkyne (1.5-5.0 equiv.) and $[Rh(OAc)_2]_2$ (0.005 equiv.) in CH_2C1_2 (c = 0.67 M) was added, by means of a syringe pump, ethyl diazoacetate **43** (1.0 equiv.) in CH_2Cl_2 (c = 2.0 M) over 4 h at rt. After the addition, stirring was continued for 3 h. Then, the reaction mixture was filtered through a small column of silica gel, which was washed with $CHCl_3$ to remove the catalyst. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography (Hexane/EtOAc) to afford cyclopropenylketones **44e**, **44f**, **48**, **49**.

(2,3-Diethyl-2-cyclopropen-1-yl)phenylmethanone (44e). Prepared according to **general**

procedure C from 3-hexyne (1.7g, 20.5 mmol) and diazoacetate **43** (2.0 g, 13.7 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 10:1). **44e** was obtained as a colorless oil (870 mg, 4.34 mmol, 31%). **IR (neat):** 1699 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.05-8.00 (m, 2H), 7.57-7.42 (m, 3H), 3.16 (s, 1H), 2.55-2.41 (m, 4H), 1.16 (t, *J* = 7.4 Hz, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 204.7, 138.9, 132.1, 128.3, 127.9, 105.8, 27.6, 18.2, 12.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}O$: 201.1274, found: 230.1273.

(2-Methyl-3-phenyl-2-cyclopropen-1-yl)phenylmethanone (44f). Prepared according to **general procedure C** from 1-phenyl-1-propyne (716 mg, 4.11 mmol) and diazoacetate **43** (600 mg, 2.74 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 20:1). **44f** was obtained as a colorless oil (323 mg, 1.38 mmol, 34%). **IR (neat):** 1667 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.24-7.96 (m, 2H), 7.64-7.21 (m, 8H), 3.50 (s, 1H), 2.37 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 203.0, 138.5, 132.4, 129.3, 128.6, 128.5, 128.4, 128.1, 127.1, 106.1, 104.7, 27.5, 10.8; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}O$: 235.1117, found: 235.1117.

[2-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-cyclopentan-1-yl]-2-cyclopropene-1-yl]phenylmethanone (48). Prepared according to **general procedure C** from 1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-ethynylcyclopentane (2.80 g, 13.2 mmol) and diazoacetate **43** (380 mg, 2.74 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **48** was obtained as a colorless oil (560 mg, 1.63 mmol, 63%). **IR (neat):** 1675 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.13-7.77 (m, 2H), 7.70-7.32 (m, 4H), 6.39 (s, 1H), 3.35 (s, 1H), 2.02-1.41 (m, 10H), 0.87 (s, 8H), 0.11 (s, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 203.0, 138.3, 132.6, 128.6, 128.2, 118.8, 93.5, 81.5, 40.5, 40.1, 26.6, 25.8, 23.6, 23.3, 18.2, -2.80, -2.76; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{31}O_2Si$: 343.2088, found: 343.2086.

[2-(3,17β-Dimethoxyestra-1,3,5(10)-trien-17-yl)-2-cyclopropen-1-yl]phenylmethanone (49). Prepared according to **general procedure C** from (17α)-3,17-dimethoxy-19-norpregna-1,3,5(10)-trien-20-yne (1.43 g, 4.4 mmol) and diazoacetate **43** (643 mg, 2.74 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 10:1). **49** was obtained a 6:4 mixture of diastereomers of diastereomers (green oil, 856 mg, 1.93 mmol, 44%). **IR (neat):** 1689 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.06-8.02 (m, 2H), 7.58-7.54 (m, 1H), 7.50-7.46 (m, 2H), 7.20-7.16 (m, 1H), 6.77-6.76 (m, 6/10H), 6.72-6.68 (m, 4/10H + 1H), 6.61 (d, *J* = 8.7 Hz, 1H), 3.774 (s, 12/10H), 3.768 (s, 18/10H), 3.38 (s, 12/10H), 3.36-3.35 (m, 1H), 3.26 (s, 18/10H), 2.73-2.94 (2H), 2.33-1.98 (m, 4H), 1.92-1.70 (m, 3H), 1.65-1.36 (m, 4H), 1.08-1.31 (2H), 0.96 (s, 18/10H), 0.93-0.95 (s, 12/10H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 203.3, 202.9, 157.4, 157.4, 138.4, 138.3, 137.91, 137.86, 132.64, 132.59, 132.5, 132.3, 128.52, 128.47, 128.1, 128.0, 126.3, 117.3, 116.6, 113.74, 113.68, 111.5, 111.4, 98.4, 96.8, 89.1, 88.3, 55.2, 53.6, 53.5, 50.2, 49.4, 48.4, 48.3, 43.8, 43.3, 39.1, 33.8, 33.71, 33.67, 33.2, 29.7,

27.3, 27.0, 26.7, 26.6, 26.4, 26.3, 22.94, 22.90, 13.6, 13.5. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{35}O_3$: 443.2581, found: 443.2582.

General procedure D: preparation of cyclopropenylimines 7e, 7f, 17, 19 [Table S2, eq 1]. To a solution of cyclopropenylketone **44e**, **44f**, **48** or **49** (1.00 equiv.) in MeOH and pyridine (10:1, 0.135 M) was added *O*-methylhydroxylamine hydrochloride **45c** (2.00 equiv.) under Ar atmosphere at 0 °C. After being stirred for 2 h at rt, the reaction mixture was diluted with aq. 1 M HCl and extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel to give a cyclopropenylimine **7e**, **7f**, **17** or **19**.

(*Z*)-(2,3-Diethyl-2-cyclopropen-1-yl)phenylmethanone *O*-methyloxime (7e). Following **general procedure D**, cyclopropenylketone **44e** (300 mg, 1.50 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (250 mg, 3.00 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 50:1) gave 263 mg of **7e** (1.14 mmol, 76%) as a 3:1 mixture of *E*/*Z* isomers. Further purification for separation of geometric isomers by medium-pressure column chromatography (Hexane/Et_2O/EtOAc = 200:2:1) gave (*Z*)-**7e** and (*E*)-**7e**. (*Z*)-**7e**: colorless oil. **IR (neat):** 3060, 2875, 1673 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.34-7.22 (m, 3H), 7.07-7.04 (m, 2H), 3.78 (s, 3H), 2.45 (s, 1H), 2.36-2.28 (m, 4H), 1.05 (t, *J* = 7.5 Hz, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.4, 133.8, 127.6, 127.6, 127.3, 111.3, 61.6, 26.1, 19.2, 12.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1538; (*E*)-**7e**: colorless oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.26 (m, 5H), 3.92 (s, 3H), 2.82 (s, 1H), 2.341 (q, *J* = 7.5 Hz, 2H), 2.337 (q, *J* = 7.5 Hz, 2H), 1.05 (t, *J* = 7.5 Hz, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.4, 135.8, 127.9, 127.9, 127.6, 110.5, 61.7, 20.6, 19.5, 12.1.

(*Z*)-(2-Methyl-3-phenyl-2-cyclopropen-1-yl)phenylmethanone *O*-methyloxime (*E*/*Z*)-7f Following **general procedure D**, cyclopropenylketone **44f** (100 mg, 0.427 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (71.3 mg, 0.854 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 50:1) gave 78.0 mg of **7f** (0.323 mmol, 76%) as a 3:1 mixture of *E*/*Z* isomers. Further purification for separation of geometric isomers by medium-pressure column chromatography (Hexane/Et_2O/EtOAc = 200:2:1) gave (*Z*)-**7f** and (*E*)-**7f**. (*Z*)-**7f**: colorless oil. **IR (neat):** 3060, 2815, 1682 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.48- 7.20 (m, 8H), 7.05-7.01 (m, 2H), 3.83 (s, 3H), 2.81 (s, 1H), 2.18 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.3, 133.4, 129.0, 128.8, 128.5, 128.2, 127.9, 127.8, 127.4, 110.7, 109.2, 61.7, 25.8, 11.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}NO$: 264.1383, found: 264.1380; (*E*)-**7c**: colorless oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.49-7.19 (m, 8H), 4.00 (s, 3H), 3.23 (s, 1H), 2.19 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.4, 135.5, 129.0, 128.6, 128.5, 128.2, 128.2, 127.8, 109.9, 108.6, 61.8, 20.1, 11.9.

(*Z*)-[2-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-cyclopentan-1-yl]-2-cyclopropene-1-yl]phenylmethanone *O*-methyloxime (17). Following **general procedure D**, cyclopropenylketone **48** (420 mg, 1.23 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (205 mg, 2.45 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 322 mg of **17** (0.866 mmol, 70%) as a 3:1 mixture of *E*/*Z* isomers. Further purification for separation of geometric isomers by medium-pressure column chromatography (Hexane/Et_2O/EtOAc = 200:2:1) gave (*Z*)-**17** and (*E*)-**17**. (*Z*)-**17**: colorless oil. **IR (neat):** 3056, 3026, 2819, 1619 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.39-7.25 (m, 3H), 7.22-7.17 (m, 2H), 6.55 (d, *J* = 1.5 Hz, 1H), 3.80 (s, 3H), 2.68 (d, *J* = 1.5 Hz, 1H), 1.78-1.56 (m, 8H), 0.83 (s, 9H), -0.07 (s, 3H), -0.12 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 161.5, 132.5, 128.4, 128.2, 127.8, 124.4, 98.8, 81.6, 61.6, 39.9, 39.8, 25.7, 25.5, 23.4, 23.1, 18.1, -3.0, -3.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{34}NO_2Si$: 372.2353, found: 372.2361.

(*Z*)-[2-(3,17β-Dimethoxyestra-1,3,5(10)-trien-17-yl)-2-cyclopropen-1-yl]phenylmethanone *O*-methyloxime (19). Following **general procedure D**, cyclopropenylketone **49** (250 mg, 0.564 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (94 mg, 1.13 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 224 mg of **19** (0.474 mmol, 84%) as a 3:1 mixture of *E*/*Z* isomers. Further purification for separation of geometric isomers by medium-pressure column chromatography (Hexane/Et_2O/EtOAc = 200:2:1) gave (*Z*)-**19** and (*E*)-**19**. (*Z*)-**19**: colorless oil. **IR (neat):** 3056, 3026, 2832, 1613 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.38- 7.28 (m, 5H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.88 (d, *J* = 1.5 Hz, 1H), 6.67 (dd, *J* = 8.7, 2,7 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.23 (s, 3H), 2.84-2.78 (m, 2H), 2.60 (d, *J* = 1.5 Hz, 1H), 2.24-1.18 (m, 13H), 0.94 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 161.2, 157.4, 137.9, 133.0, 132.5, 128.6, 128.5, 127.9, 126.3, 123.5, 113.8, 111.5, 103.3, 87.5, 61.7, 55.2, 53.4, 49.4, 48.3, 43.4, 39.2, 34.1, 33.6, 29.8, 27.1, 26.4, 24.8, 22.9, 13.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{38}NO_3$: 472.2846, found: 472.2847.

General procedure E: preparation of cyclopropenylketones 51a-51h [Table S2, eq 2]. To the appropriate alkyne (1.0-1.5 equiv.) and $Rh_2(esp)_2$ (0.003 equiv.) in CH_2Cl_2 (*c* = 0.67 M) was added, by means of a syringe pump, ethyl diazoacetate **43** (1.0 equiv.) in CH_2Cl_2 (*c* = 2.0 M) over 4 h at rt. After the addition, stirring was continued for 3 h. Then, the reaction mixture was filtered through a small column of silica gel, which was washed with $CHCl_3$ to remove the catalyst. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography (Hexane/EtOAc) to afford cyclopropenylketone **51a-51h**.

1-Acetyl-2-phenyl-2-cyclopene-1-carboxylic acid ethyl ester (51a). Prepared according to **general procedure E** from ethynylbenzene (392 mg, 3.84 mmol) and diazoacetate **50** (600 mg, 3.84 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 3:1). **51a** was obtained as a yellow oil (269 mg,

4.34 mmol, 30%). **IR (neat):** 1726, 1699 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.80-7.33 (m, 5H), 7.08-6.80 (s, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.25 (s, 3H), 1.24 (t, *J* = 6.2 Hz, 4H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 206.1, 171.3, 130.6, 130.2, 128.9, 123.9, 113.1, 96.1, 61.0, 40.7, 28.1, 14.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{15}O_3$: 231.1016, found: 231.1014.

Acetyl-2-(4-chlorophenyl)-2-cyclopene-1-carboxylic acid ethyl ester (51b). Prepared according to **general procedure E** from 1-chloro-4-ethynylbenzene (524 mg, 3.84 mmol) and diazoacetate **50** (787 mg, 5.76 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 3:1). **51b** was obtained as a pale orange oil (363 mg, 1.38 mmol, 36%). **IR (neat):** 1725, 1699 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** 7.66-7.47 (m, 2H), 7.47-7.32 (m, 2H), 6.95 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 206.1, 171.3, 136.9, 131.5, 129.5, 122.7, 112.3, 96.9, 61.3, 40.8, 28.3, 14.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}O_3Cl$: 265.0626, found: 265.0624.

1-Acetyl-2-(4-trifluoromethylphenyl)-2-cyclopene-1-carboxylic acid ethyl ester (51c). Prepared according to **general procedure E** from 1-ethynyl-4-(trifluoromethyl)benzene (850 mg, 5.00 mmol) and diazoacetate **50** (780.0 mg, 5.00 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 3:1). **51c** was obtained as an orange oil (189 mg, 0.634 mmol, 13%). **IR (neat):** 1728, 1701 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71 (s, 4H), 7.08 (s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 2.32 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 205.5, 171.0, 132.2 (q, *J* = 31.6 Hz), 130.4, 127.5, 126.3 (q, *J* = 271 Hz), 125.9 (*J* = 3.9 Hz), 112.0, 99.0, 61.3, 40.7, 28.4, 14.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}O_3F_3$: 299.0890, found: 299.0889.

1-Acetyl-2-(4-fluorophenyl)-2-cyclopene-1-carboxylic acid ethyl ester (51d). Prepared according to **general procedure E** from 1-ethynyl-4-fluoromethybenzene (769 mg, 6.40 mmol) and diazoacetate **50** (1000 mg, 6.40 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 3:1). **51d** was obtained as a colorless oil (190 mg, 0.77 mmol, 12%). **IR (neat):** 1726, 1699 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72-7.38 (m, 2H), 7.18-7.08 (m, 2H), 6.90 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 206.0, 171.2, 163.8 (d, *J* = 253.6 Hz), 132.3, 120.3 (d, *J* = 2.8 Hz), 116.3 (d, *J* = 22.2 Hz), 112.1, 95.7, 61.1, 40.7, 28.1, 14.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}O_3F$: 249.0922, found: 249.0922.

1-Acetyl-2-(4-methylphenyl)-2-cyclopene-1-carboxylic acid ethyl ester (51e). Prepared according to **general procedure E** from 4-ethynyltoluene (743 mg, 6.40 mmol) and diazoacetate **50** (1000 mg, 6.40 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 3:1). **51e** was obtained as a colorless oil (711 mg, 2.91 mmol, 46%). **IR (neat):** 1717, 1699 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.86 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.40 (s,

3H), 2.24 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 206.4, 171.4, 141.1, 130.2, 129.7, 121.1, 113.1, 94.9, 61.0, 40.7, 28.0, 21.6, 14.1; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{15}H_{17}O_3$: 245.1172, found: 245.1171.

1-Acetyl-2-(4-bromophenyl)-2-cyclopene-1-carboxylic acid ethyl ester (51f). Prepared according to **general procedure E** from 1-bromo-4-ethynylbenzene (1.15 g, 6.40 mmol) and diazoacetate **50** (1.00 mg, 6.40 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 3:1). **51f** was obtained as a colorless oil (564 mg, 1.82 mmol, 29%). **IR (neat):** 1723, 1699 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.59 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 6.96 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.27 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 205.8, 171.1, 132.3, 131.6, 125.2, 123.0, 112.3, 97.0, 61.2, 40.6, 28.2, 14.1; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{14}H_{14}O_3Br$: 309.0121, found: 309.0119.

1-Acetyl-2-(3-methylphenyl)-2-cyclopene-1-carboxylic acid ethyl ester (51g). Prepared according to **general procedure E** from 3-ethynyltoluene (0.48 mL, 3.84 mmol) and diazoacetate **50** (600 mg, 3.84 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 3:1). **51g** was obtained as a colorless oil (333 mg, 1.36 mmol, 35%). **IR (neat):** 1726, 1701 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.58-6.98 (m, 4H), 6.93 (s, 1H), 4.19 (qd, J = 7.2, 1.9 Hz, 2H), 2.37 (s, 3H), 2.23 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 206.0, 171.1, 138.5, 131.3, 130.5, 128.7, 127.2, 123.6, 113.1, 95.7, 60.8, 40.5, 27.8, 21.0, 13.9; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{15}H_{17}O_3$: 245.1172, found: 245.1171.

1-Acetyl-2-(2-fluorophenyl)-2-cyclopene-1-carboxylic acid ethyl ester (51h). Prepared according to **general procedure E** from 1-ethynyl-2-fluorobenzene (769 mg, 6.40 mmol) and diazoacetate **50** (1.00 g, 6.40 mmol), purified by chromatography (SiO_2, Hexane/EtOAc = 3:1). **51h** was obtained as an orange oil (401 mg, 1.62 mmol, 25%). **IR (neat):** 1723, 1699 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58-7.34 (m, 2H), 7.30-7.10 (m, 2H), 7.07 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.30 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 206.0, 171.1, 161.5 (d, J = 253 Hz), 132.0 (d, J = 8.6 Hz), 124.5 (d, J = 3.8 Hz), 115.9 (d, J = 20.4 Hz), 112.7 (d, J = 14.5 Hz), 107.5 (d, J = 2.8 Hz), 98.6 (d, J = 3.8 Hz), 61.1, 39.4, 28.1, 14.1; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{14}H_{14}O_3F$: 249.0922, found: 249.0921.

General procedure F: preparation of cyclopropenylimines 13a-13h [Table S2, eq 2]. To a solution of cyclopropenylketone **51a-51h** (1.00 equiv.) in MeOH and pyridine (10:1, 0.135 M) was added *O*-methylhydroxylamine hydrochloride **45c** (2.00 equiv.) under Ar atmosphere at 0 °C. After being stirred for 2 h at rt, the reaction mixture was diluted with aq. 1 M HCl and extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The

obtained residue was purified by flash column chromatography on silica gel to give a cyclopropenylimine **13a-13h**.

(*E*)-1-[1-(Methoxyimino)ethyl]-2-phenyl-2-cyclopropene-1-carboxylic acid ethyl ester (13a). Following **general procedure F**, cyclopropenylketone **51a** (270 mg, 1.17 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (196 mg, 2.35 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 199 mg of (*E*)-**13a** (0.765 mmol, 65%) as a pale yellow oil. **IR (neat):** 3065, 2819, 1721, 1624 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.65-7.62 (m, 2H), 7.46-7.39 (m, 3H), 7.06 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 2.01 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.4, 157.1, 130.1, 129.9, 128.7, 125.3, 117.0, 98.9, 61.4, 61.0, 33.8, 14.5, 14.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}NO_3$: 260.1282, found: 260.1282.

(*E*)-2-(4-Chlorophenyl)-1-[1-(methoxyimino)ethyl]-2-cyclopropene-1-carboxylic acid ethyl ester (13b). Following **general procedure F**, cyclopropenylketone **51b** (550 mg, 2.08 mmo) and *O*-methylhydroxylamine hydrochloride **45c** (348 mg, 4.17 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 412 mg of (*E*)-**13b** (1.44 mmol, 69%) as a pale yellow oil. **IR (neat):** 2991, 2819, 1723, 1626, 1050 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.61-7.56 (m, 2H), 7.42-7.37 (m, 2H), 7.10 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 2.00 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.4, 157.0, 136.2, 131.6, 129.2, 124.2, 116.1, 100.1, 61.7, 61.3, 34.1, 14.6, 14.5; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_3Cl$: 294.0896, found: 294.0891.

(*E*)-1-[1-(Methoxyimino)ethyl]-2-(4-trifluoromethylphenyl)-2-cyclopropene-1-carboxylic acid ethyl ester (13c). Following **general procedure F**, cyclopropenylketone **51c** (189 mg, 0.633 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (106 mg, 1.27 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 151 mg of (*E*)-**13c** (0.461 mmol, 73%) as a yellow oil. **IR (neat):** 2991, 2819, 1723, 1626, 1050 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.21 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 2.01 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 172.6, 156.3, 131.4 (q, *J* = 32.5 Hz), 130.2, 128.7, 125.41 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 270.0 Hz), 115.79, 102.17, 61.55, 61.30, 34.23, 14.54, 14.45; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}NO_3F_3$: 328.1155, found: 328.1159.

(*E*)-2-(4-Fluorophenyl)-1-[1-(methoxyimino)ethyl]-2-cyclopropene-1-carboxylic acid ethyl ester (13d). Following **general procedure F**, cyclopropenylketone **51d** (190 mg, 0.765 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (127 mg, 1.53 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 68.0 mg of (*E*)-**13d** (0.245 mmol,

32%) as an orange oil. **IR (neat):** 2987, 2819, 1723, 1626, 1239 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.66-7.59 (m, 2H), 7.13-7.05 (m, 2H), 7.01 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 1.99 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 172.9, 163.2 (d, *J* = 249.0 Hz), 156.6, 131.9 (d, *J* = 9.0 Hz), 121.6 (d, *J* = 3.0 Hz), 115.71 (d, *J* = 21.8 Hz), 115.68, 98.5 (d, *J* = 3.0 Hz), 61.4, 61.1, 34.0, 14.5, 14.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_3F$: 278.1187, found: 278.1190.

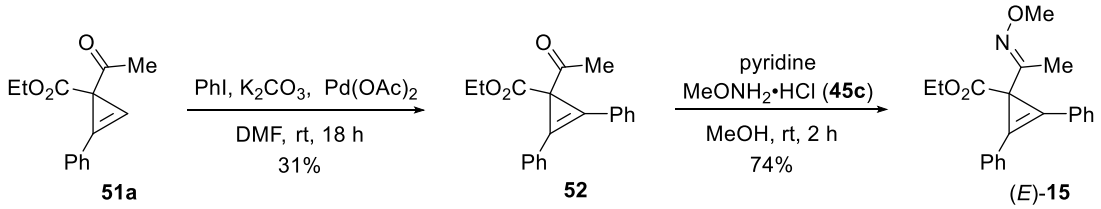
(*E*)-1-[1-(Methoxyimino)ethyl]-2-(4-methylphenyl)-2-cyclopropene-1-carboxylic acid ethyl ester (13e). Following **general procedure F**, cyclopropenylketone **51e** (427 mg, 1.75 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (292 mg, 3.50 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 20:1) gave 285 mg of (*E*)-**13e** (1.04 mmol, 60%) as a yellow oil. **IR (neat):** 2983, 2823, 1721, 1607 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.52-7.48 (m, 2H), 7.23-7.19 (m, 2H), 6.96 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 2.38 (s, 3H), 2.00 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.2, 156.9, 140.1, 129.9, 129.2, 122.3, 116.6, 97.5, 61.4, 61.0, 33.9, 21.8, 14.7, 14.5; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{20}NO_3$: 274.1438, found: 274.1442.

(*E*)-2-(4-Bromophenyl)-1-[1-(methoxyimino)ethyl]-2-cyclopropene-1-carboxylic acid ethyl ester (13f). Following **general procedure F**, cyclopropenylketone **51f** (320 mg, 1.03 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (172 mg, 2.07 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 167 mg (0.494 mmol, 52%) of (*E*)-**13f** as an orange oil. **IR (neat):** 2983, 2823, 1721, 1607 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.58-7.54 (m, 2H), 7.53-7.50 (m, 2H), 7.11 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 1.99 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.1, 156.7, 131.9, 131.5, 124.4, 124.3, 115.9, 100.0, 61.4, 61.1, 33.8, 14.3, 14.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_3Br$: 338.0386, found: 338.0394.

(*E*)-1-[1-(Methoxyimino)ethyl]-2-(3-methylphenyl)-2-cyclopropene-1-carboxylic acid ethyl ester (13g). Following **general procedure F**, cyclopropenylketone **51g** (333 mg, 1.36 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (227 mg, 2.73 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 20:1) gave 289 mg of (*E*)-**13g** (1.06 mmol, 78%) as a yellow oil. **IR (neat):** 2983, 2815, 1718, 1626 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.41 (d, *J* = 8.1 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.01 (s, 1H), 4.15 (br q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 2.36 (s, 3H), 2.00 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.0, 156.7, 138.1, 130.5, 130.3, 128.3, 127.0, 125.0, 116.8, 98.5, 61.3, 60.9, 33.9, 21.4, 14.6, 14.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{20}NO_3$: 274.1438, found: 274.1440.

(*E*)-2-(2-Fluorophenyl)-1-[1-(methoxyimino)ethyl]-2-cyclopropene-1-carboxylic acid ethyl

ester (13h). Following **general procedure F**, cyclopropenylketone **51h** (276 mg, 1.11 mmol) and *O*-methylhydroxylamine hydrochloride **45c** (186 mg, 2.22 mmol) were used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 190 mg of (*E*)-**13h** (0.684 mmol, 62%) as a yellow oil. **IR (neat):** 2983, 2815, 1718, 1626 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.60 (dt, *J* = 7.2, 1.8 Hz, 1H), 7.41-7.34 (m, 1H), 7.22 (s, 1H), 7.21-7.09 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 2.01 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.1, 161.4 (d, *J* = 253.5 Hz), 156.8, 131.7 (d, *J* = 8.3 Hz), 131.5 (d, *J* = 2.1 Hz), 124.1 (d, *J* = 3.8 Hz), 115.6 (d, *J* = 19.5 Hz), 113.9 (d, *J* = 13.5 Hz), 111.3 (d, *J* = 2.3 Hz), 101.7 (d, *J* = 4.5 Hz), 61.2, 60.9, 32.6, 14.1, 14.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_3F$: 278.1187, found: 278.1189.



Scheme S1. Preparation of cyclopropenylimine (*E*)-**15**.

Preparation of 2,3-diphenylcyclopropenylketone 52 [Scheme S1]. To a solution of cyclopropenylketone **51a** (425 mg, 1.8 mmol) in DMF were added iodobenzene (0.22 ml, 2.0 mmol), K_2CO_3 (550 mg, 4.6 mmol) and $Pd(OAc)_2$. The mixture was heated to 30 °C. After being stirred for 18 h, the reaction mixture was filtered through celite with diethyl ether and washed with sat. aq. NH_4Cl three times. The Organic layer was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 170 mg of **52** (0.558 mmol, 31%) as a pale yellow oil.

Acetyl-2,3-diphenyl-2-cyclopene-1-carboxylic acid ethyl ester (52). IR (neat): 2983, 2815, 1718, 1626 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.83-7.66 (m, 4H), 7.62-7.33 (m, 6H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.12 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 206.1, 170.8, 130.2, 129.2, 125.4, 108.2, 61.1, 43.6, 27.3, 14.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{19}O_3$: 307.1329, found: 307.1332.

Preparation of (*E*)-15 [Scheme S1]. To a solution of cyclopropenylketone **52** (220 mg, 0.656 mmol) in MeOH and pyridine (10:1, 0.135 M) was added *O*-methylhydroxylamine hydrochloride **45c** (117 mg, 1.31 mmol) under Ar atmosphere at 0 °C. After being stirred for 2 h at rt, the reaction mixture was diluted with aq. 1 M HCl and extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel to give 174 mg of cyclopropenylimine (*E*)-**15** (0.519 mmol,

74%) as a pale yellow solid.

(*E*)-1-[1-(Methoxyimino)ethyl]-2,3-diphenyl-2-cyclopropene-1-carboxylic acid ethyl ester (15). IR (neat): 3060, 2819, 1721, 1626 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.77 (d, *J* = 7.2 Hz, 4H), 7.50-7.37 (m, 6H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 2.01 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 172.8, 156.5, 130.1(2), 129.4, 128.8, 126.7, 110.6, 61.5, 60.8, 36.0, 14.5, 14.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}NO_3$: 336.1594, found: 336.1591.

[Scheme 21, eq 1]. To a solution of cyclopropenylimine **7e** (30.0 mg, 0.13 mmol) in THF (5.0 mL) was added $CuCl_2$ (1.8 mg, 0.013 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 40:1) to afford *N*-alkoxypyrrole **11e** (19.5 mg, 65%) as a colorless oil.

2,3-Diethyl-1-methoxy-5-phenyl-1*H*-pyrrole (11e). IR (neat): 3065, 2866, 1602, 1510 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.68-7.65 (m, 2H), 7.37-7.32 (m, 2H), 7.22-7.16 (s, 1H), 6.09 (s, 1H), 3.68 (s, 3H), 2.65 (q, *J* = 7.5 Hz, 2H), 2.44 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H), 1.19 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 131.6, 128.4, 128.1, 125.9, 125.8, 125.7, 117.7, 103.1, 65.6, 19.2, 16.9, 15.5, 14.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1540.

[Scheme 21, eq 2]. To a solution of cyclopropenylimine **7f** (40.0 mg, 0.15 mmol) in THF (5.0 mL) was added $CuCl_2$ (2.0 mg, 0.015 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 40:1) to afford *N*-alkoxypyrrole **11f** (18.7 mg, 47%, pale pink oil) and **11f'** (8.2 mg, 21%, pale yellow oil).

1-Methoxy-2-methyl-3,5-diphenyl-1*H*-pyrrole (11f). IR (neat): 3065, 2866, 1602, 1510 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.68-7.65 (m, 2H), 7.37-7.32 (m, 2H), 7.22-7.16 (s, 1H), 6.09 (s, 1H), 3.68 (s, 3H), 2.65 (q, *J* = 7.5 Hz, 2H), 2.44 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H), 1.19 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 131.6, 128.4, 128.1, 125.9, 125.8, 125.7, 117.7, 103.1, 65.6, 19.2, 16.9, 15.5, 14.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO$: 230.1539, found: 230.1540.

Methoxy-3-methyl-2,5-diphenyl-1*H*-pyrrole (11f'). IR (neat): 3060, 2823, 1604, 1523 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.72-7.68 (m, 2H), 7.44-7.33 (m, 6H), 7.26-7.17 (m, 2H), 6.37 (s, 1H),

3.74 (s, 3H), 2.47 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 136.5, 131.2, 128.6, 128.4, 127.4, 126.8, 126.4, 126.2, 125.4, 122.9, 117.7, 103.2, 65.5, 9.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}NO$: 264.1383, found: 264.1380.

General procedure G: synthesis of 1,2,3,4-tetrasubstituted pyrroles 14 [Scheme 21, eq 3]. To a solution of cyclopropenylimine **13** (1.00 equiv.) in THF (*c* = 0.025 M) was added $CuCl_2$ (0.1 equiv.) at rt. After being stirred under reflux for 2 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc) to afford 1,2,3,4-tetrasubstituted pyrrole **14**.

1-Methoxy-2-methyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (14a). Following **general procedure G**, (*E*)-**13a** (77.0 mg, 0.334 mmol) was used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 59.3 mg of **14a** (0.229 mmol, 77%) as a yellow oil. **IR (neat):** 2983, 2815, 1718, 1626 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.36-7.20 (m, 5H), 6.69 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 2.53 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.8, 135.0, 131.5, 129.1, 127.3, 126.2, 122.8, 113.1, 106.0, 66.8, 59.4, 14.3, 10.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}NO_3$: 260.1281, found: 260.1287.

4-(4-Chlorophenyl)-1-methoxy-2-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (14b). Following **general procedure G**, (*E*)-**13b** (100 mg, 0.385 mmol) was used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 82.7 mg of **14b** (0.319 mmol, 83%) as a white solid. **IR (neat):** 2983, 2815, 1718, 1626 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.26 (m, 4H), 6.68 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 2.52 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.6, 133.5, 132.0, 131.8, 130.4, 127.4, 121.6, 113.2, 105.9, 66.8, 59.5, 14.4, 10.2.10.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_3Cl$: 294.0891, found: 294.0896.

1-Methoxy-2-methyl-4-(4-trifluoromethylphenyl)-1*H*-pyrrole-3-carboxylic acid ethyl ester (14c). Following **general procedure G**, (*E*)-**13c** (59.0 mg, 0.18 mmol) was used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 53.8 mg of **14c** (0.165 mmol, 91%) as a white solid. **IR (neat):** 1699, 1618, 1531, 1326 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.58-7.55 (m, 2H), 7.49-7.46 (m, 2H) 6.75 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.02 (s, 3H), 2.54 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.8, 139.0 (d, *J* = 1.5 Hz), 132.3, 129.8, 128.4 (q, *J* = 32.3 Hz), 124.5 (q, *J* = 270.0 Hz), 124.4 (q, *J* = 3.8 Hz), 121.7, 113.8, 106.2, 66.9, 59.6, 14.1, 10.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}NO_3F_3$: 328.1155, found: 328.1159.

4-(4-Fluorophenyl)-1-methoxy-2-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (14d).

Following **general procedure G**, (*E*)-**13d** (68.8 mg, 0.245 mmol) was used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 57.4 mg of **14d** (0.207 mmol, 84%) as a colorless oil. **IR (neat):** 1697, 198, 1525, 1278 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.33-7.23 (m, 2H), 7.02-6.94 (m, 2H), 6.66 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 2.52 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.0, 161.8 (d, *J* = 243.0 Hz), 131.8, 131.2 (d, *J* = 3.8 Hz), 130.9 (d, *J* = 7.5 Hz), 122.0, 114.2 (d, *J* = 21.0 Hz), 113.2, 106.1, 66.7, 59.4, 14.1, 9.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_3F$: 278.1187, found: 278.1191.

1-Methoxy-2-methyl-4-(4-methylphenyl)-1*H*-pyrrole-3-carboxylic acid ethyl ester (14e). Following **general procedure G**, (*E*)-**13e** (100 mg, 0.366 mmol) was used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 75.4 mg of **14e** (0.275 mmol, 75%) as a yellow oil. **IR (neat):** 1695, 1609, 1527 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.25-7.22 (m, 2H), 7.12-7.09 (m, 2H), 6.67 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 2.52 (s, 3H), 2.35 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.8, 135.7, 131.9, 131.4, 129.0, 128.1, 122.8, 112.9, 106.0, 66.8, 59.4, 21.4, 14.4, 10.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for: $C_{16}H_{20}NO_3$ 274.1438, found: 274.1440.

4-(4-Bromophenyl)-1-methoxy-2-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (14f). Following **general procedure G**, (*E*)-**13f** (58.0 mg, 0.172 mmol) was used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 44.4 mg of **14f** (0.132 mmol, 77%) as a white solid. **IR (neat):** 1697, 1566, 1516, 1069 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.46-7.41 (m, 2H), 7.26-7.21 (m, 2H), 6.70 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.00 (s, 3H), 2.53 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.9, 134.2, 132.1, 131.0, 130.6, 121.9, 120.4, 113.3, 106.0, 66.8, 59.5, 14.2, 10.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_3Br$: 338.0386, found: 338.1389.

1-Methoxy-2-methyl-4-(3-methylphenyl)-1*H*-pyrrole-3-carboxylic acid ethyl ester (14g). Following **general procedure G**, (*E*)-**13g** (100 mg, 0.366 mmol) was used. Purification by flash column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 75.2 mg of **14g** (0.275 mmol, 75%) as a pale yellow oil. **IR (neat):** 1695, 1607, 1516 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.23-7.04 (m, 4H), 6.68 (s, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 2.52 (s, 3H), 2.35 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.9, 136.6, 134.8, 131.5, 129.9, 127.2, 126.9, 126.3, 122.8, 113.0, 106.0, 66.7, 59.4, 21.6, 14.3, 10.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{20}NO_3$: 274.1438, found: 274.1439.

4-(2-Fluorophenyl)-1-methoxy-2-methyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (14h). Following **general procedure G**, (*E*)-**13h** (50.0 mg, 0.180 mmol) was used. Purification by flash

column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 42.2 mg of **14h** (0.151 mmol, 84%) as a white solid. **IR (neat):** 2983, 2819, 1723, 1626, 1241 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** 7.30-7.21 (m, 2H), 7.12-7.02 (m, 2H), 6.74 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.00 (s, 3H), 2.54 (s, 3H), 1.08 (t, *J* =7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.9, 160.4 (d, *J* = 244.5 Hz), 131.6, 131.4 (d, *J* = 3.0 Hz), 128.2 (d, *J* = 6.8 Hz), 123.5, 123.3 (d, *J* = 3.8 Hz), 115.6, 114.9 (d, *J* = 22.5 Hz), 113.8, 107.2, 66.8, 59.3, 13.9, 9.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_3F$: 278.1187, found: 278.1189.

[Scheme 21, eq 4]. A solution of (*E*)-**15** (30 mg, 0.0893 mmol) and $CuCl_2$ (1.2 mg, 0.0089 mmol) in chlorobenzene (0.1 mL) was added to a sealed tube. After being stirred at 140 °C 8 h, the reaction mixture was then allowed to cool to rt and concentrated at reduced pressure. The residue was purified by preparative TLC (Benzene) and gave 16.6 mg of **16** (0.0495 mmol, 56%) as a pale pink solid.

1-Methoxy-2-methyl-4,5-diphenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (16). IR (neat): 1695, 1604, 1529 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.28-7.14 (m, 10H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.61 (s, 3H), 2.63 (s, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.9, 135.0, 131.0, 130.7, 129.6, 129.2, 127.8, 127.1, 126.9, 125.9, 125.0, 120.3, 106.9, 65.7, 59.4, 14.2, 10.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}NO_3$: 336.1594, found: 336.1592.

[Scheme 22, eq 1]. To a solution of cyclopropenylimine (*Z*)-**17** (30.0 mg, 0.15 mmol) in THF (5.0 mL) was added $CuCl_2$ (2.0 mg, 0.015 mmol) at rt. After being stirred under reflux for 0.5 h, the reaction mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 20:1) gave 9.5 mg of **18** (0.0395 mmol, 49%) as a pale yellow oil.

4-(1-Cyclopenten-1-yl)-1-methoxy-2-phenyl-1*H*-pyrrole (18). IR (neat): 2849, 1600, 1508 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.67-7.63 (m, 2H), 7.39-7.34 (m, 2H), 7.27-7.21 (m, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 5.84 (m, 1H), 3.78 (s, 3H), 2.62-2.54 (m, 2H), 2.51-2.43 (m, 2H), 1.97 (quint, *J* = 7.2 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 136.2, 130.6, 128.7, 128.3, 126.6, 126.3, 121.5, 117.4, 113.9, 101.7, 66.6, 33.7, 33.1, 23.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}NO$: 240.1383, found: 240.1382.

[Scheme 22, eq 2]. To a solution of (*Z*)-**19** (19.0 mg, 0.0403 mmol) in THF (1.5 mL) was added $CuCl_2$ (0.54 mg, 0.0040 mmol, 10 mol %) under an Ar atmosphere at rt. This mixture was heated to reflux and stirred for 3 h. The reaction mixture was then allowed to cool to rt and concentrated at reduced pressure. Purification by preparative TLC (Toluene/Hexane = 5:1) gave 9.9 mg of **20** (0.0225 mmol, 56%) as a red oil.

Methoxy-4-(3-methoxyestra-13,5(10),16-tetraen-17-yl)-2-phenyl-1*H*-pyrrole (20). IR (neat): 3034, 2853, 2831, 1608, 1500 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ : δ 7.67-7.64 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.27-7.19 (m, 4H), 6.97 (d, *J* = 2.1 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 5.82-5.80 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.94-2.87 (m, 2H), 2.43-2.24 (m, 4H), 2.11-1.92 (m, 1H), 1.80-1.64 (m, 4H), 1.01 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.4, 148.4, 138.0, 133.0, 130.8, 128.5, 126.7, 126.5, 126.0, 121.7, 115.9, 113.8, 113.4, 111.4, 102.7, 66.6, 56.4, 55.2, 47.3, 44.2, 37.3, 35.8, 31.0, 29.8, 27.7, 26.8, 16.5; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{34}NO_2$: 440.2584, found: 440.2588.

Preparation of cyclopropenylimine 21a [Scheme 22, eq 3]. To a solution of cyclopropenylketone **44a** (200 mg, 1.00 mmol) in MeOH and pyridine (92 mL, 0.135 M, 10:1) was added 4-(aminooxy)-2-butenoic acid ethyl ester hydrochloride (362 mg, 2.00 mmol) under an Ar atmosphere at 0 °C. After being stirred for 2 h at rt, the reaction mixture was diluted with aq. 1 M HCl and extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel (Hexane/EtOAc = 50:1) to give 362 mg of **21a** (0.585 mmol, 60%) as a colorless oil and a 1:1 mixture of *E*/*Z* isomers as a pale yellow oil.

(*E*/*Z*)-4-[[(2-Butyl-2-cyclopropen-1-yl)-1-phenylidene]amino]oxy]-2-butenoic acid ethyl ester (21a). IR (neat): 3056, 3026, 1723, 1650 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.39-7.13 (m, 5H), 7.17-6.94 (m, 2H), 6.47-6.44 (m, 2H), 6.10 (dt, *J* = 15.9, 1.8 Hz, 1/ 2H), 5.90 (dt, *J* = 15.9, 1.8 Hz, 1/2H), 4.83 (dd, *J* = 4.5, 2.1 Hz, 4/ 2H), 4.67 (dd, *J* = 4.5, 2.1 Hz, 4/2H), 4.20 (quint, *J* = 7.2 Hz, 2H), 2.91 (d, *J* = 1.8 Hz, 1/2H), 2.48 (d, *J* = 1.8 Hz, 1/2H), 2.43-2.36 (m, 2H), 1.52-1.41 (m, 2H), 1.32-1.23 (m, 10.5H), 0.85 (br t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.3, 166.3, 165.3, 164.1, 144.6, 144.5, 134.7, 133.2, 128.5, 128.2, 128.1, 128.0, 127.9, 127.7, 121.39, 121.36, 120.4, 119.3, 98.5, 97.9, 72.4, 72.2, 60.34, 60.29, 28.8, 28.6, 25.7, 25.4, 22.9, 22.1, 17.3, 14.2, 13.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{26}NO_3$: 328.1907, found: 328.1906.

Preparation of cyclopropenylimine 21b [Scheme 22, eq 3]. To a solution of (2-methylphenyl-2-cyclopropen-1-yl)-phenylmethanone (250 mg, 1.07 mmol) in MeOH and pyridine (92 mL, 0.135 M, 10:1) was added 4-(aminooxy)-2-butenoic acid ethyl ester hydrochloride (386 mg, 2.13 mmol) under an Ar atmosphere at 0 °C. After being stirred for 2 h at rt, the reaction mixture was diluted with aq. 1 M HCl and extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by flash column chromatography on silica gel (Hexane/EtOAc = 50:1) to give 157 mg of **21b** (0.436 mmol, 41%) as a colorless oil and a 2:1 mixture of *E*/*Z* isomers as a pale yellow oil.

(*E*/*Z*)-4-[[(2-methylphenyl-2-cyclopropen-1-yl)-1-phenylidene]amino]oxy]-2-butenoic acid ethyl ester (21b). IR (neat): 3027, 1727, 1651 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.39−7.13 (m, 10H), 6.59 (s, 1H), 6.08 (d, *J* = 15.9 Hz, 2/3H), 5.91 (d, *J* = 15.9 Hz, 1/3H), 4.82-4.73 (m, 4/3H), 6.02-5.82 (m, 2/3H), 4.31-4.11 (m, 2H), 3.74 (s, 2H), 2.99 (s, 2/3H), 2.60 (s, 1/3H), 1.42−1.09 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.3, 164.4, 163.5, 144.6, 144.4, 136.6, 136.3, 134.6, 133.0, 128.5, 128.5, 128.2, 128.1, 128.0, 127.9, 127.7, 126.6, 126.6, 121.4, 119.4, 118.3, 100.1, 99.4, 72.2, 60.3, 32.5, 32.2, 23.6, 18.0, 14.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{26}NO_3$: 328.1907, found: 328.1906.

Preparation of pyrrolo[1,2-*b*]isoxazole 22a [Scheme 22, eq 3]. To a solution of **21a** (50.0 mg, 0.152 mmol) in THF (6.1 mL) was added $CuCl_2$ (2.10 mg, 0.0152 mmol) under an Ar atmosphere at rt. This mixture was heated to reflux and stirred for 0.5 h. The reaction mixture was then allowed to cool to rt, diluted with sat. aq. $NaHCO_3$, and extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude monocyclic pyrrole, which was used for the next step without further purification. To the solution of the crude monocyclic pyrrole in DCE (15.0 mL) was added $Sc(OTf)_3$ (150 mg, 0.305 mmol) under an Ar atmosphere at rt. After being stirred at reflux for 0.5 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 26.5 mg of **22a** (0.0809 mmol, 53%) as a pale yellow oil.

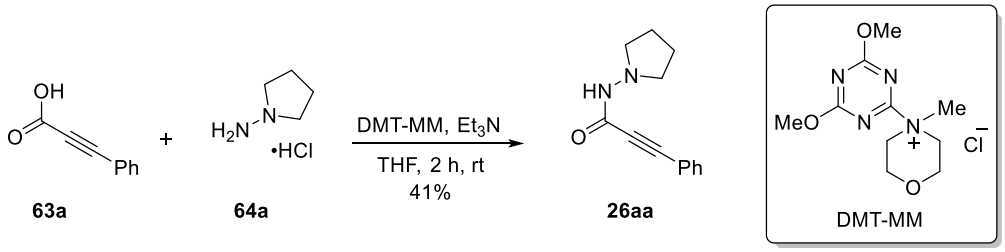
4-Butyl-6-phenylpyrrolo[1,2-b]isoxazole-3-acetic acid ethyl ester (22a). IR (neat): 3067, 1734, 1608, 1518 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.63-7.60 (m, 2H), 7.35-7.29 (m, 2H), 7.17-7.11 (m, 1H), 6.13 (s, 1H), 5.05 (t, *J* = 7.5 Hz, 1H), 4.63 (dd, *J* = 8.1, 5.1 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.95-3.86 (m, 1H), 2.87 (dd, *J* = 16.8, 4.2 Hz, 1H), 2.65 (dd, *J* = 16.8, 7.5 Hz, 1H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.61-1.52 (m, 2H), 1.40 (quint, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.6, 130.7, 128.5, 125.6, 124.7, 124.4, 121.8, 112.5, 105.6, 81.7, 60.9, 36.8, 36.2, 33.4, 26.0, 22.5, 14.2, 14.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{24}NO_3$: 328.1751, found: 362.1749.

Preparation of pyrrolo[1,2-*b*]isoxazole 22b [Scheme 22, eq 3]. To a solution of **21b** (50.0 mg, 0.138 mmol) in THF (5.5 mL) was added $CuCl_2$ (1.86 mg, 0.0138 mmol) under an Ar atmosphere at rt. This mixture was heated to reflux and stirred at this temperature for 0.5 h. The reaction mixture was then allowed to cool to rt and extracted with $CHCl_3$ and sat. aq. $NaHCO_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude monocyclic pyrrole, which was used for the next step without further purification. To a solution of the crude monocyclic pyrrole in DCE (14.0 mL) was added $Sc(OTf)_3$ (135 mg, 0.276 mmol) under an Ar

atmosphere at rt. After being stirred at reflux for 0.5 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (Hexane/EtOAc = 10:1) gave 24.8 mg of **22b**.

4-Phenylmethyl-6-phenylpyrrolo[1,2-*b*]isoxazole-3-acetic acid ethyl ester (22b). IR (neat): 3064, 1729, 1603, 1517 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.62-7.58 (m, 2H), 7.33-7.11 (m, 8H), 6.12 (s, 1H), 5.00 (t, *J* = 7.5 Hz, 1H), 4.60 (dd, *J* = 8.4, 4.5 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 2H), 3.76-3.67 (m, 1H), 2.50 (d, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.5, 141.4, 130.6, 128.6, 128.5, 128.4, 126.0, 125.8, 125.2, 124.4, 122.0, 110.9, 106.3, 81.7, 60.8, 36.5, 36.2, 32.8, 14.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{24}NO_3$: 362.1751, found: 362.1753.

[Scheme 22, eq 4]. A solution of *N*-alkoxy pyrrole **11a** (200 mg, 0.870 mmol) in AcOH was passed through the H-cube®,which was equipped with a cartridge filled with Pd/C catalyst. The solution was flowed at a rate of 1.0 mL/min with a pressure of 10 atm. After the solution was concentrated in vacuo, **11a** was confirmed by ^{1}H NMR. Then, the residue was dissolved in AcOH and repassed through the the H-cube® (Pd/C, 0.5 mL/min, 20 atm). After confirmed that **11a** was completely consumed by ^{1}H NMR, the resulting residue was purified by column chromatography (SiO_2, Hexane/EtOAc = 5:1) to afford pyrazole **11'** (90.0 mg, 0.450 mmol, 52%).



Scheme S2. Synthesis of *N*-pyrrolidinylalkynylhydrazide from phenylpropiolic acid.

[Scheme S2]. To a solution of a propiolic acid **63a** (400 mg, 2.74 mmol) in THF (c = 0.35 M) were added 1-aminopyrrolidine (400 mg, 2.74 mmol), Et_3N (1.6 mL, 11.5 mmol), and finally DMT-MM (907 mg, 3.28 mmol) at rt. Then, the mixture was stirred for 2 h. After stirring, the mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated at rt. The residue was purified by flash silica gel column chromatography (SiO_2, Hexane/EtOAc = 1:1) to afford a propiolamide **26aa** (240 mg, 1.12 mmol, 41%).

3-Phenyl-*N*-(pyrrolidin-1-yl)propiolamide (26aa). IR (neat): 3444, 2216, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.75 and 7.41-7.29 (br s, 1H), 7.56-7.49 (m, 2H), 7.41-7.29 (m, 3H), 2.98-2.90 (m, 4H), 1.89-1.82 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.4, 152.0, 132.5, 132.3, 129.9, 129.8, 128.3, 128.2, 120.7, 120.0, 90.9, 85.5, 81.9, 81.6, 55.8, 55.1, 22.1, 22.0; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1179, found: 215.1173.

[Table 7, entry 1]. To a solution of the alkynylhydrazide **26aa** (50 mg, 0.23 mmol) in DCE (5.0 mL) were added $CuBr_2$ (5.18 mg, 0.023 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (10.3 mg, 21%).

3-Phenyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27aa). Colorless oil. **IR (neat):** 1651 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.45-7.38 (m, 5H), 5.67 (s, 1H), 3.84 (t, J = 6.0 Hz, 2H), 3.28 (t, J = 6.0 Hz, 2H), 1.99-1.81 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.5, 157.4, 129.7, 128.6, 128.5, 127.8, 99.6, 50.0, 40.5, 23.4, 23.1; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1179, found: 215.1173.

[Table 7, entry 2]. To a solution of the alkynylhydrazide **26aa** (30 mg, 0.14 mmol) in DCE (5.0 mL)

was added CuBr (2.0 mg, 0.014 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 30:1) to afford pyrazolopyridazine **27aa** (1.5 mg, 5%).

[Table 7, entry 5]. To a solution of the alkynylhydrazide **26aa** (35 mg, 0.16 mmol) in MeCN (2.5 mL) was added $CuBr_2$ (3.65 mg, 0.023 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (7.0 mg, 20%).

[Table 7, entry 6]. To a solution of the alkynylhydrazide **26aa** (59.0 mg, 0.28 mmol) in EtOH (5 mL) was added $CuBr_2$ (6.25 mg, 0.028 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (14.3 mg, 25%).

[Table 7, entry 7]. To a solution of the alkynylhydrazide **26aa** (50.0 mg, 0.23 mmol) in PhCl (5.0 mL) was added $CuBr_2$ (5.18 mg, 0.023 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (20.6 mg, 42%).

[Table 7, entry 8]. To a solution of the alkynylhydrazide **26aa** (34.8 mg, 0.16 mmol) in PhCl (10 mL) was added $AuBr_3$ (14 mg, 0.023 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (9.0 mg, 23%).

[Table 7, entry 9]. To a solution of the alkynylhydrazide **26aa** (75.0 mg, 0.35 mmol) in PhCl (5.0 mL) was added $PicAuCl_2$ (13.6 mg, 0.035 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with

$CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (5.3 mg, 7%).

[Table 7, entry 10]. To a solution of the alkynylhydrazide **26aa** (50.0 mg, 0.23 mmol) in PhCl (5.0 mL) was added $(PPh_3)AuCl$ (11.4 mg, 0.023 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (17.1 mg, 35%).

[Table 8, entry 1]. To a solution of the alkynylhydrazide **26aa** (50.0 mg, 0.23 mmol) in PhCl (5.0 mL) were added **L1** (2.7 mg, 0.017 mmol) and $CuBr_2$ (3.8 mg, 0.017 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (10.0 mg, 28%).

[Table 8, entry 2]. To a solution of the alkynylhydrazide **26aa** (25.0 mg, 0.12 mmol) in PhCl (5.0 mL) were added **L2** (2.2 mg, 0.012 mmol) and $CuBr_2$ (2.7 mg, 0.012 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (17.4 mg, 68%).

[Table 8, entry 3]. To a solution of the alkynylhydrazide **26aa** (62.5 mg, 0.29 mmol) in PhCl (7.3 mL) were added **L3** (6.1 mg, 0.029 mmol) and $CuBr_2$ (6.5 mg, 0.029 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (40.1 mg, 64%).

[Table 8, entry 4]. To a solution of the alkynylhydrazide **26aa** (41.1 mg, 0.18 mmol) in PhCl (4.5 mL) were added **L5** (4.2 mg, 0.018 mmol) and $CuBr_2$ (6.5 mg, 0.018 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to

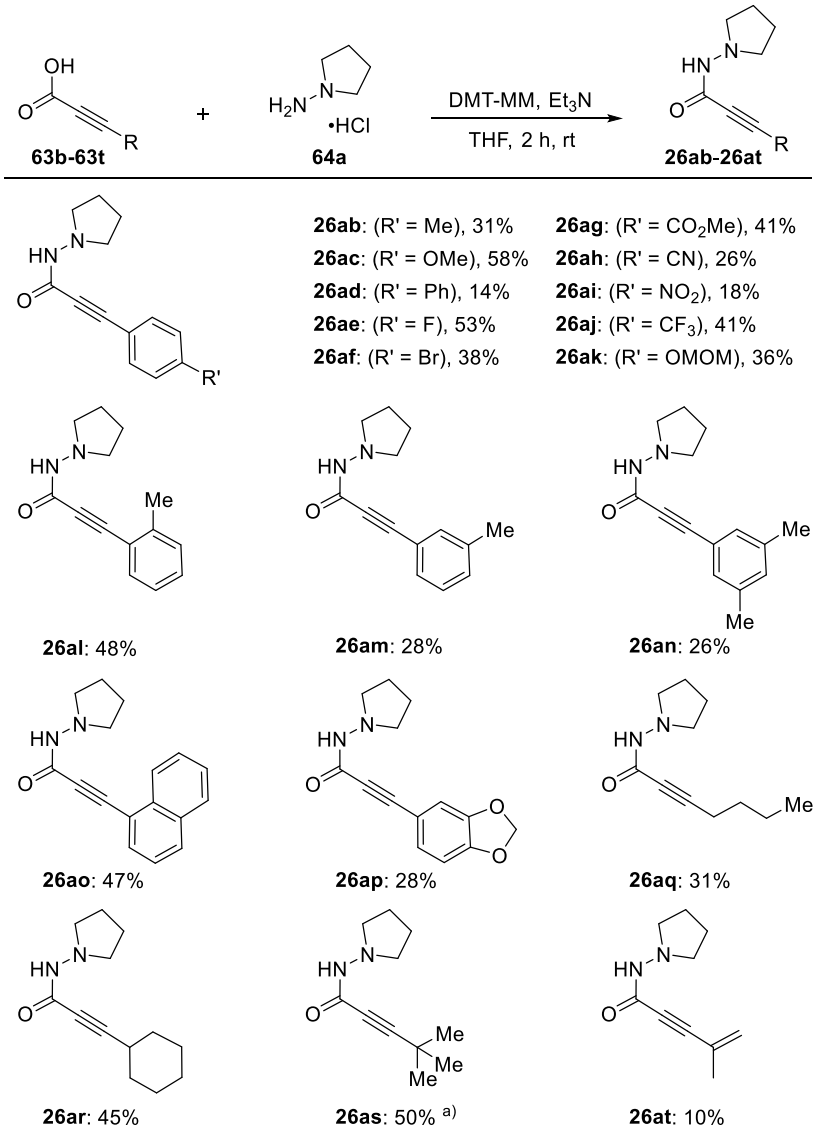
afford pyrazolopyridazine **27aa** (28.8 mg, 70%).

[Table 8, entry 5]. To a solution of the alkynylhydrazide **26aa** (33.3 mg, 0.16 mmol) in PhCl (4.5 mL) were added **L5** (5.6 mg, 0.016 mmol) and $CuBr_2$ (3.5 mg, 0.016 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (31.1 mg, 93%).

[Table 8, entry 6]. To a solution of the alkynylhydrazide **26aa** (31.1 mg, 0.14 mmol) in PhCl (5.0 mL) were added **L5** (5.0 mg, 0.014 mmol) and $CuBr_2$ (3.1 mg, 0.014 mmol). The mixture was stirred at 100 °C for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (22.0 mg, 71%).

[Table 8, entry 7]. To a solution of the alkynylhydrazide **26aa** (46.2 mg, 0.22 mmol) in PhCl (5.4 mL) were added **L5** (3.9 mg, 0.011 mmol) and $CuBr_2$ (2.4 mg, 0.011 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (35.0 mg, 76%).

Table S3. Preparation of alkynylhydrazides **26ab**-**26at**.



a) The reaction was carried out for 24 h.

General procedure H: preparation of alkynylhydrazides 26ab-26at [Table S3]. To a solution of a propiolic acid **63b-63t** (1.0 equiv.) in THF (c = 0.35 M) were added 1-aminopyrrolidine hydrochrolide **64a** (1.2 equiv.), Et_3N (4.2 equiv.), and finally DMT-MM (1.2 equiv.) at rt. Then, the mixture was stirred for 2 h. After stirring, the mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated at a temperature below 20 °C. The residue was purified by flash silica gel column chromatography (Hexane/EtOAc) to afford propiolamides **26ab**-**26at**.

***N*-(Pyrrolidin-1-yl)-3-(*p*-tolyl)propiolamide (26ab).** Prepared according to **general procedure H** from propiolic acid **63b** (300 mg, 1.87 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ab** was obtained as a pale orange oil (131 mg, 0.574 mmol, 31%); **IR (neat):** 3440, 2214, 1652 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.69 and 7.46-7.39 (br s, 1H), 7.46-7.39 (m, 2H), 7.17-7.11 (m, 2H), 3.00-2.90 (m, 4H), 2.37 and 2.34 (s, 3H), 1.89-1.84 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.5, 152.2, 140.4, 140.3, 132.5, 132.2, 129.1, 129.0, 117.6, 116.9, 91.3, 85.9, 81.5, 81.2, 55.8, 55.1, 22.1, 22.0, 21.5, 21.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1335, found: 229.1335.

(3-(4-Methoxyphenyl)-*N*-(pyrrolidin-1-yl)propiolamide (26ac). Prepared according to **general procedure H** from propiolic acid **63c** (400 mg, 2.27 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ac** was obtained as a white crystal (322.3 mg, 1.32 mmol, 58%). **m.p.:** 100-102 °C; **IR (neat):** 3435, 2210, 1639 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.71 and 7.55 (br s, 1H), 7.42-7.34 (m, 2H), 6.79-6.72 (m, 2H), 3.73 and 3.70 (s, 3H), 2.89-2.82 (m, 4H), 1.79-1.76 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 160.7, 160.6, 157.5, 152.3, 134.3, 133.9, 113.9, 113.8, 112.4, 111.7, 91.5, 85.9, 81.2, 80.8, 55.7, 55.09, 55.06, 55.0, 22.0, 21.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_2$: 245.1285, found: 245.1282.

3-([1,1'-Biphenyl]-4-yl)-*N*-(pyrrolidin-1-yl)propiolamide (26ad). Prepared according to **general procedure H** from propiolic acid **63d** (445 mg, 2.00 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ad** was obtained as a pale yellow crystal (80.7 mg, 0.278 mmol, 14%). **m.p.:** 152-153 °C; **IR (neat):** 2836, 2213, 1644 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.66-7.35 (m, 9H), 6.69 (br s, 1H), 3.00-2.92 (m, 4H), 1.93-1.87 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.3, 152.1, 142.7, 142.6, 139.8, 139.7, 133.1, 132.9, 128.8(2), 127.92, 127.87, 127.04, 126.96(2), 126.93, 119.6, 118.8, 90.9, 85.6, 82.5, 82.2, 56.0, 55.3, 22.15, 22.08; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O$: 291.1492, found: 291.1490.

3-(4-Fluorophenyl)-*N*-(pyrrolidin-1-yl)propiolamide (26ae). Prepared according to **general procedure H** from propiolic acid **63e** (400 mg, 2.43 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ae** was obtained as a white crystal (298 mg, 1.28 mmol, 53%). **m.p.:** 103-105 °C; **IR (neat):** 3453, 2218, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ **7**.92 and 7.58-7.47 (br s, 1H), 7.58-7.47 (m, 2H), 7.10-6.98 (m, 2H), 2.99-2.92 (m, 4H), 1.88-1.84 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.9, 161.6, 157.3, 151.9, 134.6 (d, *J* = 8.7 Hz), 134.4 (d, *J* = 8.7 Hz), 116.8 (d, *J* = 3.4 Hz), 116.1 (d, *J* = 3.4 Hz), 115.9 (d, *J* = 5.7 Hz), 115.6 (d, *J* = 5.8 Hz) , 89.8, 84.4, 81.8, 81.4, 55.8, 55.1, 22.04, 21.97; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_2OF$: 233.1085, found: 233.1084.

3-(4-Bromophenyl)-*N*-(pyrrolidin-1-yl)propiolamide (26af). Prepared according to **general procedure H** from propiolic acid **63f** (400 mg, 1.95 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26af** was obtained as a white crystal (216 mg, 0.735 mmol, 38%); **m.p.:** 126-127 °C; **IR (neat):** 2222, 1625, 694 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ **7**.49-7.33 (m, 4H), **7**.49-7.33 and 6.96 (br s, 1H), 2.98-2.89 (m, 4H), 1.90-1.84 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.8, 151.4, 133.7, 133.5, 131.6, 131.5, 124.5, 124.3, 119.6, 118.8, 89.6, 84.4, 82.8, 82.6, 56.2, 55.4, 22.4, 22.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_2OBr$: 293.0284, found: 293.0280.

Methyl 4-(3-oxo-3-(pyrrolidin-1-ylamino)prop-1-yn-1-yl)benzoate (26ag). Prepared according to **general procedure H** from propiolic acid **63g** (400 mg, 1.96 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ag** was obtained as a white crystal (220 mg, 0.808 mmol, 41%). **m.p.:** 141 °C; **IR (neat):** 3417, 2221, 1716, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.16 (br s, 1H), 8.04-7.93 (m, 2H), 7.62-7.51 (m, 2H), 3.93 and 3.91 (s, 3H), 3.02-2.97 (m, 4H), 1.95-1.80 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.8, 165.7, 156.8, 151.4, 132.0, 131.9, 130.6, 130.5, 129.1(2), 125.1, 124.4, 89.2, 84.1, 83.84, 83.75, 55.6, 54.7, 52.0(2), 21.9, 21.8. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1234, found: 273.1236.

3-(4-Cyanophenyl)-*N*-(pyrrolidin-1-yl)propiolamide (26ah). Prepared according to **general procedure H** from propiolic acid **63h** (400 mg, 0.209 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1); **26ah** was obtained as a brown crystal (95.8 mg, 18%). **m.p.:** 155 °C; **IR (neat):** 2220, 1626, 1523 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.26-8.21 (m, 2H), 7.74-7.67 (m, 2H), 7.13 and 6.80 (br s, 1H), 2.99-2.92 (m, 4H), 1.92-1.86 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.1, 150.7, 147.9, 147.7, 133.1, 133.0, 127.5, 126.5, 123.5, 123.4, 87.8, 85.6, 82.7(2), 56.4, 55.5, 22.42, 22.37; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_3O_3$: 260.1023, found: 260.1027.

3-(4-Nitrophenyl)-*N*-(pyrrolidin-1-yl)propiolamide (26ai). Prepared according to **general procedure H** from propiolic acid **63i** (400 mg, 0.209 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ai** was obtained as a brown crystal (95.8 mg, 18%); **m.p.:** 155 °C; **IR (neat):** 2220, 1626, 1523 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.26-8.21 (m, 2H), 7.74-7.67 (m, 2H), 7.13 and 6.80 (br s, 1H), 2.99-2.92 (m, 4H), 1.92-1.86 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.1, 150.7, 147.9, 147.7, 133.1, 133.0, 127.5, 126.5, 123.5, 123.4, 87.8, 85.6, 82.7(2), 56.4, 55.5, 22.42, 22.37; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_3O_3$: 260.1023, found: 260.1027.

***N*-(Pyrrolidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propiolamide (26aj).** Prepared according to **general procedure H** from propiolic acid **63j** (400 mg, 1.87 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1); **26aj** was obtained as a pale orange crystal (218 mg, 0.772 mmol, 41%).

m.p.: 99-101 °C; **IR (neat):** 2222, 1652, 1320 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ **7**.76-7.67 (m, 2H), 7.58-7.48 (m, 2H) 7.08 and 7.76-7.67 (br s, 1H), 3.00-2.93 (m, 4H), 1.90-1.83 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.1, 151.4, 135.1, 134.9, 132.1 (dd, *J* = 20.9, 7.9 Hz), 131.6, 131.4, 129.8, 129.5, 125.8 (q, *J* = 5.1 Hz), 122.1 (q, *J* = 137.6 Hz), 119.0 (q, *J* = 2.2 H), 86.5(2), 85.4, 80.7, 55.8, 55.2, 22.1, 22.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}N_2OF_3$: 283.1053, found: 283.1051.

3-(4-(Methoxymethoxy)phenyl)-*N*-(pyrrolidin-1-yl)propiolamide (26ak). Prepared according to **general procedure H** from propiolic acid **63k** (536 mg, 2.60 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ak** was obtained as a colorless oil (278 mg, 1.01 mmol, 36%); **IR (neat):** 2830, 2213, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.48-7.40 (m, 2H), 7.48-7.40 and 7.07 (br s, 1H), 6.97-6.93 (m, 2H), 5.16 and 5.14 (s, 2H), 3.43 and 3.42 (s, 3H), 2.93-2.86 (m, 4H), 1.86-1.79 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 158.5, 158.4, 157.5, 152.2, 134.3, 134.0, 116.1, 116.0, 113.8, 113.0, 94.0(2), 91.2, 85.8, 81.3, 81.0, 56.1, 56.0, 55.9, 55.3, 22.1, 22.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3$: 275.1390, found: 275.1383.

***N*-(Pyrrolidin-1-yl)-3-(*o*-tolyl)propiolamide (26al).** Prepared according to **general procedure H** from propiolic acid **63l** (400 mg, 2.50 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26al** was obtained as a white crystal (276 mg, 1.21 mmol, 48%). **m.p.:** 99 °C; **IR (neat):** 3448, 2212, 1646 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.91 and 7.33-7.11 (br s,1H), 7.54 and 7.47 (d, *J* = 7.8 Hz, 1H), 7.33-7.11 (m, 3H), 3.02-2.92 (m, 4H), 2.50 and 2.45 (s, 3H), 1.90-1.82 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.7, 152.1, 141.8, 141.3, 133.0, 132.8, 129.93, 129.87, 129.5, 129.4, 125.5(2), 120.5, 119.8, 89.5, 85.6, 85.4, 84.4, 55.7, 55.1, 22.1, 22.0, 20.5, 20.1. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1335, found: 229.1332.

***N*-(Pyrrolidin-1-yl)-3-(*m*-tolyl)propiolamide (26am).** Prepared according to **general procedure H** from propiolic acid **63m** (400 mg, 2.50 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26am** was obtained as a white crystal (162 mg, 0.711 mmol, 28%). **m.p.:** 99 °C; **IR (neat):** 2838, 2217, 1639 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.67 and 7.37-7.20 (br s, 1H), 7.37-7.20 (m, 4H), 2.98-2.90 (m, 4H), 2.34 and 2.31 (s, 3H), 1.90-1.83 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.4, 152.0, 138.1, 138.0, 133.0, 132.8, 130.8, 130.7, 129.6, 129.4, 128.2, 128.1, 120.5, 119.8, 91.2, 85.7, 81.6, 81.3, 55.9, 55.2, 22.1, 22.0, 21.01, 20.99; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1335, found: 229.1332.

3-(3,5-Dimethylphenyl)-*N*-(pyrrolidin-1-yl)propiolamide (26an). Prepared according to **general procedure H** from propiolic acid **63n** (400 mg, 2.30 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26an** was obtained as a pale yellow oil (143 mg, 0.590 mmol, 26%); **IR (neat):**

3478, 2216, 1635 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.85 and 7.61 (br s, 1H), 7.17-7.12 (m, 2H), 7.03-7.00 (m, 2H), 3.00 and 2.90 (m, 4H), 2.29 and 2.25 (s, 6H), 1.88-1.83 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.4, 152.1, 137.81, 137.76, 131.71, 131.65, 130.0, 129.9, 120.2, 119.6, 91.4, 85.9, 81.3, 80.9, 55.7, 55.0, 22.0, 21.9, 20.80, 20.77; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1485.

3-(Naphthalen-1-yl)-*N*-(pyrrolidin-1-yl)propiolamide (26ao). Prepared according to **general procedure H** from propiolic acid **63o** (400 mg, 2.01 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc =1:1). **26ao** was obtained as a pale yellow crystal (250 mg, 0.946 mmol, 47%). **m.p.:** 105-108 °C; **IR (neat):** 2975, 2235, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** 8.55 and 8.323 (d, *J* = 7.8 Hz, 1H), 8.00-7.36 (m, 7H), 4.02 (br s, 4H), 1.94-1.89 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.7, 152.1, 134.0, 133.2, 132.9, 132.8, 132.4, 132.1, 130.7, 130.5, 128.2(2), 127.2, 126.9, 126.6, 126.5, 125.9, 125.7, 125.1, 124.9, 118.3, 117.6, 88.7, 86.5, 83.7(2), 55.8, 55.2, 22.1, 22.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O$: 265.1335, found: 265.1330.

3-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(pyrrolidin-1-yl)propiolamide (26ap). Prepared according to **general procedure H** from propiolic acid **63p** (300 mg, 1.58 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ap** was obtained as a brown oil (111 mg, 0.431 mmol, 28%); **IR (neat):** 2841, 2213, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.43 and 7.20 (br s, 1H), 7.13-6.75 (m, 3H), 6.01 and 5.99 (s, 2H), 3.00-2.90 (m, 4H), 1.90-1.84 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.4, 152.2, 149.30, 149.27, 147.4, 147.3, 128.1, 127.8, 113.8, 113.0, 112.3, 111.9, 108.52, 108.46, 101.51, 101.48, 91.2, 85.8, 80.7, 80.4, 55.9, 55.3, 22.1, 22.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1077, found: 259.1074.

***N*-(Pyrrolidin-1-yl)hept-2-ynamide (26aq).** Prepared according to **general procedure H** from propiolic acid **63q** (400 mg, 3.17 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26aq** was obtained as a colorless oil (194 mg, 0.999 mmol, 31%); **IR (neat):** 3470, 2237, 1648 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.88 and 7.24 (br s, 1H), 2.95-2.86 (m, 4H), 2.38 and 2.29 (t, *J* = 6.9 Hz, 2H), 1.88-1.80 (m, 4H), 1.60-1.38 (m, 4H) 0.93 and 0.91 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.3, 152.0, 93.8, 88.0, 74.1, 73.7, 55.6, 54.8, 29.45, 29.40, 21.8(2), 21.6, 21.4, 18.5, 18.0, 13.2(2). **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{19}N_2O$: 195.1492, found: 195.1491.

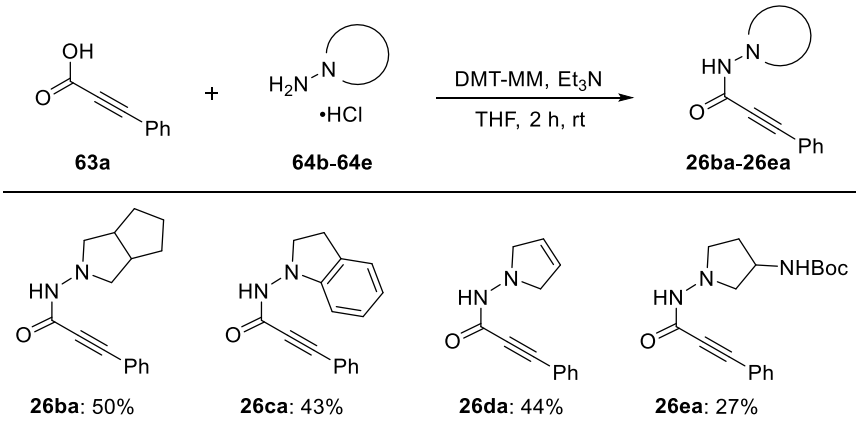
3-Cyclohexyl-*N*-(pyrrolidin-1-yl)propiolamide (26ar). Prepared according to **general procedure H** from propiolic acid **63r** (400 mg, 2.63 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ar** was obtained as a colorless oil (259 mg, 1.18 mmol, 45%); **IR (neat):** 3421, 2230, 1639 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.84 and 6.57 (br s, 1H), 2.94-2.84 (m, 4H), 2.64-2.42 (m, 1H), 1.89-1.26 (m, 14H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.5, 152.2, 97.2, 91.7, 74.1, 73.9, 55.7, 55.1,

31.5, 31.4, 28.8, 28.7, 25.7, 25.4, 24.5, 24.1, 22.0, 21.97; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{21}N_2O$: 221.1648, found: 221.1647.

4,4-Dimethyl-*N*-(pyrrolidin-1-yl)pent-2-ynamide (26as). Prepared according to **general procedure H** from propiolic acid **63s** (400 mg, 3.17 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26as** was obtained as a colorless crystal (308 mg, 1.59 mmol, 50%). **m.p.:** 94 °C; **IR (neat):** 3470, 2225, 1639 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.48 and 7.20 (br s, 1H), 2.95-2.84 (m, 4H), 1.88-1.80 (m, 4H), 1.29 and 1.26 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.5, 152.2, 101.0, 95.3, 72.8, 72.2, 55.5, 55.2, 30.0(2), 27.6, 27.3, 22.1, 22.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{19}N_2O$: 195.1492, found: 195.1492.

4-Methyl-*N*-(pyrrolidin-1-yl)pent-4-en-2-ynamide (26at). Prepared according to **general procedure H** from propiolic acid **63t** (300 mg, 2.73 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26at** was obtained as a pale yellow oil (49.2 mg, 0.276 mmol, 10%); **IR (neat):** 3470, 2213, 1638 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.39 and 6.95 (br s, 1H), 5.52 (br s, 1H), 5.45-5.44 (m, 1H), 2.97-2.87 (m, 4H), 1.95 and 1.91 (s, 3H), 1.90-1.82 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.3, 151.9, 126.3, 125.9, 125.1, 124.5, 92.0, 86.5, 80.8, 80.5, 55.9, 55.2, 22.5, 22.4, 22.1, 22.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{15}N_2O$: 179.1179, found: 179.1177.

Table S4. Preparation of alkynylhydrazides **26ba-26ea**.



General procedure I: preparation of alkynylhydrazides 26ba-26ea [Table S4]. To a solution of phenyl propiolic acid **63a** (1.0 equiv.) in THF (*c* = 0.35 M) were added hydrazine hydrochloride **64b-64i** (1.2 equiv.), TEA (4.2 equiv.) and finally DMT-MM (1.2 equiv.) at rt. Then, the mixture was stirred for 2 h. After stirring, the mixture was quenched by water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue

was purified by silica gel column chromatography (SiO_2, Hexane/EtOAc) to afford propiol amide **26ba**-**26ea**.

***N*-(Hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-phenylpropiolamide (26ba).** Prepared according to **general procedure I** from phenyl propiolic acid (300 mg, 2.05 mmol) and hydrazine hydrochloride **64b** (400 mg, 2.46 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 2:1). **26ba** was obtained as a white crystal (259 mg, 1.02 mmol, 50%). **m.p.:** 143-144 °C; **IR (neat):** 3470, 2216, 1648 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.57-7.31 (m, 5H) 7.57-7.31 and 6.77 (br s, 1H), 3.30 (dd, *J* = 7.8, 7.8 Hz, 1H), 2.88-2.78 (m, 2H), 2.67-2.57 (br, 2H), 2.41 (dd, *J* = 6.3, 6.3 Hz, 1H), 1.82-1.48 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.3, 151.7, 132.6, 132.4, 130.0, 129.9, 128.4, 128.4, 120.9, 120.1, 90.4, 85.4, 82.0, 81.8, 63.3, 62.5, 40.4, 40.4, 34.0, 32.0, 26.6, 25.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O$: 255.1491, found: 255.1492.

***N*-(Indolin-1-yl)-3-phenylpropiolamide (26ca).** Prepared according to **general procedure I** from phenyl propiolic acid (400 mg, 2.73 mmol) and hydrazine hydrochloride **64c** (416 mg, 3.28 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ca** was obtained as a white crystal (308 mg, 1.17 mmol, 43%). **m.p.:** 137 °C; **IR (neat):** 2214, 1646 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.57-7.28 (m, 5H), 7.18-7.09 (m, 2H), 6.94-6.73 (m, 2H), 3.61 (dd, *J* = 8.1, 8.1 Hz, 2H), 3.03 (dd, *J* = 8.1, 8.1 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 158.4, 152.8, 150.4, 150.1, 132.4, 132.3, 130.02, 129.97, 128.3, 128.1, 127.7(2), 127.3, 127.1, 124.7, 124.6, 121.5, 121.1, 120.0, 119.6, 109.9, 109.7, 91.0, 86.6, 81.4, 80.9, 57.3, 56.0, 27.5(2); **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}N_2O$: 263.1179, found: 263.1180.

***N*-(2,5-Dihydro-1*H*-pyrrol-1-yl)-3-phenylpropiolamide (26da).** Prepared according to **general procedure I** from phenyl propiolic acid (400 mg, 2.73 mmol) and hydrazine hydrochloride **64d** (276 mg, 3.28 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26da** was obtained as a white crystal (258 mg, 1.22 mmol, 44%). **m.p.:** 98-99 °C; **IR (neat):** 2216, 1652 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.83 and 7.62 (br s, 1H), 7.58-7.50 (m, 2H), 7.43-7.31 (m, 3H), 5.79 (br s, 2H), 3.93 and 3.85 (br s, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 158.0, 152.5, 132.6, 132.4, 130.0, 129.9, 128.4, 128.3, 126.3, 126.3, 120.6, 119.9, 91.2, 85.6, 81.9, 81.5, 62.4, 61.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O$: 213.1022, found: 213.1021.

***tert*-Butyl (1-(3-phenylpropiolamido)pyrrolidin-3-yl)carbamate (26ea).** Prepared according to **general procedure I** from phenyl propiolic acid (400 mg, 2.73 mmol) and hydrazine hydrochloride **64d** (516 mg, 3.28 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **26ea** was obtained as a colorless oil (191 mg, 0.729 mmol, 27%). **m.p.:** 152 °C; **IR (neat):** 3431, 2217, 1691 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.87 and 7.58-7.31 (br s, 1H), 7.58-7.31 (m, 5H), 5.56 and 5.09

(d, *J* = 8.1 Hz, 1H), 4.22 (br s, 1H), 3.32-2.81 (m, 4H), 2.31-2.18 (m, 1H), 1.78 (br s, 1H), 1.44 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.75, 155.68, 155.5, 152.7, 133.0, 132.7, 130.45, 130.37, 128.8, 128.7, 120.8, 120.1, 91.4, 86.2, 82.0, 81.8, 79.7, 62.3, 60.9, 54.2, 53.3, 49.3, 48.9, 31.7, 31.4, 28.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}N_3O_3$: 330.1812, found: 330.1815.

General procedure J: synthesis of pyrazolopyridazines 27ab-27at, 27ba-27ea [Table 9]. To a solution of the alkynylhydrazides **26ab-26at, 26ba-26ea** (1.0 equiv.) in PhCl (*c* = 0.4 M) was added bathocuproine (10 mol%) and finally $CuBr_2$. The mixture was stirred under reflux until completion (from 0.5 h to 1 d). The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH) to afford pyrazolopyridazine **27ab-27at, 27ba-27ea**.

3-(*p*-Tolyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27ab). Prepared according to **general procedure J** from phenyl propiolamide **26ab** (77.7 mg, 0.340 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27ab** was obtained as an orange crystal (74.3 mg, 3.25 mmol, 96%). **m.p.:** 119 °C; **IR (neat):** 3418, 2957, 1635 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.33-7.24 (m, 4H), 5.65 (s, 1H), 3.85 (t, *J* = 6.0 Hz, 2H), 3.28 (t, *J* = 5.4 Hz, 2H), 2.40 (s, 3H), 1.98-1.81 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.0, 157.9, 140.2, 129.5, 127.9, 125.9, 99.3, 50.0, 40.4, 23.3, 23.0, 21.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1336, found: 229.1132.

3-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27ac). Prepared according to **general procedure J** from phenyl propiolamide **26ac** (93.0 mg, 0.381 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27ac** was obtained as an orange crystal (81.4 mg, 0.333 mmol, 86%). **m.p.:** 156 °C; **IR (neat):** 3444, 2957, 1613 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.36 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 5.62 (s, 1H), 3.85 (s, 3H), 3.84 (t, *J* = 5.4 Hz, 2H), 3.27 (t, 5.4 Hz, 2H), 1.98-1.81 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.1, 160.9, 157.8, 129.5, 121.2, 114.3, 99.0, 55.3, 50.2, 40.4, 23.4, 23.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_2$: 245.1285, found: 245.1279.

3-([1,1'-Biphenyl]-4-yl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27ad). Prepared according to **general procedure J** from phenyl propiolamide **26ad** (57.4 mg, 0.198 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27ad** was obtained as a pale yellow oil (47.9 mg, 0.165 mmol, 83%); **IR (neat):** 3426, 2954, 1650 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.70-7.34 (m, 9H), 5.74 (s, 1H), 3.86, (t, *J* = 6.0 Hz, 2H), 3.34 (t, *J* = 5.7 Hz, 2H), 2.01-1.83 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.9, 157.6, 142.9, 139.9, 128.9, 128.6, 127.9, 127.7, 127.6, 127.0, 100.0, 50.2, 40.5, 23.4, 23.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O$: 291.1492, found: 291.1489.

3-(4-Fluorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27ae). Prepared according to **general procedure J** from phenyl propiolamide **26ae** (84.4 mg, 0.363 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27ae** was obtained as a pale orange crystal (77.7 mg, 0.335 mmol, 92%). **m.p.:** 126-127 °C; **IR (neat):** 3413, 2959, 1619 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.43-7.36 (m, 2H), 7.20-7.10 (m, 2H), 5.65 (s, 1H), 3.84 (t, *J* = 6.0 Hz, 2H), 3.25 (t, *J* = 5.7 Hz, 2H), 1.99-1.81 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.0 (d, *J* = 40.1 Hz), 161.9, 156.8, 130.0 (d, *J* = 8.5 Hz), 125.0 (d, *J* = 6.3 Hz), 116.1 (d, *J* = 21.9 Hz), 100.1, 50.1, 40.4, 23.3, 23.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_2OF$: 233.1085, found: 233.1082.

3-(4-Bromophenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27af). Prepared according to **general procedure J** from phenyl propiolamide **26af** (89.0 mg, 0.304 mmol). Purified by preparative TLC (SiO_2, EtOAc/MeOH = 20:1). **27af** was obtained as a red crystal (83.8 mg, 0.286 mmol, 94%). **m.p.:** 155 °C; **IR (neat):** 3425, 2955, 1647 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.58 (d, *J* = 5.7 Hz, 2H), 7.28 (d, *J* = 5.7 Hz, 2H), 5.67 (s, 1H), 3.84 (t, *J* = 5.4 Hz, 2H), 3.26 (t, *J* = 5.1 Hz, 2H), 2.00-1.82 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.2, 156.2, 131.8, 129.3, 127.5, 124.1, 100.2, 50.1, 40.5, 23.4, 23.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_2OBr$: 293.0284, found: 293.0281.

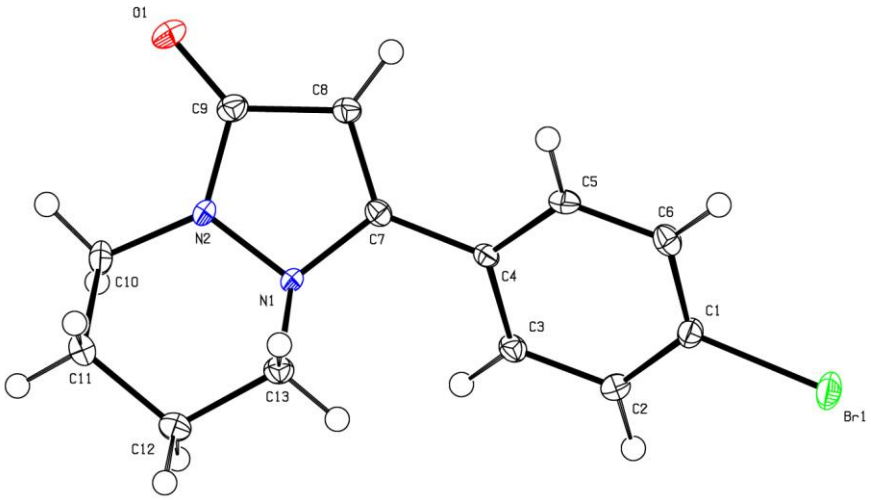


Figure S1. X-ray structure of **27af** (CCDC 1993619).

Single crystals of **27af** ($C_{13}H_{13}BrN_2O$) was used for the X-ray crystallographic analysis. A suitable crystal was measured on a dtrek-CrysAlisPro-abstract goniometer imported rigaku-d*trek images diffractometer. The crystal was kept at 100 K during data collection. Using Olex2 [59], the structure was solved with the ShelXT [60] structure solution program using Intrinsic Phasing and refined with the ShelXL[61] refinement package using Least Squares minimization.

Figure S1. Crystal Data and Structure Refinement for **27af**.

Empirical formula $C_{13}H_{13}BrN_2O$
Formula weight 293.16
Temperature/K 100
Crystal system triclinic
Space group P-1
a/Å 7.6664(3)
b/Å 7.8291(4)
c/Å 10.2682(5)
α/° 93.108(4)
β/° 91.344(4)
γ/° 108.410(4)
Volume/Å3 583.37(5)
Z 2
ρcalcg/cm3 1.669
μ/mm-1 3.507
F(000) 296.0
Crystal size/mm3 0.03 × 0.03 × 0.02
Radiation MoKα (λ = 0.71073)
2Θ range for data collection/° 3.976 to 62.624
Index ranges -11 ≤ h ≤ 11, -10 ≤ k ≤ 11, -14 ≤ l ≤ 14
Reflections collected 11256
Independent reflections 3472 [Rint = 0.0591, Rsigma = 0.0605]
Data/restraints/parameters 3472/0/154
Goodness-of-fit on F2 1.021
Final R indexes [I>=2σ (I)] R1 = 0.0381, wR2 = 0.0780
Final R indexes [all data] R1 = 0.0515, wR2 = 0.0832
Largest diff. peak/hole / e Å-3 0.46/-0.48

Methyl 4-(1-oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-3-yl)benzoate (27ag). Prepared according to **general procedure J** from phenyl propiolamide **26ag** (89.0 mg, 0.327 mmol). Purfied by preparative TLC (EtOAc/MeOH = 10:1). **27ag** was obtained as a pale orange crystal (60.4 mg, 0.221 mmol, 68%). **m.p.:** 185 °C; **IR (neat):** 3422, 2954, 1638 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.10 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 5.76 (s, 1H), 3.94 (s, 3H), 3.86 (t, *J* = 6.0 Hz, 2H), 3.27 (t, *J* = 5.7 Hz, 2H), 2.00-1.82 (m, 4H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.9, 164.2, 156.4, 132.9, 131.2, 129.9, 127.9, 101.1, 52.5, 50.3, 40.7, 23.5, 23.2. **HRMS (ESI):** *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1234, found: 273.1231.

4-(1-Oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-3-yl)benzonitrile (27ah). Prepared

according to **general procedure J** from phenyl propiolamide **26ah** (60.2 mg, 0.252 mmol). Purfied by preparative TLC (EtOAc/MeOH = 10:1). **27ah** was obtained as a pale orange crystal (46.8 mg, 0.196 mmol, 78%). **m.p.:** 217-218 °C; **IR (neat):** 3431, 2228, 1646 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 5.80 (s, 1H), 3.88 (t, *J* = 6.0 Hz, 2H), 3.27 (t, *J* = 6.0 Hz, 2H), 2.03-1.84 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.1, 155.7, 133.2, 132.6, 128.7, 117.9, 113.6, 101.9, 50.2, 40.5, 23.2, 22.8; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}N_3O$: 240.1131, found: 240.1125.

3-(4-Nitrophenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27ai). Prepared according to **general procedure J** from phenyl propiolamide **26ai** (56.2 mg, 0.217 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27ai** was obtained as a yellow crystal (43.1 mg, 0.166 mmol, 77%). **m.p.:** 224.8-225.1 °C; **IR (neat):** 3436, 1635, 1519 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.31 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 9.0 Hz, 2H), 5.83 (s, 1H), 3.88 (t, *J* = 5.7 Hz, 2H), 3.27 (t, *J* = 5.7 Hz, 2H), 2.04-1.84 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.7, 155.0, 148.3, 134.7, 128.8, 124.0, 102.3, 50.4, 40.7, 23.4, 23.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_3O_3$: 260.1030, found: 260.1026.

3-(4-(Trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27aj). Prepared according to **general procedure J** from phenyl propiolamide **26aj** (33.0 mg, 0.117 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27aj** was obtained as a pale orange crystal (27.3 mg, 0.0967 mmol, 83%). **m.p.:** 122 °C; **IR (neat):** 3437, 1652 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 5.76 (s, 1H), 3.87 (t, *J* = 5.7 Hz, 2H), 3.27 (t, *J* = 5.7 Hz, 2H), 2.01-1.83 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.4, 156.2, 132.4, 131.9 (q, *J* = 32.9 Hz), 128.5, 125.9 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.4 Hz), 101.4, 50.1, 40.5, 23.3, 22.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}F_3N_2O$: 283.1053, found: 283.1047.

3-(4-(Methoxymethoxy)phenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27ak). Prepared according to **general procedure J** from phenyl propiolamide **26ak** (52.0 mg, 0.190 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27ak** was obtained as a pale orange oil (38.4 mg, 0.141 mmol, 74%); **IR (neat):** 3427, 1637 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.35 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.63 (s, 1H), 5.22 (s, 2H), 3.84 (t, *J* = 5.7 Hz, 2H), 3.49 (s, 3H), 3.28 (t, 5.7 Hz, 2H), 1.99-1.81 (m ,4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.0, 158.5, 157.6, 129.5, 122.3, 116.4, 99.2, 94.1, 56.1, 50.1, 40.4, 23.4, 23.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3$: 275.1390, found: 275.1384.

3-(*o*-Tolyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27al). Prepared according to **general procedure J** from phenyl propiolamide **26al** (73.0 mg, 0.320 mmol). Purified by preparative

TLC (EtOAc/MeOH = 20:1). **27al** was obtained as a pale orange oil (68.7 mg, 0.301 mmol, 94%); **IR (neat):** 3428, 2223, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.38-7.22 (m, 4H), 5.54 (s, 1H), 3.85 (br s, 2H), 3.15 (br s, 2H), 2.33 (s, 3H), 1.88 (br s, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.2, 155.5, 136.6, 130.6, 129.6, 129.5, 128.4, 125.9, 99.7, 48.0, 40.6, 23.0, 22.5, 19.8; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1335, found: 229.1330.

3-(*m*-Tolyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27am). Prepared according to **general procedure J** from phenyl propiolamide **26am** (75.0 mg, 0.329 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27am** was obtained as a pale orange oil (64.6 mg, 0.283 mmol, 86%); **IR (neat):** 3432, 1652 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.37-7.20 (m, 4H), 5.67 (s, 1H), 3.85 (t, *J* = 5.7 Hz, 2H), 3.29 (t, *J* = 5.7 Hz), 2.41 (s, 3H), 1.99-1.82 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.9, 158.0, 138.7, 130.7, 128.8, 128.70, 128.66, 125.2, 99.7, 50.0, 40.4, 23.3, 23.0, 21.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1335, found: 229.1331.

3-(3,5-Dimethylphenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27an). Prepared according to **general procedure J** from phenyl propiolamide **26an** (105 mg, 0.430 mmol). Purified by preparative TLC (AcOEt/MeOH, 20:1). **27an** was obtained as a pale orange oil (74.7 mg, 0.306 mmol, 71%); **IR (neat):** 3412, 1622 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.62 and 7.09-7.02 (br s, 1H), 7.08 (s, 1H), 7.02 (s, 1H), 5.65 (s, 1H), 3.85 (t, *J* = 6.0 Hz, 2H), 3.29 (t, *J* = 6.0 Hz, 2H), 2.37 (s, 6H), 1.99-1.81 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.1, 158.2, 138.6, 131.6, 128.8, 125.9, 99.6, 50.0, 40.5, 23.4, 23.1, 21.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1488.

3-(Naphthalen-1-yl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27ao). Prepared according to **general procedure J** from phenyl propiolamide **26ao** (90.0 mg, 0.340 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27ao** was pale yellow oil (68.3 mg, 0.258 mmol, 76%). **IR (neat):** 3430, 2226, 1634 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.09-8.03 (m, 1H), 7.94-7.86 (m, 2H), 7.56-7.45 (m, 4H), 5.72 (s, 1H), 3.92 (br s, 2H), 3.13 (t, *J* = 5.4 Hz, 2H), 1.91-1.81 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.0, 154.5, 133.3, 130.9, 130.1, 128.3, 127.8, 127.1, 126.3, 126.2, 124.9, 124.5, 100.8, 48.2, 41.0, 23.3, 22.8; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}N_2O$: 265.1336, found: 265.1333.

3-(Benzo[*d*][1,3]dioxol-5-yl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27ap). Prepared according to **general procedure J** from phenyl propiolamide **26ap** (66.0 mg, 0.256 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **27ap** was pale orange crystal (52.2 mg, 0.202 mmol, 79%). **m.p.:** 193 °C; **IR (neat):** 3419, 2230, 1634 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.94-6.87 (m, 3H), 6.03 (s, 2H), 5.62 (s, 1H), 3.83 (t, *J* = 6.0 Hz, 2H), 3.28 (t, *J* = 5.7 Hz, 2H), 3.13 (t, *J* =

5.4 Hz, 2H), 1.98-1.81 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.0, 157.8, 149.2, 148.1, 122.7, 122.4, 108.8, 108.3, 101.6, 99.6, 50.3, 40.5, 23.5, 23.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1077, found: 259.1076.

3-Butyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27aq). Prepared according to **general procedure J** from phenyl propiolamide **26aq** (41.5 mg, 0.214 mmol). Purified by preparative TLC (EtOAc/MeOH = 15:1). **27aq** was obtained as a pale orange oil (30.0 mg, 0.154 mmol, 72%); **IR (neat):** 3446, 1622 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 5.28 (s, 1H), 3.72 (t, *J* = 5.4 Hz, 2H), 3.40 (t, *J* = 5.4 Hz, 2H), 2.39 (t, *J* = 6.9 Hz, 2H), 1.96-1.79 (m, 4H), 1.63-1.53 (m, 2H), 1.46-1.34 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.9, 156.7, 96.6, 46.3, 40.6, 29.5, 25.4, 23.1, 22.4, 22.2, 13.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{19}N_2O$: 195.1492, found: 195.1493.

3-Cyclohexyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27ar). Prepared according to **general procedure J** from phenyl propiolamide **26ar** (43.5 mg, 0.197 mmol). Purified by preparative TLC (EtOAc/MeOH = 3:1). **27ar** was obtained as a pale yellow oil (40.7 mg, 0.184 mmol, 94%); **IR (neat):** 3412, 2224, 1634 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 5.26 (s, 1H), 3.71 (t, *J* = 5.4 Hz, 2H), 3.42 (t, *J* = 5.4 Hz, 2H), 2.36-2.28 (m, 1H), 1.95-1.71 (m, 9H), 1.41-1.25 (m, 5H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.1, 161.8, 95.0, 46.6, 40.7, 35.0, 31.9, 26.0, 25.7, 23.2, 22.5; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{21}N_2O$: 221.1648, found: 221.1647.

3-(*tert*-Butyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27as). Prepared according to **general procedure J** from phenyl propiolamide **26as** (50 mg, 0.257 mmol), (Reaction time = 24 h). Purified by preparative TLC (EtOAc/MeOH = 15:1). **27as** was obtained as a pale orange oil (48.1 mg, 0.250 mmol, 96%); **IR (neat):** 3412, 1603 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 5.31 (s, 1H), 3.73 (t, *J* = 5.4 Hz, 2H), 3.58 (t, *J* = 5.4 H, 2H), 1.96-1.77 (m ,4H), 1.30 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.6, 164.7, 96.3, 49.3, 40.8, 31.9, 29.1, 23.4, 22.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{19}N_2O$: 195.1492, found: 195.1491.

3-(Prop-1-en-2-yl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27at). Prepared according to **general procedure J** from phenyl propiolamide **26at** (38.0 mg, 0.213 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **27at** was obtained as an orange crystal (29.0 mg, 0.250 mmol, 76%). **m.p.:** 80 °C; **IR (neat):** 3437, 2223, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 5.54 (s, 1H), 5.31 (s, 1H), 5.22 (s, 1H), 3.79 (t, *J* = 6.0 Hz, 2H), 3.35 (t, *J* = 5.7 Hz, 2H), 2.00 (s, 3H), 1.96-1.78 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.7, 158.7, 133.0, 118.7, 100.0, 50.4, 40.2, 23.3, 23.2, 21.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{15}N_2O$: 179.1179, found: 179.1182.

3-Phenyl-5a,6,7,8,8a,9-hexahydro-1*H*,5*H*-cyclopenta[*d*]pyrazolo[1,2-*a*]pyridazin-1-one (27ba).

Prepared according to **general procedure J** from phenyl propiolamide **26ba** (70.0 mg, 0.275 mmol). Purified by preparative TLC (EtOAc/MeOH = 20:1). **27ba** was obtained as a pale orange oil (62.1 mg, 0.244 mmol, 89%); **IR (neat):** 3425, 2220, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ **7**.48-7.40 (m, 5H), 5.67 (s, 1H), 3.91 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.79 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.47 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.21 (dd, *J* = 12.3, 6.6 Hz, 1H), 2.47-2.35 (m, 2H), 1.92-1.45 (m, 6H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.5, 156.7, 129.9, 128.9, 128.8, 128.0, 98.7, 49.7, 41.4, 37.4, 36.9, 27.9, 27.7, 22.8; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O$: 255.1492, found: 255.1489.

1-Phenyl-5,6-dihydro-3*H*-pyrazolo[1,2-*a*]cinnolin-3-one (27ca). Prepared according to **general procedure J** from phenyl propiolamide **26ca** (40.0 mg, 0.152 mmol). Purified by preparative TLC (EtOAc/MeOH). **27ca** was obtained as a red oil (25.1 mg, 0.0956 mmol, 63%). **IR (neat):** 3412, 1621 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ **7**.48-7.44 (m, 5 H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 5.69 (s, 1H), 4.14 (t, *J* = 6.0 Hz, 2H), 3.12 (t, *J* = 6.0 Hz, 2H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 161.4, 147.0, 134.6, 129.93, 129.92 128.9, 128.7, 128.3, 127.1, 124.9, 118.5, 99.2, 40.0, 27.4, one carbon peak could not be observed probably due to overlap; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}N_2O$: 263.1179, found: 263.1172.

3-Phenyl-5,8-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (27da). Prepared according to **general procedure J** from phenyl propiolamide **26da** (90.0 mg, 0.424 mmol). Purified by preparative TLC (EtOAc/MeOH = 3:1). **27da** was obtained as a brown oil (81.3 mg, 0.383 mmol, 90%); **IR (neat):** 3427, 2229, 1634 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.44 (br s, 5H), 6.07-6.02 (m, 1H), 5.91-5.86 (m, 1H), 5.74 (s, 1H), 4.36-4.34 (m, 2H), 3.92-3.86 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.5, 157.9, 130.0, 128.8, 128.7, 128.1, 121.2, 120.3, 99.8, 48.0, 41.4. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O$: 213.1022, found: 213.1026.

***tert*-Butyl(1-oxo-3-phenyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-6-yl)carbamate (27ea).** Prepared according to **general procedure J** from phenyl propiolamide **26ea** (90.0 mg, 0.273 mmol). Purified by preparative TLC (EtOAc/MeOH = 3:1). **27ea** was obtained as a pale yellow oil (71.9 mg, 0.218 mmol, 80%); **IR (neat):** 3263, 2248, 1635 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.48-7.39 (m, 5H), 5.71 (s, 1H), 5.24 (d, *J* = 7.5 Hz, 1H), 4.10-3.92 (m, 2H), 3.84-3.75 (m, 1H), 3.46 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.14 (br dd, *J* = 5.7, 5.7 Hz, 1H), 2.13-2.01 (m, 1H), 1.88-1.77 (m, 1H), 1.44 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.1, 158.4, 155.0, 130.2, 129.0, 128.3, 128.0, 100.4, 79.9, 53.6, 45.0, 37.7, 28.7, 28.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}N_3O_3$: 330.1812, found: 330.1812.

Transformation from 27aq to 28 [Scheme 27]. To a solution of **27aq** (75.0 mg, 0.386 mmol) in AcOH (3.9 mL) was added PtO_2 (87.8 mg, 0.386 mmol) and flushed with H_2. The suspension was

stirred at rt under H_2 atmosphere. After 1 week, the suspension was filtered through silica gel with MeOH and resulting solution was concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 5:1) to afford **28** as a pale yellow oil (71.6 mg, 0.364 mmol, 94%).

3-Butylhexahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (28). IR (neat): 3476, 1694 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 4.13-4.10 (br, 1H), 3.17-3.14 (br, 1H), 2.87 (br, 2H), 2.70 (dd, *J* = 16.5, 8.1 Hz, 1H), 2.29 (br t, *J* = 10.5 Hz, 1H), 2.17 (dd, *J* = 16.2, 9.0 Hz, 1H), 1.78-1.63 (m, 4H), 1.49-1.25 (m, 6H), 0.91 (t, *J* = 9.0 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.7, 62.7, 56.0, 41.4, 36.4, 33.4, 28.1, 24.0, 22.8, 22.6, 13.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{21}N_2O$: 197.1648, found: 197.1650.

Transformation from 27aa to 29a [Scheme 27]. To a solution of **27aa** (20.0 mg, 0.0933 mmol) was added 60% aqueous nitric acid (61 μL) portionwise at 0 °C. After the addition was complete the temperature of the reaction mixture was raised to 60 °C and then stirring was continued at that temperature for 1.5 h. After cooling the reaction mixture was quenched with ice water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/MeOH = 5:1) to afford **29a** as a pale yellow crystal (21.8 mg, 0.0841 mmol, 90%).

2-Nitro-3-phenyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (29a). m.p.: 279 °C; **IR (KBr):** 3453, 1691 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.58-7.51 (m, 3H), 7.42-7.39 (m, 2H), 3.90 (t, *J* = 5.7 Hz, 2H), 3.57 (t, *J* = 5.7 Hz, 2H), 2.03-1.94 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.7, 155.0, 148.3, 134.7, 128.8, 124.0, 102.3, 50.4, 40.7, 23.4, 23.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_3O_3$: 260.1030, found: 260.1026.

Transformation from 27aa to 29b [Scheme 27]. To a solution of **27aa** (30.0 mg, 0.140 mmol) in $CHCl_3$ (4.7 mL) was added NIS (34.0 mg, 0.150 mmol). The mixture was stirred at 50 °C under Ar atmosphere. After 1.5 h, the mixture was quenched by aq. 1 N NaOH. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by short silica gel column chromatography (EtOAc/MeOH) to afford **29b** as a pale yellow crystal (40.7 mg, 0.120 mmol, 85%).

2-Iodo-3-phenyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (29b). m.p.: 169-171 °C; **IR (neat):** 3432, 1651 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.53-7.50 (m, 5H), 3.90 (t, *J* = 6.0 Hz, 2H), 3.25 (t, *J* = 6.0Hz, 2H), 1.94-1.81 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.4, 156.9, 130.3, 129.2, 128.8, 128.6, 62.5, 50.4, 41.7, 23.2, 22.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_2OI$: 341.0146, found: 341.0141.

Transformation from 27aq to 29c [Scheme 27]. To a solution of **27aq** (30.0 mg, 0.154 mmol) in MeOH (0.6 mL) was added diphenyl disulfide (50.4 mg, 0.231 mmol), AgOAc (38.6 mg, 0.231 mmol) and DABCO (0.4 mg). The mixture was stirred at rt under Ar atmosphere. After 5 h, the mixture was quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/MeOH = 5:1) to afford **6** as a pale orange oil (28.3 mg, 0.0936 mmol, 61%).

3-Butyl-2-(phenylthio)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (29c). IR (neat): 3429, 2223, 1652 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.20-7.04 (m, 5H), 3.79 (t, *J* = 5.7 Hz, 2H), 3.59 (t, *J* = 6.0 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.00-1.86 (m, 4H), 1.49-1.26 (m, 4H), 0.86 (t, *J* = 7.5 Hz). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.7, 159.6, 138.0, 128.6, 126.4, 125.1, 96.6, 46.6, 41.8, 30.5, 24.5, 23.1, 22.4, 22.2, 13.6. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{23}N_2OS$: 303.1526, found: 303.1522.

Transformation from 27aq to 29d [Scheme 27]. To a solution of **27aq** (21.8 mg, 0.112 mmol) in Bu_2O (1.1 mL) was added AuCl (1.3 mg), pyridine (10.8 μL, 0.134 mmol) and TIPS-EBX (57.5 mg, 0.134 mmol). The mixture was stirred at rt under Ar atmosphere. After 11.5 h, the reaction mixture was quenched by brine. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/MeOH = 5:1) to afford **29d** as a brown oil (33.6 mg, 0.0897 mmol, 80%).

3-Butyl-2-((triisopropylsilyl)ethynyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (29d). IR (neat): 2141, 1644 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 3.69 (t, *J* = 5.4 Hz, 2 H), 3.50 (t, *J* = 5.4 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.96-1.80 (m, 4H), 1.65-1.55 (m, 2H), 1.46-1.33 (m, 2H), 1.10 (s, 21H), 0.94 (t, *J* = 7.2 Hz); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.7, 157.9, 97.2, 95.2, 94.1, 46.3, 41.4, 30.2, 25.1, 23.0, 22.5, 22.0, 18.7, 13.7, 11.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{39}N_2OSi$: 375.2826, found: 375.2820.

Transformation from 27aq to 30 [Scheme 27]. To a solution of **27aq** (90.0 mg, 0.463 mmol) in toluene (4.6 mL) was added Lawesson's reagent (187 mg, 0.463 mmol). The mixture was stirred at 100 °C. After 6 h, the mixture was concentrated. The residue was extracted with $CHCl_3$ and aq. 1 N NaOH three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 7:1) to afford **30** as a pale orange oil (68.3 mg, 0.324 mmol, 70%).

3-Butyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-1-thione (30). IR (neat): 3409, 1530 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.10 (s, 1H), 4.19 (br t, *J* = 5.4 Hz, 2H), 3.78 (br s, *J* = 5.7 Hz, 2H), 2.48 (t, *J* = 7.5 Hz, 2H), 2.05 (br t, *J*= 3.0 Hz, 4H), 1.64-1.54 (m, 2H), 1.47-1.34 (m, 2H), 0.941 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.6, 150.1, 110.9, 45.9, 44.6, 29.1, 24.5, 22.0, 21.2, 21.1, 13.5; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{19}N_2S$: 211.1264, found: 211.1260.

[Scheme 28]. A solution of alkynylhydrazide **26aa** (32 mg, 0.149 mmol) in PhCl (3.7 mL, 0.04 M) was stirred at reflux for 0.5 h. After cooled to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 10:1) to afford spiro aminimide **65** as a white solid (ca. 14.7 mg) and **26aa** (ca. 8.3 mg); (**26aa**:**65** = 4:7).

2-Oxo-4-phenyl-1,5-diazaspiro[4.4]non-3-en-5-ium-1-ide (65). IR (neat): 3392, 2211, 1585 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.58-7.52 (m, 3H), 7.41-7.38 (m, 2H), 6.49 (s, 1H), 3.71-3.65 (m, 2H), 3.51 (m, 2H), 2.69-2.59 (m, 2H), 2.18-2.12 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 175.2, 158.8, 131.0, 129.8, 129.4, 127.0, 126.4, 63.9, 23.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1179, found: 215.1179.

[Scheme 29]. A solution of aminimide **65** (26.8 mg, 0.125 mmol) in PhCl (3.1 mL, 0.04 M) was stirred at reflux for 0.5 h, After cooled to rt, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** as a white solid (21.6 mg, 81%).

[Scheme 30]. A solution of the alkynylhydrazide **26aa** (38.0 mg, 0.177 mmol) in PhCl (4.4 mL, 0.04 M) was added TBAB (5.7 mg, 0.0177 mmol). The reaction mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (11.8 mg, 31%), aminimide **65** (10.0 mg, 26%) and impure **26aa** (14.2 mg, ca. 37%).

Preparation of *N*-methylalkynylhydrazide 66 [Scheme 31]. To a solution of **26aa** (230 mg, 1.07 mmol) in MeI (3.3 mL, 53.7 mmol) was added NaH (47.2 mg, 1.18mmol) at 0 °C. After 5 min, the mixture was warmed up to rt and stirred for 10 min. Then, the mixture was quenched by water at 0 °C. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative TLC (Hexane/EtOAc = 3:1) to afford **66** as a colorless oil (33.6 mg, 0.147 mmol, 14%).

***N*-Methyl-3-phenyl-*N*-(pyrrolidin-1-yl)propiolamide (66). IR (neat):** 3490, 2214, 1639 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.54-7.51 (m, 2H), 7.39-7.31 (m, 3H), 2.98 (s, 3H), 2.95 (br, 4H), 1.90-1.85 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.8, 132.4, 129.4, 128.3, 121.5, 89.3, 83.0, 49.0(2), 22.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1335, found: 229.1334.

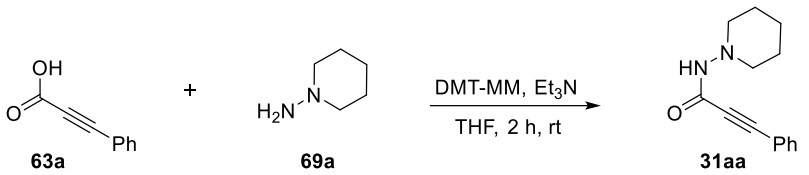
Preparation of acyclic hydrazide 67 [Scheme 32]. Prepared according to **general procedure I** from phenyl propiolic acid (400 mg, 2.73 mmol) and 1,1-diethylhydrazine trifluoroacetate (663 mg, 3.28 mmol). Purified by chromatography (SiO_2, EtOAc/MeOH = 1:1). **67a** was obtained as a white crystal (362 mg, 1.67 mmol, 61%).

***N*',*N*'-Diethyl-3-phenylpropiolohydrazide (67). m.p.:** 84 °C; **IR (neat):** 3438, 2215, 1651 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.57-7.51 (m, 2H), 7.40-7.30 (m, 3H), 7.40-7.30 and 7.14 (s, 1H), 2.86-2.77 (m, 4H), 1.18-1.13 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 158.7, 152.9, 132.23, 132.21, 129.8, 129.6, 128.24, 128.17, 120.7, 119.9, 91.0, 85.5, 82.1, 81.8, 52.6, 51.9, 12.1, 11.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O$: 217.1335, found: 217.1337.

Cyclization-migration reaction of acyclic hydrazide 67 [Scheme 32]. To a solution of the propiol amide **67** (50 mg, 0.231 mmol) in PhCl (5.8 mL, 0.4 M) were added bathocuproine (8.3 mg, 0.0231 mmol) and $CuBr_2$ (5.2 mg 0.0231 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and quenched by sat. aq. $NaHCO_3$. The mixture was extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (SiO_2, EtOAc/MeOH = 20:1) to afford pyrazolone **68a** (30.7 mg, 71%).

1-Ethyl-5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (68a). m.p.: 128 °C; **IR (KBr):** 2965, 1561 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.49-7.38 (m, 5H), 5.68 (s, 1H), 3.99 (q, *J* = 7.2 Hz, 1H), 1.40 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 161.7, 145.1, 130.5, 128.8, 128.7(2), 91.2, 43.6, 15.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2O$: 189.1022, found: 189.1024.

第6節　第 3 章第 1 節の実験



Scheme S5. Synthesis of *N*-piperidinylalkynylhydrazide from phenylpropiolic acid.

[Scheme S5]. To a solution of a propiolic acid (400 mg, 2.73 mmol) in THF (7.8 mL, 0.35 M) were added 1-aminopiperidine (402 mg, 3.28 mmol), Et_3N (1.6 mL, 11.5 mmol), and finally DMT-MM (907 mg, 3.28 mmol) at rt. Then, the mixture was stirred for 2 h. After stirried, the mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated at rt. The residue was purified by flash silica gel column chromatography (SiO_2, Hexane/EtOAc = 1:1) to afford a propiolamide **31aa** (267 mg, 1.17 mmol, 42%).

3-Phenyl-*N*-(piperidin-1-yl)propiolamide (31aa). IR (neat): 3448, 2217, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.70-7.47 (m, 2H), 7.47-7.16 (m, 3H), 7.47-7.16 and 6.94 (br s, 1H), 2.97-2.56 (m, 4H), 1.87-1.59 (m, 4H), 1.57 (2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.9, 151.0, 132.7, 132.4, 130.0, 129.9, 128.4, 128.4, 120.9, 120.0, 90.5, 85.3, 82.1, 81.7, 57.6, 56.8, 25.6, 25.1, 23.1, 23.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1335, found: 229.1334.

[Table 10, entry 1]. To a solution of alkynylhydrazide **31aa** (53 mg, 0.23 mmol) in PhCl (5.0 mL) were added $CuBr_2$ (5.2 mg, 0.023 mmol) and bathocuproine (8.3 mg, 0.023 mmol). The mixture was stirred under reflux for 0.5 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (22.4 mg, 42%).

3-Phenyl-6,7,8,9-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2]diazepin-1-one (32aa). m.p.: 112-113 °C; **IR (neat):** 3418, 1624 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.54-7.27 (m, 5H), 5.50 (s, 1H), 4.10 (t, *J* = 4.2 Hz, 2H), 3.79 (t, *J* = 4.8 Hz, 2H), 1.59-1.94 (6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.6, 151.1, 129.5, 129.3, 128.7, 128.3, 95.1, 49.2, 42.9, 29.3, 28.6, 28.3. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1336, found: 229.1330.

[Table 10, entry 2]. To a solution of the alkynylhydrazide **31aa** (34 mg, 0.15 mmol) in PhCl (5.0 mL) were added $AuBr_3$ (6.4 mg, 0.015 mmol) and bathocuproine (5.4 mg, 0.015 mmol). The mixture was stirred under reflux for 1 h. The reaction mixture was evaporated under reduced pressure and the

residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (18 mg, 53%).

[Table 10, entry 3]. To a solution of the alkynylhydrazide **31aa** (48 mg, 0.21 mmol) in PhCl (5.0 mL) were added $AuBr_3$ (9.2 mg, 0.021 mmol). The mixture was stirred under reflux for 1 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (18 mg, 52%).

[Table 10, entry 7]. To a solution of the alkynylhydrazide **31aa** (125 mg, 0.547 mmol) in PhCl (14 mL) were added AuI (17.7 mg, 0.0547 mmol). The mixture was stirred under reflux for 12 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (116 mg, 92%).

[Table 10, entry 8]. To a solution of the alkynylhydrazide **31aa** (30.0 mg, 0.131 mmol) in PhCl (3.3 mL) were added CoI_2 (4.1 mg, 0.0131 mmol). The mixture was stirred under reflux for 12 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (26.0 mg, 87%).

[Table 10, entry 11]. To a solution of the alkynylhydrazide **31aa** (30.0 mg, 0.131 mmol) in 1-pentanol (3.3 mL) were added AuI (4.3 mg, 0.0131 mmol). The mixture was stirred under reflux for 12 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (26.8 mg, 89%).

[Table 10, entry 12]. To a solution of the alkynylhydrazide **31aa** (30.0 mg, 0.131 mmol) in 1-pentanol (3.3 mL) were added AuI (4.3 mg, 0.0131 mmol). The mixture was stirred under reflux for 12 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (1.1 mg, 4%) and aminimide **70** (26.4 mg, 88%).

2-Oxo-4-phenyl-1,5-diazaspiro[4.5]dec-3-en-5-ium-1-ide (70). m.p.: 207-208 °C; **IR (neat):** 3400, 2223, 1587 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.68-7.46 (m, 3H), 7.46-7.31 (m, 2H), 6.38 (s, 1H), 3.55-3.32 (m, 2H), 3.20-2.97 (m, 2H), 2.78-2.53 (m, 2H), 2.04-1.62 (m, 3H), 1.52-1.05 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 175.3, 163.6, 130.9, 130.1, 129.2, 126.7, 125.7, 61.8, 22.0, 21.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1335, found: 229.1334.

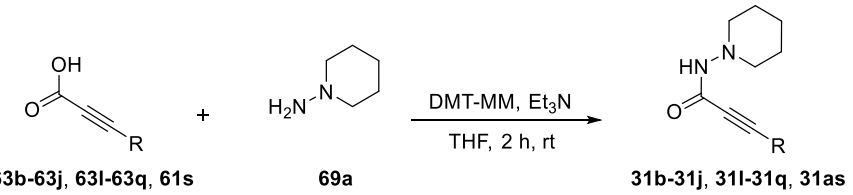
[Table 10, entry 13]. To a solution of the alkynylhydrazide **31aa** (30.0 mg, 0.131 mmol) in 1-pentanol (3.3 mL) were added AuI (4.3 mg, 0.0131 mmol). The mixture was stirred under reflux for

12 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford aminimide **70** (15.0 mg, 50%).

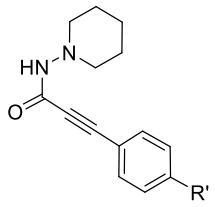
[Table 10, entry 14]. To a solution of the alkynylhydrazide **31aa** (91.6 mg, 0.401 mmol) in PhCl (10.0 mL) were added AuI (6.5 mg, 0.020 mmol). The mixture was stirred under reflux for 20 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (69.8 mg, 76%).

[Table 10, entry 15]. To a solution of alkynylhydrazide **31aa** (50.0 mg, 0.219 mmol) in PhCl (5.5 mL, 0.04 M) were stirred under reflux for 12 h. Then, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (10.7 mg, 15%), spiro aminimide **70** (36.1 mg, 72%) and **31aa** (10.7 mg, 15%).

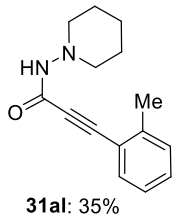
Table S6. Preparation of alkynylhydrazides **31ab-31aj**, **31al-31aq**, **31as**.



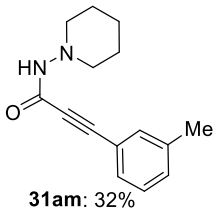
63b-63j, **63l-63q**, **61s**　　**69a**　　**31b-31j**, **31l-31q**, **31as**



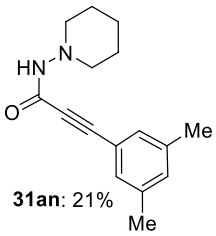
31ab: (R' = Me), 31%
31ac: (R' = OMe), 43%
31ad: (R' = Ph), 10%
31ae: (R' = F), 37%
31af: (R' = Br), 20%
31ag: (R' = CO_2Me), 25%
31ah: (R' = CN), 24%
31ai: (R' = NO_2), 12%
31aj: (R' = CF_3), 15%



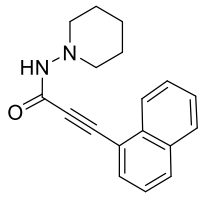
31al: 35%



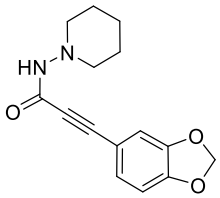
31am: 32%



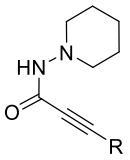
31an: 21%



31ao: 47%



32ap: 46%



31aq: (R = *n*Bu), 31%
31as: (R = *t*Bu), 20%

General procedure K: preparation of alkynylhydrazides 31ab-31ak, **31al-31aq**, **31as [Table S6].** To a solution of a propiolic acid (1.0 equiv.) in THF (*c* = 0.35 M) were added 1-aminopiperidine (1.2 equiv.), Et_3N (4.2 equiv.), and finally DMT-MM (1.2 equiv.) at rt. Then, the mixture was stirred for 2 h. After stirred, the mixture was quenched with water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated at rt. The residue was purified by flash silica gel column chromatography (Hexane/EtOAc) to afford a propiolamide **31ab-31ak**, **31al-31aq**, **31as**.

***N*-(Piperidin-1-yl)-3-(*p*-tolyl)propiolamide (31ab).** Prepared according to **general procedure K** from 3-(*p*-tolyl)propiolic acid (300 mg, 1.87 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ab** was obtained as a colorless oil (157 mg, 0.649 mmol, 31%). **IR (neat):** 3453, 2214, 1643 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.75 and 7.27-7.01 (br s, 1H), 7.59-7.34 (m,

2H), 7.27-7.01 (m, 2H), 2.98-2.63 (m, 4H), 2.37 and 2.34 (s, 3H), 1.85-1.56 (m, 4H), 1.56-1.27 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.1, 151.2, 140.4(2), 132.5, 132.3, 129.1(2), 117.7, 116.9, 91.0, 85.6, 81.7, 81.2, 57.4, 56.7, 25.5, 25.0, 23.0, 22.9, 21.5, 21.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}N_2O$: 243.1492, found: 243.1489.

3-(4-Methoxyphenyl)-*N*-(piperidin-1-yl)propiolamide (31ac). Prepared according to **general procedure K** from 3-(4-methoxyphenyl)propiolic acid (300 mg, 1.70 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ac** was obtained as a white solid (187 mg, 0.722 mmol, 43%). **m.p.:** 121 °C. (decomposed); **IR (neat):** 3440, 2212, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.60-7.37 (m, 2H), 7.60-7.37 and 6.99 (br s, 1H), 6.94-6.67 (m, 2H), 3.82 (s, 3H), 3.02-2.63 (m, 4H), 1.85-1.58 (m, 4H), 1.57-1.31 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 160.90, 160.86, 157.2, 151.3, 134.5, 134.1, 114.1(2), 112.7, 111.8, 91.2, 85.8, 81.3, 81.0, 57.5, 56.8, 55.2(2), 25.6, 25.1, 23.0, 22.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2$: 259.1441, found: 259.1439.

3-([1,1'-Biphenyl]-4-yl)-*N*-(piperidin-1-yl)propiolamide (31ad). prepared according to **general procedure K** from 3-([1,1'-biphenyl]-4-yl)propiolic acid (400 mg, 1.79 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ad** was obtained as a pale orange solid (52.5 mg, 0.278 mmol, 10%). **m.p.:** 199 °C; **IR (neat):** 3436, 2216, 1646 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.75-7.26 (m, 9H), 6.96 and 6.74 (br s, 1H), 3.08-2.58 (m, 4H), 1.84-1.63 (m, 4H), 1.58-1.30 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.5, 150.8, 142.6, 142.5, 139.7, 139.6, 133.0, 132.7, 128.7(2), 127.81, 127.76, 127.1, 126.9, 126.9, 126.8, 119.5, 118.6, 90.5, 85.4, 82.6, 82.3, 57.9, 57.1, 25.9, 25.4, 23.3, 23.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O$: 305.1648, found: 305.1646.

3-(4-Fluorophenyl)-*N*-(piperidin-1-yl)propiolamide (31ae). Prepared according to **general procedure K** from 3-(4-fluorophenyl)propiolic acid (300 mg, 1.83 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ae** was obtained as a white solid (167 mg, 0.68 mmol, 37%). **m.p.:** 143-144 °C; **IR (neat):** 3453, 2220, 1642 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.05 and 7.67-7.43 (br s, 1H), 7.67-7.43 (m, 2H), 7.21-6.90 (m, 2H), 3.01-2.60 (m, 4H), 1.86-1.56 (m, 4H), 1.56-1.30 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.9 (d, J = 5.2 Hz), 161.6 (d, J = 5.2 Hz), 156.9, 150.9, 134.7 (d, J = 9.2 Hz), 134.4 (d, J = 8.6 Hz), 116.8 (d, J = 2.9 Hz), 116.1 (d, J = 3.4 Hz), 115.8, 115.5, 89.4, 84.1, 82.0, 81.5, 57.3, 56.5, 25.5, 25.0, 22.9, 22.8; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}N_2OF$: 247.1241, found: 247.1239.

3-(4-Bromophenyl)-*N*-(piperidin-1-yl)propiolamide (31af). Prepared according to **general procedure K** from 3-(4-bromophenyl)propiolic acid (300 mg, 1.33 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31af** was obtained as a white solid (80.0 mg, 0.260 mmol, 20%). **m.p.:** 206-207 °C; **IR (neat):** 3453, 2223, 1640, 732 cm^{-1}; **^{1}H NMR (300 MHz,**

$CDCl_3$): 7.62-7.30 (m, 4H), 7.09 and 6.75 (br s, 1H), 2.97-2.50 (m, 4H), 1.87-1.58 (m, 4H), 1.57-1.33 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$)** δ 156.5, 150.9, 134.0, 133.8, 131.9, 131.8, 124.8, 124.6, 119.9, 119.0, 89.3, 84.3, 83.1, 82.6, 57.8, 56.9, 25.6, 25.1, 23.1, 23.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}N_2OBr$: 307.0441, found: 307.0437.

Methyl 4-(3-oxo-3-(piperidin-1-ylamino)prop-1-yn-1-yl)benzoate (31ag). Prepared according to **general procedure K** from 3-(4-(methoxycarbonyl)phenyl)propiolic acid (300 mg, 1.47 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ag** was obtained as a white solid (106 mg, 0.370 mmol, 25%). **m.p.:** 198-199 °C; **IR (neat):** 2219, 1721, 1652 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.23-7.87 (m, 2H), 7.76-7.41 (m, 2H), 6.74 and 6.68 (br s, 1H), 3.94 and 3.93 (s, 3H), 2.97-2.58 (m, 4H), 1.81-1.67 (m, 4H), 1.55-1.31 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.9, 165.8, 155.9, 150.3, 132.3, 132.2, 131.1, 130.9, 129.4, 129.3, 125.3, 124.4, 89.1(2), 84.1, 83.9, 58.0, 57.1, 52.5(2), 25.8, 25.4, 23.3, 23.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_3$: 287.1390, found: 287.1390.

3-(4-Cyanophenyl)-*N*-(piperidin-1-yl)propiolamide (31ah). Prepared according to **general procedure K** from 3-(4-cyanophenyl)propiolic acid (300 mg, 1.75 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ah** was obtained as a white solid (105 mg, 0.414 mmol, 24%). **m.p.:** 218 °C; **IR (neat):** 3439, 2227, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.81-7.56 (m, 4H), 7.47 and 6.92 (br s, 1H), 3.14-2.51 (m, 4H), 1.88-1.58 (m, 4H), 1.59-1.23 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.1, 150.2, 132.9, 132.8, 132.1, 132.1, 125.7, 124.9, 118.0, 117.8, 113.4, 113.2, 87.8, 85.3, 85.0, 82.8, 57.7, 56.8, 25.6, 25.1, 23.0, 22.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}N_3O$: 254.1288, found: 254.1286.

3-(4-Nitrophenyl)-*N*-(piperidin-1-yl)propiolamide (31ai). Prepared according to **general procedure K** from 3-(4-nitrophenyl)propiolic acid (300 mg, 1.57 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ai** was obtained as a white solid (48.8 mg, 12%). **m.p.:** 211-214 °C; **IR (neat):** 2222, 1652, 1516 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.41-8.04 (m, 2H), 7.86-7.51 (m, 2H), 7.25 and 6.80 (br s, 1H), 3.07-2.45(m, 4H), 1.88-1.58 (m, 4H), 1.55-1.29 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** 155.9, 150.1, 148.2, 148.0, 133.3, 133.2, 127.7, 126.7, 123.7, 123.6, 87.4, 85.8, 85.7, 82.5, 57.8, 56.9, 25.6, 25.1, 23.0, 22.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}N_3O_3$: 274.1186, found: 274.1183.

***N*-(Piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propiolamide (31aj).** Prepared according to **general procedure K** from 3-(4-(trifluoromethyl)phenyl)propiolic acid (300 mg, 1.40 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31aj** was obtained as a pale orange solid (61.3 mg, 0.207 mmol, 15%). **m.p.:** 218 °C; **IR (neat):** 2224, 1646, 1324 cm^{-1}; **^{1}H NMR (300 MHz,**

$CDCl_3$): δ 7.82-7.48 (m, 4H), 7.28 and 6.83 (br, 1H), 3.03-2.58 (m, 4H), 1.89-1.59 (m, 4H), 1.56-1.29 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 156.2, 150.5, 132.8, 132.6, 131.4 (q, *J* = 85.7 Hz), 125.4 (q, *J* = 10.6 Hz), 125.0, 124.9, 124.8, 123.9, 122.3, 122.2, 88.4(2), 83.8, 83.5, 57.8, 57.0, 25.6, 25.1, 23.1, 22.9. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}N_2OF_3$: 297.1209, found: 297.1205.

***N*-(Piperidin-1-yl)-3-(*o*-tolyl)propiolamide (31al).** Prepared according to **general procedure K** from 3-(*o*-tolyl)propiolic acid acid (300 mg, 1.87 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31al** was obtained as a pale orange solid (157 mg, 1.21 mmol, 35%). **m.p.:** 112-113 °C; **IR (neat):** 3184, 2212, 1651 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.75-7.42 (m, 1H), 7.42-7.09 (m, 3H), 7.04 and 6.68 (br s, 1H), 2.98-2.66 (m, 4H), 2.56 and 2.47 (s, 3H), 1.90-1.54 (m, 4H), 1.54-1.30 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 156.9, 151.2, 141.9, 141.5, 133.4, 132.9, 130.1(2), 129.6, 129.5, 125.7(2), 120.7, 119.8, 89.4, 85.7, 85.5, 84.4, 57.9, 57.0, 25.6, 25.2, 23.1, 23.0, 20.7, 20.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1492.

***N*-(Piperidin-1-yl)-3-(*m*-tolyl)propiolamide (31am).** Prepared according to **general procedure K** from 3-(*m*-tolyl)propiolic acid acid (300 mg, 1.87 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31am** was obtained as a white solid (144 mg, 0.593 mmol, 32%). **m.p.:** 126 °C; **IR (neat):** 2942, 2213, 1651 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46-7.19 (m, 4H), 7.16 and 6.77 (br s, 1H), 2.96-2.65 (m, 4H), 2.35 and 2.33 (s, 3H), 1.83-1.64 (m, 4H), 1.55-1.30 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 156.9, 151.1, 138.2, 138.1, 133.2, 132.9, 131.0, 130.9, 129.8, 129.5, 128.34, 128.29, 120.7, 119.8, 90.8, 85.6, 81.7, 81.4, 57.7, 56.9, 25.6, 25.1, 23.1, 23.0, 21.2, 21.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1492.

3-(3,5-Dimethylphenyl)-*N*-(piperidin-1-yl)propiolamide (31an). prepared according to **general procedure K** from 3-(3,5-dimethylphenyl)propiolic acid (300 mg, 1.72 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31an** was obtained as a white solid (92.0 mg, 0.359 mmol, 21%). **m.p.:** 124 °C; **IR (neat):** 2218, 1639 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.45 and 6.97 (br s, 1H), 7.25-7.10 (m, 2H), 7.08-7.00 (m, 1H), 3.08-2.57 (m, 4H), 2.31 and 2.28 (s, 6H), 1.84-1.55 (m, 4H), 1.55-1.19 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.0, 151.2, 138.0, 137.9, 131.9, 131.8, 130.3, 130.0, 120.4, 119.6, 91.1, 85.8, 81.5, 81.1, 57.6, 56.8, 25.6, 25.1, 23.0, 22.9, 21.0, 20.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}N_2O$: 257.1648, found: 257.1646.

3-(Naphthalen-1-yl)-*N*-(piperidin-1-yl)propiolamide (31ao). Prepared according to **general procedure K** from 3-(naphthalen-1-yl)propiolic acid (300 mg, 1.53 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc =1:1). **31ao** was obtained as a white solid (267 mg, 0.958 mmol, 47%). **m.p.:** 147-148 °C; **IR (neat):** 2943, 2211, 1657 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.66 and 8.33 (d, *J* = 8.2 Hz, 1H), 8.19-7.30 (m, 7H), 3.11-2.62 (m, 4H), 1.90-1.65 (m, 4H), 1.62-

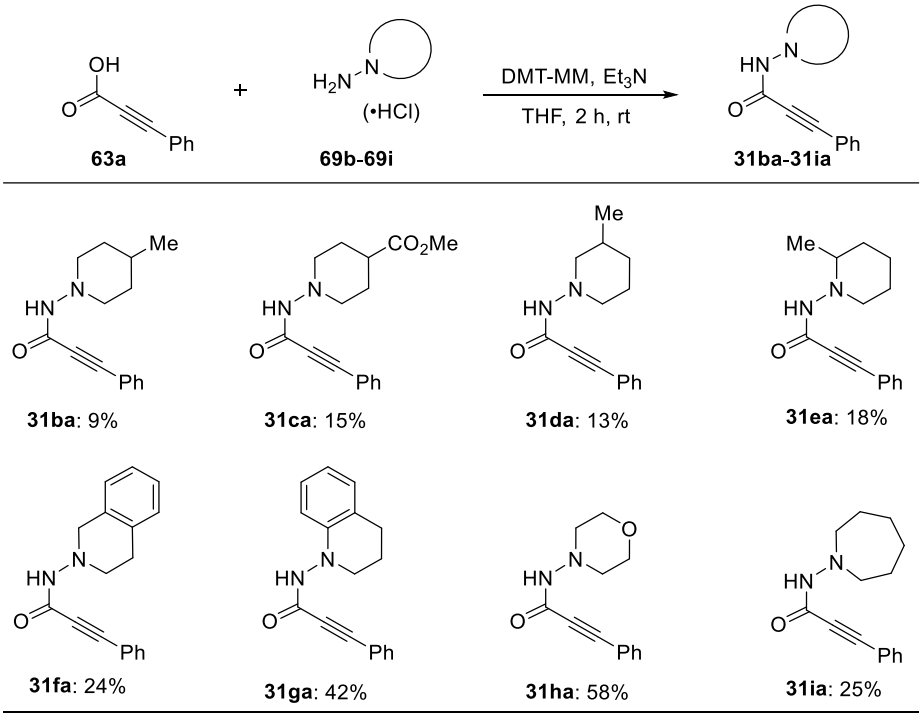
1.31 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.1, 151.1, 133.9, 133.2, 132.9, 132.8, 132.5, 132.1, 130.7, 130.5, 128.2(2), 127.2, 127.0, 126.63, 126.58, 126.3, 125.8, 125.1, 124.9, 118.4, 117.6, 88.5, 86.8, 86.6, 83.5, 57.7, 56.7, 25.7, 25.1, 23.0, 22.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2O$: 279.1492, found: 279.1488.

3-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(piperidin-1-yl)propiolamide (31ap). Prepared according to **general procedure K** from 3-(benzo[*d*][1,3]dioxol-5-yl)propiolic acid (300 mg, 1.58 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ap** was obtained as a pale yellow solid (198 mg, 0.725 mmol, 46%). **m.p.:** 240-243 °C; **IR (neat):** 3448, 2859, 2212, 1646 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.67 and 7.20 (br s, 1H), 7.18-6.61 (m, 3H), 6.01 and 5.99 (s, 2H), 3.02-2.64 (m, 4H), 1.89-1.58 (m, 4H), 1.55-1.30 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.0, 151.1, 149.3(2), 147.4(2), 128.2, 127.8, 113.8, 113.0, 112.3(2), 111.9(2), 108.5, 101.5, 90.8, 85.5, 80.8, 80.5, 57.5, 56.7, 25.6, 25.1, 23.0, 22.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1234, found: 273.1230.

***N*-(Piperidin-1-yl)hept-2-ynamide (31aq).** Prepared according to **general procedure K** from hept-2-ynoic acid (300 mg, 2.38 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31aq** was obtained as a white solid (152 mg, 0.731 mmol, 31%). **m.p.:** 94 °C; **IR (neat):** 3457, 2231, 1647 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.00 and 7.26 (br s, 1H), 3.04-2.54 (m, 4H), 2.39 and 2.29 (t, *J* = 7.1 Hz, 2H), 1.97-1.26 (m, 10H), 1.12-0.78 (m, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.8, 150.9, 93.4, 87.6, 74.2, 73.7, 57.1, 56.2, 29.4, 29.3, 25.2, 24.8, 22.8, 22.6, 21.5, 21.3, 18.3, 17.9, 13.1(2); **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{21}N_2O$: 209.1648, found: 209.1648.

4,4-Dimethyl-*N*-(piperidin-1-yl)pent-2-ynamide (31as). Prepared according to **general procedure K** from 4,4-dimethylpent-2-ynoic acid (300 mg, 2.38 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31as** was obtained as a white solid (102 mg, 0.488 mmol, 20%). **m.p.:** 114-117 °C; **IR (neat):** 3466, 2226, 1652 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.38 and 6.77 (br s, 1H), 2.95-2.53 (m, 4H), 1.88-1.55 (m, 4H), 1.55-1.35 (m, 2H), 1.30 and 1.27 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 157.2, 151.2, 100.6, 95.0, 72.9, 72.3, 57.2, 56.7, 30.0(2), 27.6, 27.2, 25.6, 25.0, 23.0, 22.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{21}N_2O$: 209.1648, found: 209.1647.

Table S7. Preparation of alkynylhydrazides **31ba-31ia**.



General procedure L: preparation of alkynylhydrazides 31ba-31ia [Table S7]. To a solution of phenyl propiolic acid (1.0 equiv.) in THF (c = 0.35 M) were added hydrazine (1.2 equiv.), TEA (4.2 equiv.) and finally DMT-MM (1.2 equiv.) at rt. Then, the mixture was stirred for 2 h. After stirred, the mixture was quenched by water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (Hexane/EtOAc) to afford propiol amides **31ba-31ia**.

***N*-(4-Methylpiperidin-1-yl)-3-phenylpropiolamide (31ba).** Prepared according to **general procedure L** from phenyl propiolic acid (400 mg, 2.73 mmol) and 4-methyl-1-piperidinamine (375 mg, 3.28 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 2:1). **31ba** was obtained as a white solid (58 mg, 0.239 mmol, 9%). **m.p.:** 112-115 °C; **IR (neat):** 3443, 2222, 1647 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.69-7.47 (m, 2H), 7.48-7.31 (m, 3H), 6.80 and 6.64 (br s, 1H), 3.32-2.99 (m, 2H), 2.64-2.26 (m, 2H), 1.81-1.60 (m, 2H), 1.60-1.30 (m, 3H), 0.945 (d, J = 6.9 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.7, 151.1, 132.8, 132.5, 130.1, 130.0, 128.5, 128.4, 120.9, 120.0, 90.6, 85.4, 82.0, 81.7, 57.1, 56.3, 33.8, 33.3, 29.7, 29.6, 21.4(2); **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1492.

Methyl 1-(3-phenylpropiolamido)piperidine-4-carboxylate (31ca). Prepared according to **general procedure L** from phenyl propiolic acid (400 mg, 2.73 mmol) and methyl 1-amino-4-

piperidinecarboxylate (518 mg, 3.27 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ca** was obtained as a white solid (115 mg, 0.400 mmol, 15%). **m.p.:** 138 °C; **IR (neat):** 2221, 1714, 1644 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.21 and 7.81 (br s, 1H), 7.70-7.18 (m, 5H), 3.70 and 3.67 (s, 3H), 3.35-2.97 (m, 2H), 2.90-2.49 (m, 2H), 2.44-2.19 (m, 1H), 2.17-1.76 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 174.6, 174.5, 156.9, 151.1, 132.4, 132.1, 129.9(2), 128.2(2), 120.4, 119.8, 90.7, 85.3, 81.9, 81.3, 55.5, 54.3, 51.5, 51.5, 39.3, 39.3, 27.8, 27.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_3$: 287.1390, found: 287.1390.

***N*-(3-Methylpiperidin-1-yl)-3-phenylpropiolamide (31da).** Prepared according to **general procedure L** from phenyl propiolic acid (400 mg, 2.73 mmol) and 3-methyl-1-piperidinamine (375 mg, 3.28 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31da** was obtained as a white solid (89 mg, 0.326 mmol, 13%). **m.p.:** 102-103 °C; **IR (neat):** 3448, 2217, 1648 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.75-7.47 (m, 2H), 7.47-7.28 (m, 3H), 7.07 and 6.78 (br s, 1H), 3.25-3.01 (m, 2H), 2.52-2.29 (m, 1H), 2.26-2.01 (m, 1H), 2.01-1.47 (m, 5H), 0.94 and 0.89 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.8, 151.1, 132.7, 132.5, 130.1, 130.0, 128.5, 128.4, 120.9, 120.1, 90.5, 85.4, 82.1, 81.7, 64.6, 64.0, 57.2, 56.2, 31.8, 31.4, 31.0, 30.7, 24.64, 24.56 19.3, 19.0. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1492.

***N*-(2-Methylpiperidin-1-yl)-3-phenylpropiolamide (31ea).** Prepared according to **general procedure L** from phenyl propiolic acid (400 mg, 2.73 mmol) and 2-methyl-1-piperidinamine (375 mg, 3.28 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ea** was obtained as a colorless oil (120.7 mg, 0.498 mmol, 18%). **m.p.:** 103 °C; **IR (neat):** 3448, 2216, 1648 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.65-7.48 (m, 2H), 7.48-7.28 (m, 3H), 6.83-6.58 and 6.58-6.43 (br m, 1H), 3.34-3.06 (m, 1H), 2.65-2.27 (m, 2H), 1.89-1.64 (m, 4H), 1.58-1.20 (m, 2H), 1.17 (d, *J* = 5.9 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 157.6, 152.0, 132.6, 132.5, 130.1, 129.9, 128.5, 128.4, 121.0, 120.1, 90.9, 85.5, 82.1, 82.0, 60.8, 60.7, 58.3, 57.4, 33.9, 33.3, 25.9, 25.3, 23.8, 19.7. two carbon peak could not be observed probably due to overlap; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1492.

***N*-(3,4-Dihydroquinolin-1(2*H*)-yl)-3-phenylpropiolamide (31fa).** Prepared according to **general procedure L** from phenyl propiolic acid (400 mg, 2.73 mmol) and 3,4-dihydro-1(2*H*)-quinolinamine. Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31fa** was obtained as a white solid (267 mg, 1.17 mmol, 42%). **m.p.:** 129 °C; **IR (neat):** 3207, 2214, 1652 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.72-7.26 (m, 6H), 7.18-6.95 (m, 2H), 6.94-6.72 (m, 2H), 3.74-3.15 (m, 2H), 2.96-2.57 (m, 2H), 2.44-1.92 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 158.9, 152.6, 145.2, 144.7, 132.8, 132.6, 130.33, 130.25, 129.2(2), 128.5, 128.4, 127.2, 127.0, 123.4, 123.3, 120.2, 120.1, 119.8, 119.7, 113.0, 112.7, 90.5, 86.8, 81.5, 81.1, 53.2, 51.5, 26.9, 26.8, 22.4, 22.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for

$C_{18}H_{17}N_2O$: 277.1335, found: 277.1335.

***N*-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-3-phenylpropiolamide (31ga).** Prepared according to **general procedure L** from phenyl propiolic acid (500 mg, 3.42 mmol) and 3,4-dihydro-2(1*H*)-isoquinolinamine (609 mg, 4.11 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc =1:1). **31ga** was obtained as a yellow solid (231 mg, 0.834 mmol, 24%). **m.p.:** 124 °C. **IR (neat):** 3182, 2218, 1640 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.61-6.97 (m, 10H), 4.13 and 4.06 (s, 2H), 3.34-3.11 (m, 2H), 3.12-2.99 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.9, 151.6, 132.9, 132.8, 132.74, 132.69, 132.5, 130.2, 130.0, 129.8, 129.4, 128.7, 128.6, 128.5, 128.4, 126.8, 126.8, 126.7, 126.1, 120.6, 119.91, 119.85, 91.2, 85.8, 81.9, 81.5, 58.1, 57.0, 54.2, 52.6, 28.4, 27.2. **HRMS (ESI):** *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2O$: 277.1335, found: 277.1336.

***N*-Morpholino-3-phenylpropiolamide (31ha).** Prepared according to **general procedure L** from phenyl propiolic acid (300 mg, 2.05 mmol) and 4-morpholinamine (251 mg, 2.46 mmol). Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ha** was obtained as a white solid (274 mg, 1.19 mmol, 58%). **m.p.:** 150-151 °C; **IR (neat):** 3193, 2220, 1636 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.70 and 7.63-7.21 (br s, 1H), 7.63-7.21 (m, 5H), 3.92-3.67 (m, 4H), 3.01-2.73 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 156.9, 151.2, 132.6, 132.4, 130.1(2), 128.4(2), 120.5, 119.8, 90.9, 85.8, 81.8, 81.4, 66.5, 66.2, 56.4, 55.6; **HRMS (ESI):** *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_2$: 231.1128, found: 231.1128.

3-Phenyl-*N*-(apzepan-1-yl)propiolamide (31ia). Prepared according to **general procedure L** from phenyl propiolic acid (600 mg, 4.10 mmol) and 1-aminohomopiperidine. Purified by chromatography (SiO_2, Hexane/EtOAc = 1:1). **31ia** was obtained as a colorless oil (248 mg, 1.02 mmol, 25%); **IR (neat):** 3187, 2215, 1648 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.63-7.48 (m, 2H), 7.48-7.22 (m, 3H), 7.48-7.22 and 7.18 (br s, 1H), 3.22-2.87 (m, 4H), 1.88-1.57 (m, 8H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 157.4, 151.6, 132.8, 132.6, 130.2, 130.1, 128.60, 128.58, 121.1, 120.2, 90.7, 85.4, 82.24, 82.18, 59.1, 58.1, 27.1, 27.0, 26.9, 26.0; **HRMS (ESI):** *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1490.

General procedure M: synthesis of pyrazolopyridazines 32ab-32aj, 32al-32aq, 32as [Table 11]. To a solution of the propiol amide **31ab-31aj**, **31al-31aq**, **32as** (1.0 equiv.) in PhCl (*c* = 0.04 M) was added AuI. The mixture was stirred under reflux until completion (from 12 h to 72 h). The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH) to afford pyrazolopyridazine **32ab-32aj**, **32al-32aq**, **32as.**

3-(*p*-Tolyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32ab). Prepared according to

general procedure M from phenyl propiolamide **31ab** (95.0 mg, 0.392 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ab** was obtained as a white solid (82.3 mg, 0.341 mmol, 87%). **m.p.:** 126-127 °C; **IR (neat):** 3411, 2935, 1611 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.49-7.12 (m, 4H), 5.46 (s, 1H), 4.09 (t, *J* = 3.9 Hz, 2H), 3.79 (t, *J* = 4.8 Hz, 2H), 2.40 (s, 3H), 2.01-1.43 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.6, 151.3, 139.7, 129.3, 128.1, 126.4, 94.7, 49.2, 42.9, 29.3, 28.6, 28.3, 21.5; **HRMS (ESI):** *m/z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 259.1489.

3-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32ac). Prepared according to **general procedure M** from phenyl propiolamide **1ac** (42.0 mg, 0.163 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ac** was obtained as a white solid (37.2 mg, 0.144 mmol, 89%). **m.p.:** 117 °C; **IR (neat):** 3401, 2939, 1611 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.32 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.45 (s, 1H), 4.09 (t, *J* = 4.2 Hz, 2H), 3.86 (s, 3H), 3.80 (t, *J* = 4.2 Hz, 2H), 1.95-1.53 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.0, 160.6, 151.4, 129.7, 121.7, 114.2, 94.5, 55.3, 49.1, 42.6, 29.0, 28.4, 28.0; **HRMS (ESI):** *m/z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2$: 259.1441, found: 259.1438.

3-([1,1'-Biphenyl]-4-yl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32ad). Prepared according to **general procedure M** from phenyl propiolamide **31ad** (26.5 mg, 0.087 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ad** was obtained as a white solid (22.4 mg, 0.0736 mmol, 85%). **m.p.:** 165 °C; **IR (neat):** 3392, 2941, 1598 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.75-7.55 (m, 4H), 7.55-7.30 (m, 5H), 5.57 (s, 1H), 4.12 (t, *J* = 4.2 Hz, 2H), 3.85 (t, *J* = 4.2 Hz, 2H), 1.97-1.60 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.0, 151.4, 142.7, 139.9, 129.0, 128.9, 128.3, 127.9, 127.6, 127.1, 95.5, 49.4, 42.9, 29.2, 28.5, 28.1; **HRMS (ESI):** *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O$: 305.1648, found: 305.1640.

3-(4-Fluorophenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32ae). Prepared according to **general procedure M** from phenyl propiolamide **31ae** (36.7 mg, 0.149 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ae** was obtained as a white solid (32.5 mg, 0.132 mmol, 89%). **m.p.:** 160 °C; **IR (neat):** 3391, 2944, 1617 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.46-7.30 (m, 2H), 7.25-7.01 (m, 2H), 5.47 (s, 1H), 4.09 (t, *J* = 3.9 Hz, 2H), 3.77 (t, *J* = 4.8 Hz, 2H), 1.97-1.55 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 164.8 162.0 (d, *J* = 78.6 Hz), 150.2, 130.1 (d, *J* = 8.4 Hz), 125.4 (d, *J* = 3.4 Hz), 115.9 (d, *J* = 21.8 Hz), 95.3, 49.2, 42.9, 29.2, 28.5, 28.2; **HRMS (ESI):** *m/z* $[M + H]^+$ calcd for $C_{14}H_{16}N_2OF$: 247.11241, found: 247.1239.

(Bromophenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32af). Prepared according to **general procedure M** from phenyl propiolamide **31af** (40.0 mg, 0.130 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32af** was obtained as white solid (32.9 mg, 0.107 mmol,

82%). **m.p.:** 171-174 °C; **IR (neat):** 3410, 2941, 1623 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 5.51 (s, 1H), 4.10 (t, *J* = 3.9 Hz, 2H), 3.78 (t, *J* = 4.5 Hz, 2H), 2.06-1.55 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.8, 150.5, 132.1, 129.9, 128.3, 128.3, 124.1, 95.6, 49.4, 49.2, 42.7, 29.0, 28.3, 28.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}N_2OBr$: 307,0441 found: 307.0440.

Methyl 4-(1-oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-3-yl)benzoate (32ag). Prepared according to **general procedure M** from phenyl propiolamide **31ag** (47.5 mg, 0.166 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ag** was obtained as a white solid (43.5 mg, 0.152 mmol, 92%). **m.p.:** 149 °C; **IR (neat):** 3419, 2948, 1717, 1607 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.11 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 5.56 (s, 1H), 4.11 (t, *J* = 3.9 Hz, 2H), 4.02-3.87 (t, *J* = 3.9 Hz, 2H), 3.79 (t, *J* = 4.8 Hz, 2H), 2.04-1.48 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.8, 162.3, 150.0, 133.4, 131.0, 129.8, 128.2, 96.0, 52.4, 49.3, 42.9, 29.1, 28.5, 28.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_3$: 287.1390, found: 287.1387.

4-(1-Oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-3-yl)benzonitrile (32ah). Prepared according to **general procedure M** from phenyl propiolamide **31ah** (51.5 mg, 0.203 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ah** was obtained as a pale yellow solid (43.7 mg, 0.173 mmol, 85%). **m.p.:** 200-201 °C; **IR (neat):** 3340, 2943, 1626 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 5.59 (s, 1H), 4.12 (t, *J* = 3.9 Hz, 2H), 3.80 (t, *J* = 4.2 Hz, 2H), 2.01-1.61 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.4, 149.4, 133.7, 132.6, 129.0, 117.9, 113.3, 96.7, 49.3, 42.7, 28.8, 28.2, 27.8; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}N_3O$: 254.1288, found: 254.1288.

3-(4-Nitrophenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32ai). Prepared according to **general procedure M** from phenyl propiolamide **31ai** (33.7 mg, 0.130 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ai** was obtained as a yellow solid (43.1 mg, 0.166 mmol, 84%). **m.p.:** 196 °C; **IR (neat):** 3409, 2938, 1627 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.30 (d, *J* = 16.0 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 5.62 (s, 1H), 4.12 (t, *J* = 4.2 Hz, 2H), 3.80 (t, *J* = 4.2 Hz, 2H), 2.00-1.58 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.4, 149.1, 148.3, 135.5, 129.3, 124.1, 97.1, 49.4, 42.8, 28.9, 28.2, 27.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}N_3O_3$: 274.1186, found: 274.1184.

3-(4-(Trifluoromethyl)phenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (32aj). Prepared according to **general procedure M** from phenyl propiolamide **31aj** (48.5 mg, 0.164 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32aj** was obtained as a white solid (37.6 mg, 0.127 mmol, 78%). **m.p.:** 163 °C; **IR (neat):** 3410, 2941, 1619 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):**

δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 5.56 (s, 1H), 4.11 (t, *J* = 4.2 Hz, 2H), 3.80 (t, *J* = 4.5 Hz, 2H), 1.98-1.56 (m, 6H); **^{13}C NMR (75 MHz, CDCl$_3$):** δ 162.2, 149.5, 132.7, 131.4 (q, *J* = 32.6 Hz), 128.6, 125.6 (q, *J* = 3.98 Hz), 123.4 (q, *J* = 270 Hz), 96.1, 49.3, 42.8, 29.1, 28.4, 28.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}F_3N_2O$: 297.1209, found: 297.1206.

3-(*o*-Tolyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one (32al). Prepared according to **general procedure M** from phenyl propiolamide **31al** (81.0 mg, 0.336 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32al** was obtained as a pale yellow oil (60.8 mg, 0.251 mmol, 75%). **IR (neat):** 3410, 1599 cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.43-7.06 (m, 4H), 5.37 (s, 1H), 4.13 (br s, 2H), 3.60 (t, *J* = 3.9 Hz, 2H), 2.27 (s, 3H), 1.97-1.41 (m, 6H); **^{13}C NMR (101 MHz, CDCl$_3$):** δ 162.5, 148.5, 137.0, 130.5, 129.8, 129.6, 129.0, 125.9, 94.8, 47.6, 42.2, 29.1, 28.5(2), 19.8; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1489.

3-(*m*-Tolyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32am). Prepared according to **general procedure M** from phenyl propiolamide **31am** (61.0 mg, 0.252 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32am** was obtained as a pale yellow oil (55.1 mg, 0.227 mmol, 90%); **IR (neat):** 3402, 2938, 1627 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** δ 7.53-6.91 (m, 4H), 5.46 (s, 1H), 4.23-3.94 (m, 2H), 3.94-3.57 (m, 2H), 2.40 (s, 3H), 1.96-1.49 (m, 6H); **^{13}C NMR (75 MHz, CDCl$_3$):** δ 162.4, 151.1, 138.3, 130.1, 129.0, 128.7, 128.4, 125.2, 94.7, 49.0, 42.7, 29.1, 28.4, 28.2, 21.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1489.

3-(3,5-Dimethylphenyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32an). Prepared according to **general procedure M** from phenyl propiolamide **31an** (66.6 mg, 0.260 mmol). Purified by preparative TLC (AcOEt/MeOH, 5:1). **32an** was obtained as a pale brown oil (55.4 mg, 0.216 mmol, 83%); **IR (neat):** 3412, 2934, 1622 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** δ 7.09 (s, 1H), 6.99 (s, 2H), 5.47 (s, 1H), 4.10 (t, *J* = 3.9 Hz, 2H), 3.82 (t, *J* = 4.2 Hz, 2H), 2.36 (s, 6H), 1.99-1.57 (m, 6H); **^{13}C NMR (75 MHz, CDCl$_3$):** δ 162.8, 151.5, 138.4, 131.3, 129.1, 126.1, 94.7, 48.9, 42.5, 28.9, 28.2, 28.0, 21.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}N_2O$: 257.1648, found: 257.1644.

3-(Naphthalen-1-yl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32ao). Prepared according to **general procedure M** from phenyl propiolamide **31ao** (40.5 mg, 0.145 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ao** was obtained as a pale yellow oil (31.8 mg, 0.145 mmol, 79%). **m.p.:** 155-156 °C; **IR (neat):** 3416, 2941, 1618 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** δ 8.10-7.79 (m, 3H), 7.65-7.38 (m, 4H), 5.56 (s, 1H), 4.36-3.97 (m, 2H), 3.75-3.47 (m, 2H), 2.05-1.41 (m, 6H); **^{13}C NMR (75 MHz, CDCl$_3$):** δ 162.6, 147.7, 133.4, 131.5, 130.2, 128.4, 128.1, 127.1, 126.9, 126.5, 125.0, 124.9, 96.1, 48.1, 42.4, 29.1, 28.5(2); **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2O$: 279.1492, found: 279.1489.

3-(Benzo[*d*][1,3]dioxol-5-yl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32ap). Prepared according to **general procedure M** from phenyl propiolamide **31ap** (42.0 mg, 0.154 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ap** was white solid (39.1 mg, 0.202 mmol, 93%). **m.p.:** 153 °C; **IR (neat):** 3397, 2941, 1622 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.88 (d, *J* = 1.4 Hz, 2H), 6.84 (s, 1H), 6.04 (s, 2H), 5.45 (s, 1H), 4.18-3.96 (m, 2H), 3.93-3.68 (m, 2H), 1.95-1.57 (m, 6H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.9, 151.4, 148.9, 148.0, 123.1, 122.6, 108.64, 108.63, 101.6, 95.0, 49.2, 42.8, 29.0, 28.3, 28.0. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1234, found: 273.1231.

3-Butyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32aq). Prepared according to **general procedure M** from phenyl propiolamide **31aq** (70.0 mg, 0.336 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32aq** was obtained as a colorless oil (50.3 mg, 0.241 mmol, 73%). **IR (neat):** 3395, 2935, 1604 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 5.13 (s, 1H), 4.11-3.91 (m, 2H), 3.91-3.74 (m, 2H), 2.44 (t, *J* = 7.7 Hz, 2H), 1.91-1.64 (m, 6H), 1.62-1.52 (m, 2H), 1.46-1.34 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.7, 148.7, 91.5, 46.1, 41.8, 29.9, 28.9, 28.6, 28.4, 25.5, 22.0, 13.5. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{21}N_2O$: 209.1648, found: 209.1647.

3-(*tert*-Butyl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]diazepin-1-one (32as). Prepared according to **general procedure M** from phenyl propiolamide **31as** (30 mg, 0.144 mmol), (Reaction time = 72 h). Purified by preparative TLC (EtOAc/MeOH = 3:1). **32as** was obtained as a colorless oil (21.8 mg, 0.250 mmol, 73%); **IR (neat):** 3384, 2975, 1615 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 5.17 (s, 1H), 4.22-3.89 (m, 4H), 1.92-1.64 (m, 6H), 1.32 (s, 9H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 162.1, 156.3, 91.1, 48.0, 41.5, 31.7, 29.6, 28.7, 28.6, 28.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{21}N_2O$: 209.1648, found: 209.1647.

General procedure N: synthesis of pyrazolopyridazines 32ba-32ia [Table 12]. To a solution of the propiol amide **31ba-31ia** (1.0 equiv.) in PhCl (*c* = 0.04 M) was added AuI. The mixture was stirred under reflux for 12 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH) to afford pyrazolopyridazine **32ba-32ia.**

6-Methyl-3-pheny-6,7,8,9-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2]diazepin-1-one (32ba). Prepared according to **general procedure N** from phenyl propiolamide **31ba** (31.9 mg, 0.128 mmol). Purified by preparative TLC (EtOAc/MeOH = 3:1). **32ba** was obtained as a pale white solid (30.5 mg, 0.126 mmol, 42%). **m.p.:** 141 °C; **IR (neat):** 3408, 2928, 1622 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.58-7.42 (m, 3H), 7.42-7.32 (m, 2H), 5.51 (s, 1H), 4.76-4.61 (m, 1H), 4.14-3.94 (m, 1H),

3.68-3.43 (m, 2H), 2.20-1.92 (m, 1H), 1.93-1.73 (m, 2H), 1.59-1.41 (m, 1H), 1.41-1.24 (m, 1H), 1.04 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR (101 MHz, CDCl$_3$):** δ 162.7, 151.0, 129.7, 129.4, 128.8, 128.4, 95.1, 47.5, 41.2, 36.4, 36.1, 35.5, 22.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1491.

3-Phenyl-6,7,8,9-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2]diazepin-1-one (32ca). Prepared according to **general procedure N** from phenyl propiolamide **31ca** (72.5 mg, 0.253 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ca** was obtained as a pale yellow oil (58.1 mg, 0.203 mmol, 80%); **IR (neat):** 3413, 1729, 1622 cm^{-1}; **^{1}H NMR (300 MHz, CDCl$_3$):** δ 7.60-7.21 (m, 5H), 5.54 (s, 1H), 4.60-4.34 (m, 1H), 4.12-3.93 (m, 1H), 3.91-3.78 (m, 1H), 3.77-3.64 (m, 1H), 3.72 (s, 3H), 2.86-2.67 (m, 1H), 2.35-2.16 (m, 1H), 2.14-1.85 (m, 3H); **^{13}C NMR (75 MHz, CDCl$_3$):** δ 174.1, 162.8, 151.9, 129.9, 129.0, 128.9, 128.3, 95.5, 57.8, 52.0, 46.5, 44.3, 40.3, 30.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_3$: 287.1390, found: 287.1390.

6-Methyl-3-phenyl-6,7,8,9-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2]diazepin-1-one (32da). Prepared according to **general procedure N** from phenyl propiolamide **31da** (25.5 mg, 0.231 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32da** was obtained as a colorless oil (22.2 mg, 0.092 mmol, 87%); **IR (neat):** 3411, 2935, 1622 cm^{-1}; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.58-7.42 (m, 3H), 7.42-7.29 (m, 2H), 5.48 (s, 1H), 4.43 (dd, *J* = 15.0, 7.8 Hz, 1H), 3.91-3.61 (m, 2H), 3.47 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.03-1.83 (m, 2H), 1.82-1.61 (m, 2H), 1.53-1.38 (m, 1H), 0.85 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR (151 MHz, CDCl$_3$):** δ 162.7, 151.4, 129.8, 129.6, 128.9, 128.6, 94.7, 54.1, 42.8, 37.3, 34.6, 26.6, 18.3; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1492.

8-Methyl-3-phenyl-6,7,8,9-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2]diazepin-1-one (32da'). Prepared according to **general procedure N** from phenyl propiolamide **31da** (25.5 mg, 0.231 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32da'** was obtained as a colorless oil (2.5 mg, 0.010 mmol, 10%). **IR (neat):** 3370, 2928, 1619 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.56-7.42 (m, 3H), 7.42-7.35 (m, 2H), 5.53 (s, 1H), 4.37 (d, *J* = 14.6 Hz, 1H), 3.98 (dd, *J* = 14.8, 7.8 Hz, 1H), 3.67 (dd, *J* = 14.6, 9.6 Hz, 1H), 3.52 (dd, *J* = 14.9, 9.4 Hz, 1H), 2.06-1.88 (m, 2H), 1.88-1.76 (m, 1H), 1.61-1.32 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (101 MHz, CDCl$_3$):** δ 163.3, 151.2, 129.9, 129.6, 129.0, 128.7, 95.3, 49.2, 48.2, 37.5, 33.7, 26.8, 18.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1492.

9-Methyl-3-phenyl-6,7,8,9-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2]diazepin-1-one (32ea) and 5-Methyl-3-phenyl-6,7,8,9-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2]diazepin-1-one (32ea'). Prepared according to **general procedure N** from phenyl propiolamide **31ea** (52.9 mg, 0.231 mmol). Purified by preparative TLC (EtOAc/MeOH = 3:1). **32ea** and **32ea'** was obtained as a pale white solid

(22.4 mg, 0.0981 mmol, 43%); **IR (neat):** 3412, 2935, 1622 cm^{-1}; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.51-7.34 (m, 10H), 5.56 and 5.548 (s, 2H), 5.09-4.97 (m, 1H), 4.69-4.59 (m, 1H), 4.31-4.22 (m, 1H), 3.99-3.84 (m, 1H), 3.55-3.38 (m, 2H), 2.24-1.56 (m, 12H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (151 MHz, $CDCl_3$):** δ 164.7, 164.3, 154.8, 154.4, 130.3, 129.9, 129.8, 129.0, 128.9, 128.6, 128.3, 97.5, 96.4, 55.5, 51.2, 49.1, 45.5, 33.8, 32.5, 28.8, 27.4, 23.7, 22.9, 18.4, 16.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1491.

1-Phenyl-10,11-dihydro-3*H*,5*H*-benzo[*d*]pyrazolo[1,2-*a*][1,2]diazepin-3-one (32fa). Prepared according to **general procedure N** from phenyl propiolamide **31fa** (50.0 mg, 0.181 mmol). Purified by preparative TLC (EtOAc/MeOH = 3:1). **32fa** was obtained as a pale white solid (46.3 mg, 0.168 mmol, 90%); **IR (neat):** 3417, 2990, 1645 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.61-7.36 (m, 6H), 7.35-7.18 (m, 2H), 7.18-7.00 (m, 1H), 5.74 (s, 1H), 5.08 (s, 2H), 3.58 (t, *J* = 5.0 Hz, 2H), 3.14 (t, *J* = 5.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.1, 159.0, 139.3, 135.5, 130.2, 129.6, 129.3, 129.0, 128.8, 128.3, 128.0, 127.2, 100.5, 51.7, 47.6, 34.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O$: 277.1335, found: 277.1333.

1-Phenyl-6,7-dihydro-3*H*,5*H*-benzo[*c*]pyrazolo[1,2-*a*][1,2]diazepin-3-one (32ga). Prepared according to **general procedure N** from phenyl propiolamide **31ga** (50.0 mg, 0.181 mmol). Purified by preparative TLC (EtOAc/MeOH = 3:1). **32ga** was obtained as a pale white solid (44.9 mg, 0.162 mmol, 84%); **IR (neat):** 3417, 2254, 1627 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.50-7.09 (m, 7H), 7.11-6.90 (m, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.76 (s, 1H), 3.92 (br m, 2H), 2.98 (t, *J* = 7.1 Hz, 2H), 2.25-1.97 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 161.8, 147.2, 135.3, 134.6, 129.8, 129.5, 128.9, 128.6, 128.4, 128.0, 127.4, 126.1, 96.3, 38.4, 29.0, 26.2; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O$: 277.1335, found: 277.1332.

9-Phenyl-1,2,4,5-tetrahydro-7*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-7-one (32ha). Prepared according to **general procedure N** from phenyl propiolamide **31ha** (43.5 mg, 0.189 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **32ha** was obtained as a red oil (40.4 mg, 0.0176 mmol, 93%). **m.p.:** 153 °C; **IR (neat):** 3412, 1615 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.61-7.44 (m, 3H), 7.44-7.33 (m, 2H), 5.58 (s, 1H), 4.34-4.16 (m, 2H), 4.09-3.86 (m, 4H), 3.87-3.68 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 163.2, 152.9, 130.1, 129.0, 128.8, 128.4, 96.0, 70.0, 69.7, 52.2, 45.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}N_2O_2$: 231.1128, found: 231.1126.

1-(Hex-5-en-1-yl)-5-phenyl-1,2-dihydro-3H-pyrazol-3-one (71). Prepared according to **general procedure N** from phenyl propiolamide **31ia** (77.0 mg, 0.317 mmol). Purified by preparative TLC (EtOAc/MeOH = 5:1). **71** was obtained as a colorless oil (30.7 mg, 0.1276 mmol, 40%); **IR (neat):** 3017, 1641, 1559 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.54-7.28 (m, 5H), 5.86-5.54 (m, 2H), 5.03-

4.78 (m, 2H), 4.05-3.83 (m, 2H), 2.08-1.87 (m, 2H), 1.87-1.68 (m, 2H), 1.39-1.22 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 161.7, 145.6, 138.2, 130.6, 128.9, 128.74, 128.66, 114.7, 91.2, 48.4, 33.0, 29.6, 25.5; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}N_2O$: 243.1492, found: 243.1491.

Transformation from 32aa to 72 [Scheme 37]. In a 10 mL round-bottomed flask was added $POCl_3$ (18.3 μL, 0.197 mmol) to DMF (20.3 μL, 0.262 mmol) at 0 °C. After 30 min, **32aa** (30 mg, 0.131 mmol) was added to the mixture and the mixture was stirred at 85 °C for 3 h. The reaction mixture was poured into a mixture of ice and NaOH (2 N). The aqueous phase was extracted with $CHCl_3$ three times, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 5:1). **72** was obtained as a brown oil (20.8 mg, 0.081 mmol, 62%).

1-Oxo-3-phenyl-6,7,8,9-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2]diazepine-2-carbaldehyde (72). **IR (neat):** 3422, 1688, 1501 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.65 (s, 1H), 7.65-7.46 (m, 3H), 7.46-7.31 (m, 2H), 4.27-4.04 (m, 2H), 4.01-3.77 (m, 2H), 1.95-1.67 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 183.8, 160.9, 149.5, 130.8, 129.7, 128.9, 126.2, 105.6, 47.7, 41.9, 28.9, 28.8, 28.4; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_2$: 257.1285, found: 257.1282.

Transformation from 32aa to 73 [Scheme 37]. To a solution of **32aa** (30.0 mg, 0.131 mmol) in MeCN (2.0 mL) were added iodobenzene (29.0 μL, 0.262 mmol), Ag_2CO_3 (72.0 mg, 0.262 mmol) and $Pd(OAc)_2$ (11.6 mg, 0.0524 mmol) at rt. The mixture was stirred at 100 °C. After 12 h, the mixture was filtered through silica gel and washed with $CHCl_3$ and then, resulting solution was concentrated. The residue was purified by preparative TLC (EtOAc/MeOH = 5:1) to afford **73** as an orange solid (20.8 mg, 0.0683 mmol, 52%) and **32aa** was recovered (9.2 mg, 0.0403 mmol, 31%).

2,3-Diphenyl-6,7,8,9-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*][1,2]diazepin-1-one (73). IR (neat): 3421, 1619 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.61-6.97 (m, 10H), 4.31-3.99 (m, 2H), 3.86-3.54 (m, 2H), 2.00-1.57 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.2, 146.4, 131.8, 129.8, 129.6, 129.5, 129.0, 128.2, 127.9, 125.6, 106.8, 48.4, 42.9, 29.1, 28.6, 28.1; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O$: 305.1648, found: 305.1641.

Transformation from 32aa to 74 [Scheme 37]. To a solution of **32aa** (80.0 mg, 0.350 mmol) in CH_2Cl_2 (3.5 mL) was added EtOTf (136 μL, 1.05 mmol). The mixture was stirred at rt. After 4 h, the mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (NH silica gel) (EtOAc/MeOH = 10:1) to afford **74** as a pale yellow solid (130.3 mg, 0.321 mmol, 91%).

Migration reaction of aminimide 70 without AuI [Scheme 38]. A solution of aminimide **70** (33.5 mg, 0.147 mmol) in PhCl (3.7 mL, 0.04 M) was stirred under reflux for 12 h. Then, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (3.3 mg) and aminimide **70** (17.0 mg, 51%).

Migration reaction of aminimide 70 with AuI [Scheme 38]. To a solution of aminimide **70** (22.7 mg, 0.0994 mmol) in PhCl (2.5 mL, 0.04 M) was added AuI (3.2 mg, 0.0099 mmol). After being stirred under reflux for 12 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (20.9 mg, 92%).

Cyclization-migration reaction of alkynylhydrazide 31aa with TEMPO [Scheme 39]. To a solution of the alkynylhydrazide **31aa** (30.0 mg, 0.131 mmol) in PhCl (3.3 mL, 0.04 M) were added AuI (4.2 mg, 0.0131 mmol) and TEMPO (61 mg, 0.393 mmol). The reaction mixture was stirred under reflux for 12 h. The reaction mixture was cooled to rt and evaporation under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolodiazepine **32aa** (26.3 mg, 88%).

Preparation of alkynylhydrazide 75 [Scheme 40]. To a solution of phenyl propiolic acid (400 mg, 2.50 mmol) in THF (7.1 mL, 0.35 M) were added 1,1-dibuthylhydrazine trifluoroacetate (774 mg, 3.00 mmol), TEA (1.46 mL, 10.4 mmol) and finally DMT-MM (829 mg, 3.00 mmol) at rt. Then, the mixture was stirred for 2 h. After stirred, the mixture was quenched by water and extracted with $CHCl_3$ three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (Hexane/EtOAc = 1:1) to afford **75** as an orange oil (230 mg, 32%).

***N*', *N*'-Dibutyl-3-(*p*-tolyl)propiolohydrazide (75). m.p.:** 86 °C; **IR (neat):** 3018, 2217, 1615 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.59-7.34 (m, 2H), 7.26-7.05 (m, 2H), 6.66 and 6.43 (br s, 1H), 2.96-2.49 (m, 4H), 2.38 (s, 3H), 1.68-1.15 (m, 8H), 1.12-0.73 (m, 6H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 158.3, 152.8, 140.6, 140.4, 132.4, 129.3, 129.2, 117.8, 116.9, 91.3, 86.0, 81.7, 81.5, 59.1, 58.2, 29.0, 28.9, 21.6, 20.3, 13.9, 13.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{27}N_2O$: 287.2118, found: 287.2117.

Crossover experiment of alkynylhydrazides 67 and 75 [Scheme 40]. To a solution of the alkynylhydrazide **67** (50.0 mg, 0.231 mmol) and **75** in PhCl (11.6 mL, 0.04 M) was added AuI (15

mg, 0.0462 mmol). The reaction mixture was stirred under reflux for 12 h. The reaction mixture was cooled to rt and evaporation under reduced pressure. The residue was purified by preparative TLC (Hexane/EtOAc = 1:1) to afford pyrazolone **68a** (13.4 mg, 15%), **68b** (8.4 mg, 8%), **68c** (8.6 mg, 8%), **76a** (15.1 mg, 14%), **76b** (19.5 mg, 15%) and **76c** (14.7 mg, 12%).

1,2-Diethyl-5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (68b). IR (neat): 2978, 1552 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** 7.58-7.30 (m, 5H), 5.77-5.57 (s, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.99 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.4, 144.4, 130.9, 128.7, 128.6, 128.4, 90.4, 64.6, 44.0, 15.7, 14.9; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O$: 217.1335, found: 217.1334.

2-Butyl-1-ethyl-5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (68c). IR (neat): 2959, 1510 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51-7.29 (m, 5H), 5.69 (s, 1H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.99 (q, *J* = 7.2 Hz, 2H), 1.81-1.73 (m, 2H), 1.50 (m, *J* = 7.3 Hz, 3H), 1.35 (t, *J* = 7.3 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.8, 144.6, 131.1, 128.8, 128.7, 128.6, 90.5, 68.9, 44.1, 31.5, 19.3, 15.8, 14.0; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{21}N_2O$: 245.1648, found: 245.1647.

1-Butyl-5-(*p*-tolyl)-1,2-dihydro-3*H*-pyrazol-3-one (76a). IR (neat): 2965, 1525 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.17 (m, 4H), 5.63 (s, 1H), 3.91 (t, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.82-1.64 (m, 2H), 1.30-1.11 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 161.7, 145.7, 138.8, 129.4, 128.9, 127.9, 91.1, 48.5, 32.4, 21.4, 19.8, 13.7; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}N_2O$: 231.1492, found: 231.1490.

1,2-Dibutyl-5-(*p*-tolyl)-1,2-dihydro-3*H*-pyrazol-3-one (76b). IR (neat): 2959, 1515 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.17 (m, 4H), 5.64 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.92 (t, *J* = 7.3 Hz, 2H), 2.40 (s, 3H), 1.77-1.70 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.25-1.15 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.4, 144.9, 138.4, 129.3, 128.7, 128.1, 90.1, 64.6, 48.8, 32.4, 21.3, 19.7, 14.9, 13.6; **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{27}N_2O$: 287.2118, found: 287.2113.

1-Ethyl-5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (76c). IR (neat): 2960, 1516 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34-7.09 (m, 4H), 5.63 (s, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 3.91 (t, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 1.83-1.65 (m, 4H), 1.53-1.43 (m, 2H), 1.24-1.14 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$):** δ 162.6, 144.9, 138.3, 129.2, 128.7, 128.1, 90.1, 68.7, 48.8, 32.4, 31.4, 21.2, 19.7, 19.2, 13.9, 13.6. **HRMS (ESI):** *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{23}N_2O$: 259.1805, found: 259.1801.

TBAI-catalyzed cyclization-migration reaction of alkynylhydrazide 31aa. [Scheme 41]. To a

solution of the alkynylhydrazide **32aa** (50.0 mg, 0.219 mmol) in PhCl (5.5 mL, 0.04 M) was added TBAI (8.1 mg, 0.0219 mmol). The reaction mixture was stirred under reflux for 12 h. The reaction mixture was cooled to rt and evaporated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 3:1) to afford pyrazolopyridazine **32aa** (32.4 mg, 65%), aminimide **70** (5.0 mg, 10%) and impure **31aa** (10.6 mg, 21%).

Cyclization-migration reaction of hydrazide 26aa with AuI [Scheme 44]. To a solution of the alkynylhydrazide **26aa** (48.2 mg, 0.22 mmol) in PhCl (5.0 mL, 0.04 M) was added AuI (7.3 mg, 0.022 mmol). The reaction mixture was stirred under reflux for 0.5 h. The reaction mixture was cooled to rt and evaporated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 20:1) to afford pyrazolopyridazine **27aa** (28.8 mg, 60%).

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