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Generation of Donor/Donor Copper Carbenes through Copper-Catalyzed Diyne Cyclization: Enantioselective and Divergent Synthesis of Chiral Polycyclic Pyrroles

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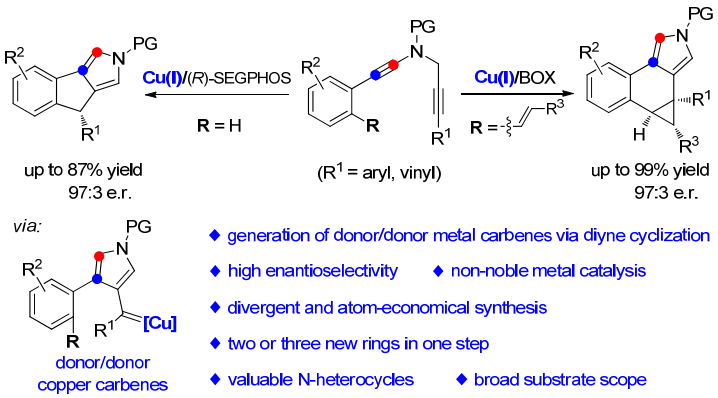
Supporting Information Placeholder

ABSTRACT: The generation of metal carbenes from readily available alkynes represents a significant advance in metal carbene chemistry. However, most of these transformations are based on the use of noble-metal catalysts and successful examples of such an asymmetric version are still very scarce. Here a copper-catalyzed enantioselective cascade cyclization of *N*-propargyl ynamides is reported, enabling the practical and atom-economical construction of diverse chiral polycyclic pyrroles in generally good to excellent yields with wide substrate scope and excellent enantioselectivities (up to 97:3 e.r.). Importantly, this protocol represents the first copper-catalyzed asymmetric diyne cyclization. Moreover, mechanistic studies revealed that the generation of donor/donor copper carbenes is presumably involved in this 1,5-diyne cyclization, which is distinctively different from the related gold catalysis, and thus it constitutes a novel way for the generation of donor/donor metal carbenes.



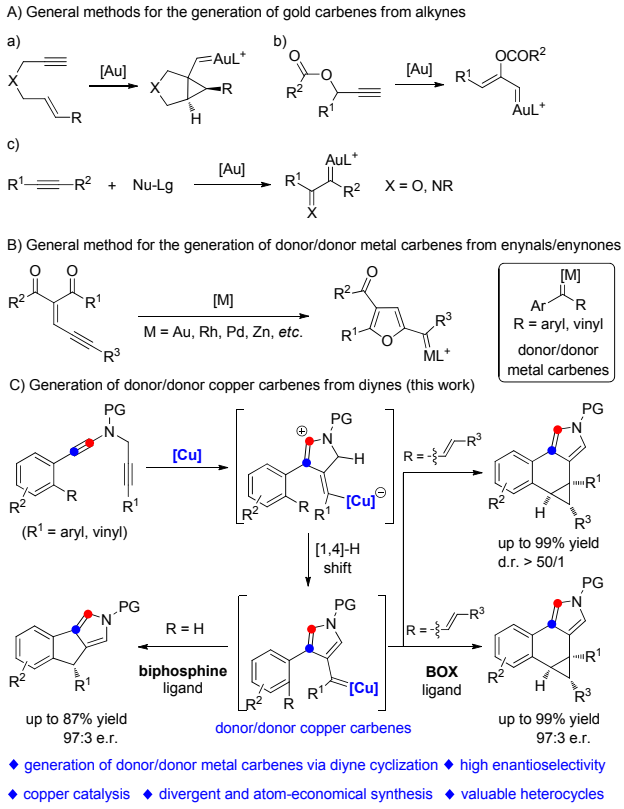
INTRODUCTION

Catalytic transformations involving metal carbenes are arguably the most important aspect of homogeneous transition metal catalysis.[1] Recently, catalytic generation of metal carbenes from readily available alkynes represents a significant advance in metal carbene chemistry,[2] and most general methods for the generation of metal carbene intermediates via this non-diazo approach include the cycloisomerization of 1,6-enynes,[3] 1,2-acyloxy migration of propargylic carboxylates,[4] alkyne oxidation with pyridine *N*-oxides or sulfoxides and alkyne amination based on azides,[5] isoxazoles[6] or sulfilimines[7] (Scheme 1A). In addition, the generation of donor/donor carbenes via transition metal-catalyzed enynal/enynone cyclization has also been nicely exploited by López, Zhu and others (Scheme 1B).[8] Nevertheless, new ways for the generation of metal carbenes from alkynes, especially those based on the use of non-noble metal catalysts and the asymmetric version, remain challenging yet highly desirable.

Over the past decades, transition metal (M: Au, Pt, Ag, Rh, Ru, Ir) catalyzed intramolecular cyclizations of 1,n-diynes (n = 3, 4, 5, 6, 7, *etc*.) have proven to be a powerful method for the rapid construction of various structurally complex cyclic molecules due to their high bond-forming efficiency and atom economy.[9-14] Among those, catalytic 1,5-diyne cyclization, primarily via metal vinylidene,[11] carbene[12] or vinyl cation intermediates,[13] has attracted increasing attention in recent years. Despite these remarkable achievements, these reactions have so far been mostly limited to the noble-metal catalysts. Moreover, no direct catalytic asymmetric intramolecular cyclizations of 1,5-diynes have been reported to the best of our knowledge.[15,16] Therefore, it is highly desirable to develop a non-noble metal catalyzed asymmetric cyclization of diynes, which not only represents an attractive and efficient strategy to build chiral cyclic molecules, but also may help to elucidate

the reaction mechanism. As a continuation of our work on developing ynamide chemistry for heterocycle synthesis,[17,18] we herein report an efficient copper-catalyzed enantioselective cascade cyclization of *N*-propargyl ynamides, which represents the first copper-catalyzed asymmetric diyne cyclization (Scheme 1C). This method enables the practical and atom-economical[19] construction of diverse chiral polycyclic pyrroles in generally good to excellent yields with wide substrate scope and excellent enantioselectivities (up to 97:3 e.r.). Furthermore, mechanistic studies revealed that the generation of donor/donor copper carbene intermediates is presumably involved in this 1,5-diyne cyclization, which is distinctively different from the related gold catalysis, and thus it constitutes a novel way for the generation of donor/donor metal carbenes.

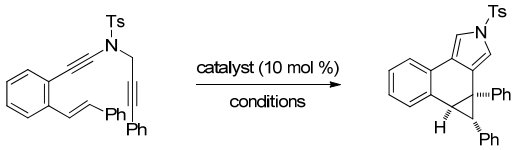
Scheme 1. Generation of Metal Carbenes from Alkynes



RESULTS AND DISCUSSION

Based on our previous work on the gold-catalyzed cyclization of *N*-propargyl ynamides,[20] we chose alkenyl *N*-propargyl ynamide **1a** as the model substrate for the initial study, and selected results are listed in Table 1.[21] Somewhat surprisingly, typical gold catalysts such as $Ph_3PAuNTf_2$ and $IPrAuNTf_2$ were not effective in catalyzing this cascade cyclization (Table 1, entries 1 and 2) and, instead, we were delighted to find that the desired tetracyclic pyrrole **2a** was obtained in 67% yield with excellent diastereoselectivity (d.r. > 50/1) in the presence of 10 mol % of $AgNTf_2$ (Table 1, entry 3). Gratifyingly, subsequent screenings on the non-noble metal catalysts (Table 1, entries 4–7) demonstrated that **2a** could be formed in 87% yield by employing $Cu(CH_3CN)_4PF_6$ as catalyst (Table 1, entry 6). Of note, the reaction proved to be less efficient when it was performed at lower temperatures (Table 1, entries 8 and 9). Other Lewis acids, including $Zn(OTf)_2$, $Y(OTf)_3$ and $Yb(OTf)_3$, and Brønsted acids failed to catalyze this cascade reaction.[21] Interestingly, the use of racemic SEGPHOS as additive could slightly improve the reaction yield (Table 1, entry 10).

Table 1. Optimization of Reaction Conditions for the Cascade Cyclization of Ynamide 1a[a]



1a **2a**

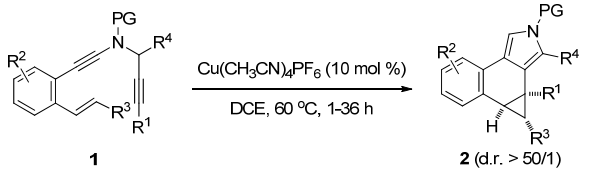
entry	catalyst	conditions	yield (%)[b] 2a	1a
1	$Ph_3PAuNTf_2$	DCE, rt, 1 h	<2	<1
2	$IPrAuNTf_2$	DCE, 60 °C, 2 h	38	<1
3	$AgNTf_2$	DCE, 60 °C, 1 h	67	<1
4	CuI	DCE, 60 °C, 24 h	<2	96
5	CuOTf	DCE, 60 °C, 24 h	<2	47
6	**$Cu(CH_3CN)_4PF_6$**	**DCE, 60 °C, 2 h**	**87**	**<1**
7	$Cu(CH_3CN)_4BF_4$	DCE, 60 °C, 2 h	75	<1
8	$Cu(CH_3CN)_4PF_6$	DCE, 50 °C, 8 h	65	<1
9	$Cu(CH_3CN)_4PF_6$	DCE, 30 °C, 60 h	25	16
10[c]	$Cu(CH_3CN)_4PF_6$	DCE, 60 °C, 6 h	91	<1

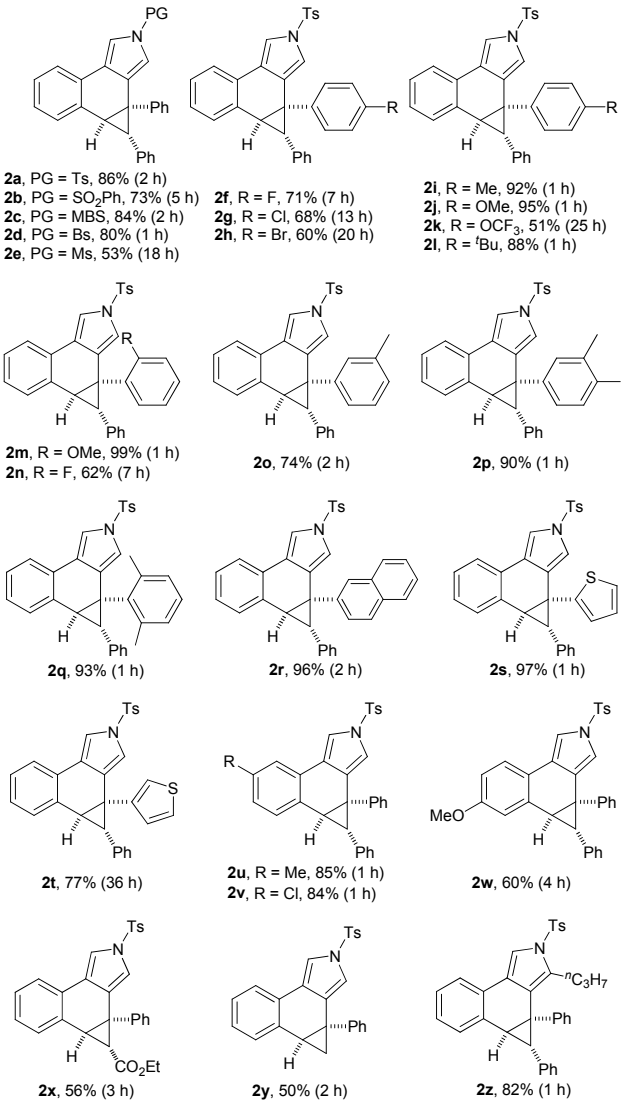
[a]Reaction conditions: **1a** (0.1 mmol), catalyst (0.01 mmol), DCE (2 mL), rt-60 °C, 1-24 h, in vials. [b]Measured by ^1H NMR using 2,6-dimethoxytoluene as the internal standard. [c] Racemic SEGPHOS (0.012 mmol) was employed as additive.

With the optimal reaction conditions in hand (Table 1, entry 6), the scope of this Cu-catalyzed cascade cyclization was then investigated. As summarized in Table 2, an initial investigation of *N*-protecting groups of the ynamides demonstrated that the reaction proceeded efficiently with various aryl sulfonyl groups to afford the desired tetracyclic pyrroles **2a**–**2d** in 73−86% yields while only 53% yield was obtained in case of Ms-protected ynamide. In addition, a wide array of aryl-substituted *N*-propargyl ynamides (R^1 = Ar) bearing both electron-donating and -withdrawing groups were well tolerated in this reaction, leading to the desired pyrrole-based cyclopropanaphthalenes **2f**–**2q** in generally good to excellent yields. The reaction was also extended to the naphthyl- and heterocycle-substituted *N*-propargyl ynamides to produce the corresponding **2r** (96%), **2s** (97%), and **2t** (77%), respectively. The method also occurred smoothly for different aryl-substituted ynamides, and the desired products **2u**–**2w** were formed in 60-85% yields. Moreover, ester-substituted ynamide (R^3 = CO_2Et) and ynamide bearing a terminal alkene moiety were suitable substrates for this tandem cyclization, furnishing the expected products **2x** and **2y** in 56% and 50% yields, respectively. Interestingly, *N*-propargyl ynamide with an *n*-propyl group on the *N*-propargyl also

underwent efficient cyclization to deliver the desired product **2z** in 82% yield. Importantly, excellent diastereoselectivities (d.r. > 50/1) were achieved in all cases.

Table 2. Reaction Scope of the Cascade Cyclization of Ynamides 1[a]

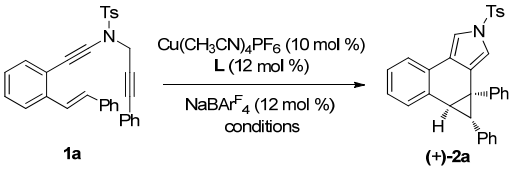


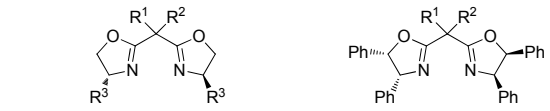


[a]Reaction conditions: **1** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (0.01 mmol), DCE (2 mL), 60 °C, 1-36 h, in vials; isolated yields are reported. PG = protecting group, MBS = 4-methoxybenzenesulfonyl, Bs = 4-bromobenzenesulfonyl.

After establishing a general and reliable method for this copper-catalyzed diyne cyclization, we focused on the development of a chiral copper complex-catalyzed enantioselective version (Table 3). To our delight, the asymmetric tandem reaction of **1a** could proceed smoothly in the presence of $Cu(CH_3CN)_4PF_6$ (10 mol %), bisoxazoline (BOX) ligands (12 mol %) and $NaBAr^F{}_4$ (12 mol %). The screening of a variety of BOX ligands **L1**–**L9** (Table 3, entries 1–9) revealed that diphenyl-substituted BOX ligands **L5**–**L9** gave the significantly improved enantioselectivities (Table 3, entries 5–9), and e.r. of 88:12 was achieved by employing **L6** as chiral ligand (Table 3, entry 6). Lowering the reaction temperature resulted in substantially increasing enantioselectivities (Table 3, entries 10 and 11), and a 99% yield with 96:4 e.r. was furnished when running the reaction at 30 °C (Table 3, entry 11). It is notable that the use of chiral copper complex significantly promotes the reaction at this temperature as the racemic reaction proceeds in low efficiency at 30 °C (Table 1, entry 9). Further solvent screening failed to improve the enantioselectivity (Table 3, entries 12 and 13).

Table 3. Optimization of Reaction Conditions for the Asymmetric Cascade Cyclization of Ynamide 1a[a]





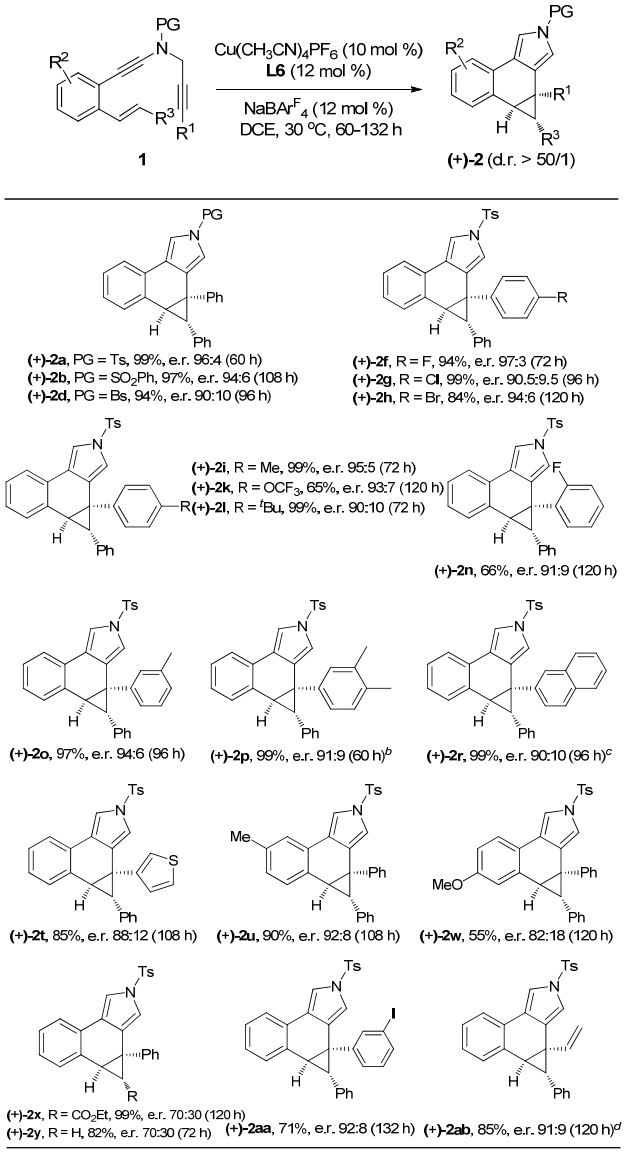
entry	L	conditions	yield (%)[b] (+)-2a	e.r.[c] (+)-2a
1	**L1**	DCE, 50 °C, 30 h	85	70:30
2	**L2**	DCE, 50 °C, 27 h	90	66:34
3	**L3**	DCE, 50 °C, 35 h	90	78:22
4	**L4**	DCE, 50 °C, 35 h	95	81.5:18.5
5	**L5**	DCE, 50 °C, 20 h	90	85:15
6	**L6**	DCE, 50 °C, 20 h	99	88:12
7	**L7**	DCE, 50 °C, 33 h	99	85:15
8	**L8**	DCE, 50 °C, 33 h	99	87:13
9	**L9**	DCE, 50 °C, 33 h	99	86:14
10	**L6**	DCE, 40 °C, 29 h	99	93:7
11	**L6**	**DCE, 30 °C, 60 h**	**99**	**96:4**
12	**L6**	DCM, 30 °C, 65 h	95	92:8
13	**L6**	$CHCl_3$, 30 °C, 65 h	95	90.5:9.5

[a]Reaction conditions: **1a** (0.05 mmol), $Cu(CH_3CN)_4PF_6$ (0.005 mmol), **L** (0.006 mmol), $NaBAr^F{}_4$ (0.006 mmol), solvent (1 mL) 30-50 °C, 20-65 h, in Schlenk tubes. [b]Measured by ^1H NMR using 2,6-dimethoxytoluene as the internal standard. [c]Deter-

mined by HPLC analysis. $NaBAr^F_4$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate.

Under the optimized reaction conditions (Table 3, entry 11), the substrate scope of the Cu-catalyzed asymmetric synthesis of tetracyclic pyrroles **(+)-2** was then examined and the results are shown in Table 4. Besides the Ts-protected model substrate, the reaction also underwent efficiently with SO_2Ph-

Table 4. Scope of the Asymmetric Cascade Cyclization of Ynamides 1[a]



[a]Reaction conditions: **1** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (0.01 mmol), **L6** (0.012 mmol), $NaBAr^F_4$ (0.012 mmol), DCE (2 mL), 30 °C, 60-132 h, in Schlenk tubes; yields are those for the isolated products; ers are determined by HPLC analysis. [b]At 25 °C. [c]**L8** was used. [d]$Cu(CH_3CN)_4PF_6$ (20 mol %), **L6** (24 mol %), $NaBAr^F_4$ (24 mol %), at 40 °C.

and Bs-protected ynamides **1**, furnishing the corresponding tetracyclic *N*-heterocycles **(+)-2b** (97%, e.r. of 94:6) and **(+)-2d** (94%, e.r. of 90:10), respectively. In addition, various aryl-substituted *N*-propargyl ynamides (R^1 = Ar) were applicable substrates to generate the desired products in 65-99% yields with the e.r. of 90:10-97:3. The absolute configuration of **(+)-2f** was confirmed by X-ray diffraction (Figure 1). Interestingly, the naphthyl-substituted ynamide **1r** and heterocycle-substituted ynamide **1t** were also suitable substrates for this reaction to give the corresponding **(+)-2r** (99%) and **(+)-2t** (85%) with good enantioselectivity, and **L8** was employed as chiral ligand in the former case. Then, other aryl-substituted ynamides such as **1u** and **1w** were investigated, and the desired products **(+)-2u** and **(+)-2w** were obtained with good enantioselectivity. Finally, it was found that the different alkenyl-substituted substrates **1x**–**1y** also underwent smooth cyclization to afford the expected products **(+)-2x** and **(+)-2y** with the e.r. of 70:30. It should be specially mentioned that the use of chiral copper complex significantly promotes the reaction efficiency, and substantially improved yields were obtained in almost all cases compared with the corresponding racemic cases. Inspired by these, we were also delighted to find that the cyclization of 3-iodophenyl and vinyl-substituted ynamides, which were not successful substrates (<30% yield) in racemic reactions, could proceed efficiently to deliver the corresponding chiral products **(+)-2aa** (71%) and **(+)-2ab** (85%), respectively. Our attempts to extend the reaction to alkyl-substituted ynamide (R^1 = alkyl) have been unsuccessful as yet.[21] Once again, excellent diastereoselectivities (d.r. > 50/1) were achieved in all cases.

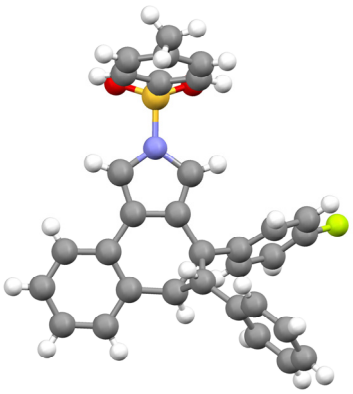
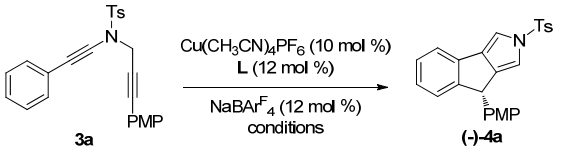


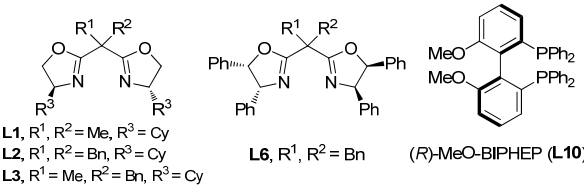
Figure 1. Structure of compound **(+)-2f** in its crystal.

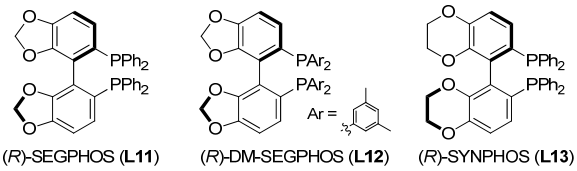
Inspired by the above copper-catalyzed asymmetric tandem cyclization/cyclopropanation reaction, we then wondered whether this asymmetric catalysis is applicable to our previous protocol on the catalytic cascade cyclization of *N*-propargyl ynamides.[20b] Particularly, this study may help to elucidate the reaction mechanism. If such an asymmetric reaction can be achieved, the proposed vinyl cation pathway is less likely as the formed chiral carbon center is not bound to the chiral copper species in this process. As outlined in Table 5, we were delighted to find that the asymmetric cascade cyclization of *N*-propargyl ynamide **3a** afforded the desired tricyclic pyrrole **(-)-4a** in excellent yields and promising enantioselectivities by employing Cu/BOX ligands as chiral metal complexes (Table

5, entries 1−4). Gratifyingly, further ligand screening revealed that the chiral biphosphine ligands **L10**–**L13** (Table 5, entries 5–8) gave the significantly improved enantioselectivities, and e.r. of 91:9 was obtained in the presence of **L11** and **L12** as chiral ligands (Table 5, entries 6 and 7). Subsequently, different solvents were investigated (Table 5, entries 9–12), and toluene was found to be the best solvent (Table 5, entry 9). A significant temperature effect was observed (Table 5, entries 13 and 14), and lowering the reaction temperature to 20 °C allowed for the isolation of **(-)-4a** with the e.r. of 97:3 (Table 5, entry 14).

Table 5. Optimization of Reaction Conditions for the Asymmetric Cascade Cyclization of Ynamide 3a[a]





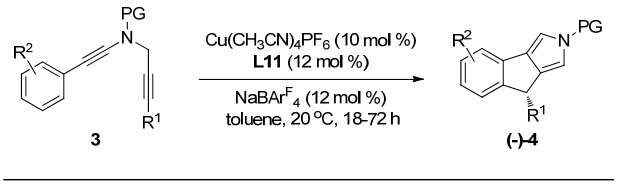


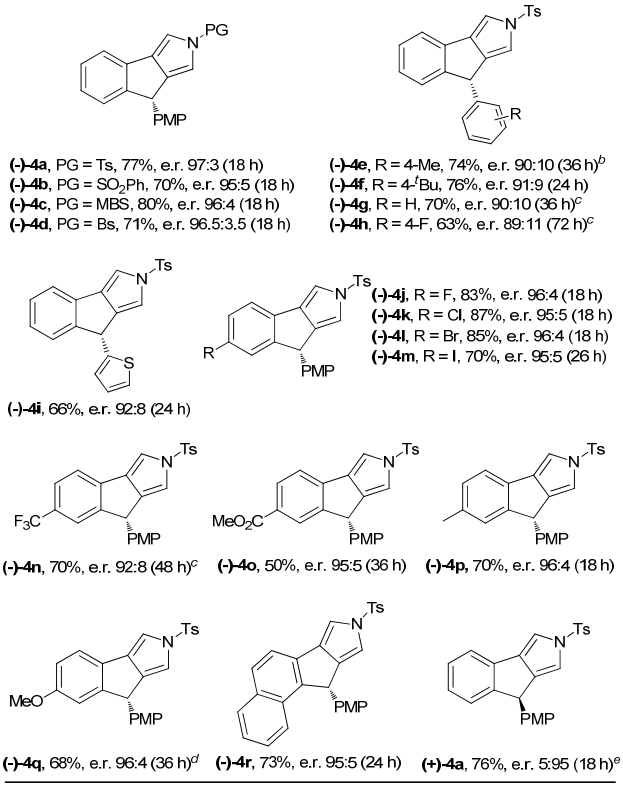
entry	L	conditions	yield (%)[b] (-)-4a	e.r.[c] (-)-4a
1	**L1**	DCE, 40 °C, 2 h	86	56:44
2	**L2**	DCE, 40 °C, 2 h	88	55:45
3	**L3**	DCE, 40 °C, 2 h	89	54:46
4	**L6**	DCE, 40 °C, 9 h	86	70:30
5	**L10**	DCE, 40 °C, 6 h	83	90:10
6	**L11**	DCE, 40 °C, 6 h	90	91:9
7	**L12**	DCE, 40 °C, 6 h	87	91:9
8	**L13**	DCE, 40 °C, 6 h	85	85.5:14.5
9	**L11**	toluene, 40 °C, 9 h	84	94.5:5.5
10	**L11**	PhCl, 40 °C, 9 h	85	93:7
11	**L11**	PhF, 40 °C, 9 h	90	93:7
12	**L11**	$PhCF_3$, 40 °C, 9 h	73	90:10
13	**L11**	toluene, 30 °C, 15 h	83	95.5:4.5
14	**L11**	**toluene, 20 °C, 24 h**	**84**	**97:3**

[a]Reaction conditions: **3a** (0.05 mmol), $Cu(CH_3CN)_4PF_6$ (0.005 mmol), **L** (0.006 mmol), $NaBAr^F_4$ (0.006 mmol), solvent (1 mL), 30-40 °C, 2-24 h, in Schlenk tubes. [b]Measured by ^1H NMR using 2,6-dimethoxytoluene as the internal standard. [c]Determined by HPLC analysis. PMP: 4-methoxyphenyl.

Based on the optimized reaction conditions (Table 5, entry 14), we also evaluated the scope of the asymmetric cascade cyclization of ynamides **3** (Table 6). Besides the Ts-protected substrate **3a**, ynamides with different *N*-protected groups such as SO_2Ph-, MBS- and Bs-protected *N*-propargyl ynamides were also tolerated, affording the corresponding tricyclic N-heterocycles **(-)-4b** (70%, 95:5 e.r.), **(-)-4c** (80%, 96:4 e.r.), **(-)-4d** (71%, 96.5:3.5 e.r.), respectively. The absolute configuration of **(-)-4d** was unambiguously determined to be (*R*) by X-ray diffraction (Figure 2). Then, various aryl-substituted ynamides (R^1 = Ar) bearing both electron-donating and -withdrawing groups were investigated to generate the desired products **(-)-4e**–**4h** in 63-76% yields with the e.r. of 89:11-91:9, and a longer reaction time was needed in the latter case. The reaction was also extended to the heterocycle-substituted ynamide **3i**. In addition, a variety of aryl- and naphthyl-substituted *N*-propargyl ynamides were also screened and

Table 6. Scope of the Asymmetric Cascade Cyclization of Ynamides 3[a]





[a]Reaction conditions: **3** (0.2 mmol), $Cu(CH_3CN)_4PF_6$ (0.02 mmol), **L11** (0.024 mmol), $NaBAr^F_4$ (0.024 mmol), toluene (3 mL), 20 °C, 18-72 h, in Schlenk tubes; yields are those for the isolated products; ers are determined by HPLC analysis. [b]At 25 °C. [c]At 30 °C. [d]At 0 °C. [e](*S*)-SEGPHOS was employed as chiral ligand.

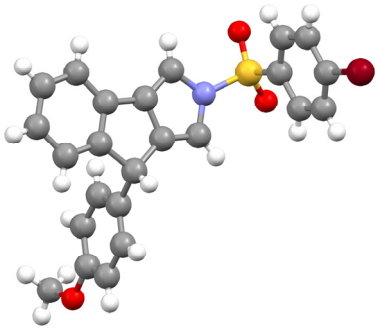
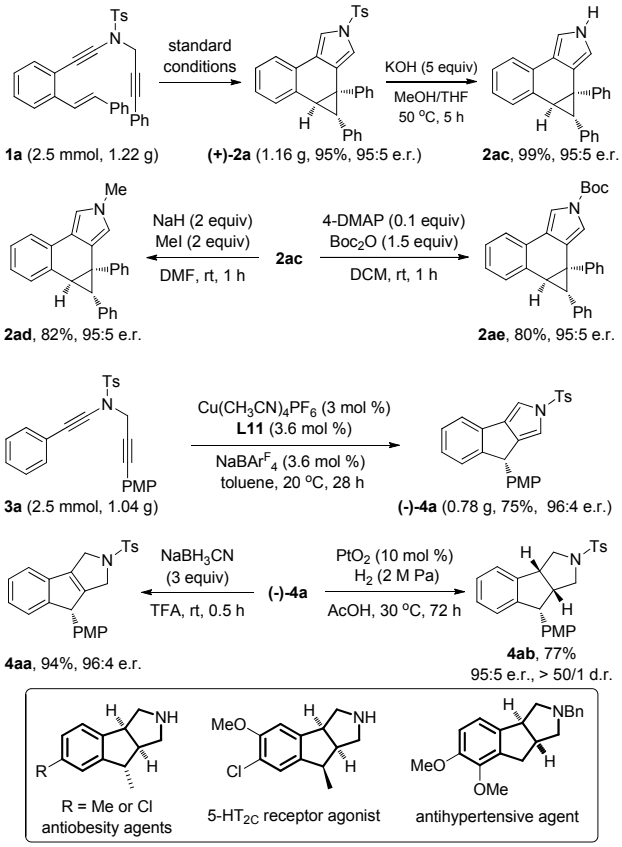


Figure 2. Structure of compound **(-)-4d** in its crystal.

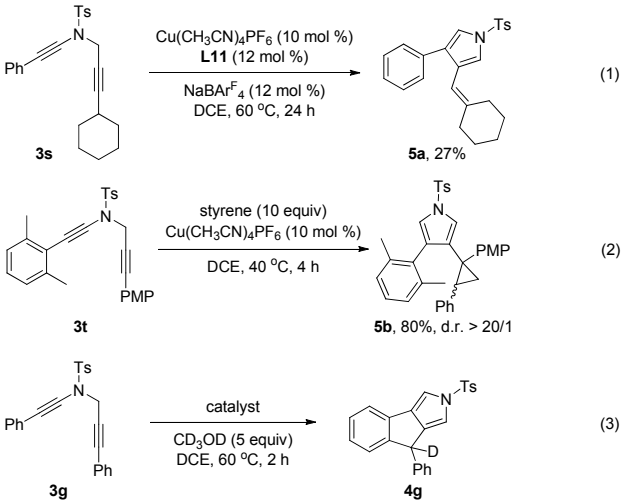
transformed into the desired pyrrole-fused indenes **(-)-4j**–**4r** in generally good to excellent yields with the e.r. of 92:8-96:4. Our attempts to extend the reaction to alkyl- or alkenyl-substituted ynamide only led to the formation of the corresponding products in low yields (<30%).[21] Finally, it was found that the reaction occurred smoothly by employing (*S*)-SEGPHOS as chiral ligand, delivering the desired **(+)-4a** in 76% yield and e.r. of 5:95 with the opposite enantioselectivity.

Scheme 2. Gram-Scale Reaction and Synthetic Transformations

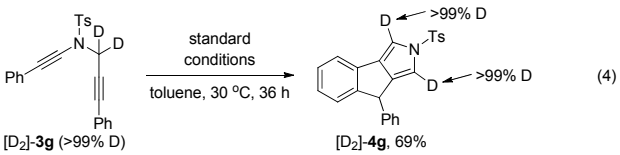


Further synthetic transformations of the as-synthesized pyrrole-based cyclopropanaphthalenes and -indenes were then explored (Scheme 2). First, facile deprotection of **(+)-2a**, which could be synthesized on a gram scale in excellent yield and enantioselectivity under the standard conditions, led to the formation of **2ac** in almost quantitative yield. Then, protection of **2ac** with Me and Boc group afforded the desired **2ad** in 82% yield and **2ae** in 80% yield, respectively. In addition, the *N*-Ts group in **(-)-4a**, prepared on a gram scale in 75% yield with the e.r. of 96:4 in the presence of only 3 mol % of $Cu(CH_3CN)_4PF_6$ and 3.6 mol % of **L11** and $NaBAr^F_4$, could be selectively reduced into the corresponding dihydropyrrole **4aa** in 94% yield and pyrrolidine **4ab** bearing three contiguous stereocenters with excellent diastereoselectivity (d.r. > 50/1) in 77% yield, respectively. Of note, this tricyclic pyrrolidine motif can be found in a variety of bioactive molecules and may be of medicinal interest.[22] Importantly, the enantioselectivity was well maintained in all these transformations.

To understand the mechanism of this diyne cyclization, several control experiments were conducted. First, it was found that when ynamide **3s** was subjected to this copper-catalyzed cascade reaction, the corresponding alkene-pyrrole **5a** was isolated in 27% yield (eq 1).[21] Interestingly, the reaction of methyl-blocked diyne **3t** with styrene under the current copper catalysis could lead to the formation of the corresponding pyrrole-based cyclopropane **5b** in 80% yield (eq 2). In addition, the reactions were also conducted in the presence of 5 equiv of CD_3OD by employing Cu(I) and Au(I) catalysts, respectively, and substantially different deuterium incorporation (<1% vs 30%) was observed (eq 3). These results further confirm that copper carbenes are presumably involved as key intermediates in such a cascade cyclization, which has been strongly supported by the realization of the above asymmetric process. Thus, the copper-catalyzed diyne cyclization is distinctively different from the related gold catalysis, where the



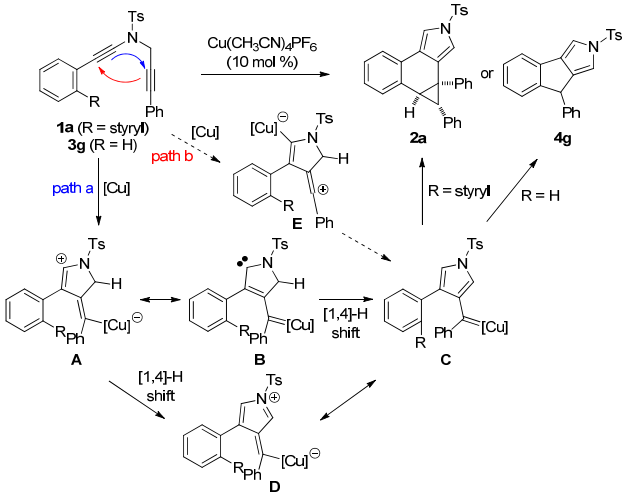
catalyst	product	yield
$Cu(CH_3CN)_4PF_6$ (10 mol %)/$NaBAr^F_4$ (12 mol %)/**L11** (12 mol %)	**4g** (<1% D)	53%
Cy-JohnPhosAuNTf$_2$ (5 mol %)	**4g** (30% D)	55%



vinyl cation intermediate is presumably involved.[20b] Moreover, we also performed deuterium labeling studies and found that two deuteriums on the methylene group of substrate are totally transferred to two deuteriums on the pyrrole α-positions, thus indicating that this process is most likely to involve an intramolecular hydride shift (eq 4). Finally, the relevant kinetic isotopic effect (KIE) studies were also performed, and no significant primary kinetic isotope effects were observed,[21] which indicated that the cleavage of aromatic C−H bond should not be involved in the rate-limiting step.

On the basis of the above experimental results and previous protocols on ynamide chemistry,[18] a plausible mechanism for the synthesis of tetracyclic pyrrole **2a** and tricyclic pyrrole **4g** is illustrated in Scheme 3 (path a). Initially, electron-rich ynamide moiety attacks the [Cu]-activated another C−C triple of **1a** to afford the vinyl copper intermediate **A**[23,24] or its resonance form **B**.[10a] Subsequent [1,4]-H shift[25,26] generates the donor/donor copper carbene intermediate **C**. Of note, C-H insertion followed by electrocyclic ring opening via the formation of Dewar pyrrole may also be possible for this process.[25b,27] Finally, intermediate **C** undergoes intramolecular cyclopropanation to deliver the desired product **2a** in the case of R = styryl. Alternatively, [1,4]-H shift may occur first and then form the copper carbene **C**. In the case of R = H, the formed donor/donor copper carbene intermediate would be trapped by the aryl group via C−H insertion, furnishing the corresponding tricyclic pyrrole **4g**. In particular, the use of chiral copper complexes would lead to the chiral tricyclic pyrroles. Instead, the vinyl cation intermediate **E**, which is generated from the phenyl acetylene group attack of [Cu]-activated ynamide (path b), is presumably involved in the related gold catalysis.[20b]

Scheme 3. Plausible Reaction Mechanism



CONCLUSION

In summary, we have developed an efficient copper-catalyzed enantioselective tandem reaction of *N*-propargyl ynamides via intramolecular cyclization-initiated cyclopropanation and C−H insertion, enabling the practical and atom-economical construction of diverse chiral polycyclic pyrroles in generally good to excellent yields with wide substrate scope and excellent enantioselectivities (up to 97:3 e.r.). To our best knowledge, this protocol represents the first copper-catalyzed asymmetric diyne cyclization. Moreover, mechanistic studies revealed that this copper-catalyzed 1,5-diyne cyclization presumably proceeds through donor/donor copper carbene intermediates, which is distinctively different from the related gold catalysis. Thus, the generation of donor/donor metal carbenes directly from diyne cyclization is achieved, which constitutes a novel way for the generation of metal carbenes via non-diazo approach. The development of non-noble metal-catalyzed asymmetric cascade cyclization of ynamides for heterocycle synthesis and mechanistic investigations are the subjects of ongoing research in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

Experimental procedures, characterizations and analytical data of products, NMR and HPLC spectra (PDF)

Crystallographic structure of **(+)-2f** (CIF)

Crystallographic structure of **(-)-4d** (CIF)

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Notes

The authors declare no competing financial interest.

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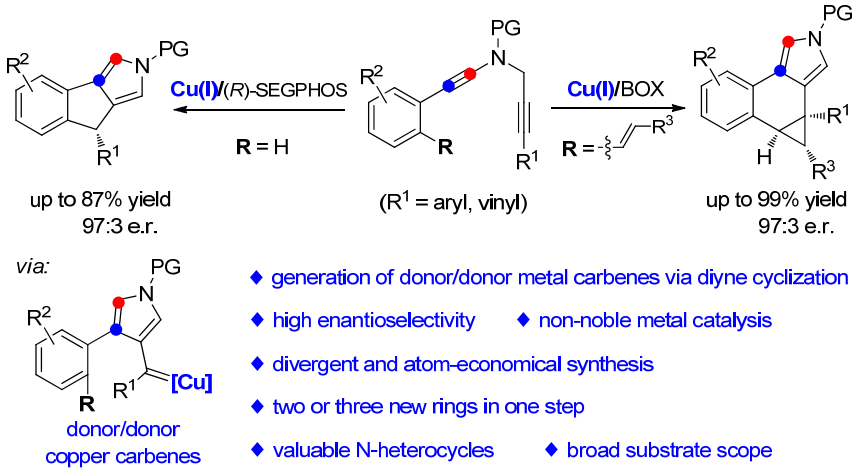
TOC Graphic:


Cu(I)/(R)-SEGPHOS
R = H
Cu(I)/BOX
R =
up to 87% yield
97:3 e.r.
(R1 = aryl, vinyl)
up to 99% yield
97:3 e.r.
via:
donor/donor
copper carbenes
♦ generation of donor/donor metal carbenes via diyne cyclization
♦ high enantioselectivity
♦ non-noble metal catalysis
♦ divergent and atom-economical synthesis
♦ two or three new rings in one step
♦ valuable N-heterocycles
♦ broad substrate scope