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Copper-Catalyzed Azide-Ynamide Cyclization for Generation of α-Imino Copper Carbenes: Divergent and Enantioselective Access to Polycyclic N-Heterocycles

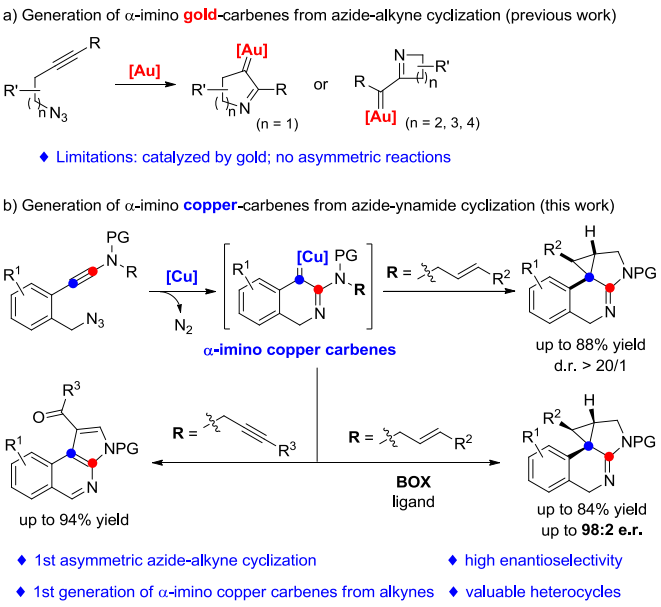
Xin Liu, Ze-Shu Wang, Tong-Yi Zhai, Chen Luo, Yi-Ping Zhang, Yang-Bo Chen, Chao Deng, Rai-Shung Liu, and Long-Wu Ye**

Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry

***Abstract**: Here an efficient copper-catalyzed cascade cyclization of azide-ynamides via α-imino copper carbene intermediates is reported, which represents the first generation of α-imino copper carbenes from alkynes. This protocol enables the practical and divergent synthesis of an array of polycyclic N-heterocycles in generally good to excellent yields with broad substrate scope and excellent diastereoselectivities. Moreover, such an asymmetric azide-ynamide cyclization has been achieved with high enantioselectivities (up to 98:2 e.r.) by employing BOX-Cu complexes as chiral catalysts. Thus, this protocol constitutes the first example of asymmetric azide-alkyne cyclization. The proposed mechanistic rationale for this cascade cyclization is further supported by theoretical calculations.*

Introduction

The generation of α-imino metal carbenes from readily available alkynes via nitrene transfer pathways represents a significant advance in metal carbene chemistry,[1-6] providing rapid access into structurally complex nitrogen-containing molecules, especially the diverse nitrogen heterocycles. As a result, various efficient synthetic methods have been established mainly based on the use of azides,[2] isoxazoles,[3] pyridine aza-ylides[4] and sulfur aza-ylides[5] as nitrene transfer reagents. Among these, catalytic azide-alkyne cyclization via α-imino metal carbenes is particularly attractive,[2] because this approach allows the efficient and rapid assembly of valuable N-heterocycles in a more flexible and atom-economic way (Scheme 1a).[7-12] In 2005, Toste and co-workers disclosed an elegant protocol for the gold-catalyzed acetylenic Schmidt reaction of homopropargyl azides,[7] which represents the first example of azide-alkyne cascade cyclization via α-imino metal carbenes. Following this concept, gold-catalyzed cascade cyclizations of azide-alkynes have been extensively exploited over the past decade by Zhang,[8] Gagosz,[9] Ohno,[10] and others.[11,12] Despite these significant achievements, these cyclizations have so far been limited to the noble-metal catalysts. Furthermore, no catalytic asymmetric azide-alkyne cyclizations have been reported to the best of our knowledge. Notably, the generation of α-imino rhodium carbenes from 1,2,3-triazoles, which are formed by copper-catalyzed cycloaddition of alkynes with azides, has also been vigorously explored, but only aldimine carbenes can be accessed by this strategy.[12c]



Scheme 1. Generation of α-imino metal carbenes from azide-alkyne cyclization.

As a continuation of our work on developing ynamide chemistry for heterocycle synthesis,[13,14,3k,l,11d,12] we herein report an efficient copper-catalyzed cascade cyclization of azide-ynamides via α-imino copper carbene intermediates (Scheme 1b), which represents the first generation of α-imino copper carbenes from alkynes.[15] This protocol enables the practical and divergent synthesis of an array of polycyclic N-heterocycles in generally good to excellent yields with broad substrate scope. Moreover, such an asymmetric azide-ynamide cyclization has been achieved with high enantioselectivities (up to 98:2 e.r.) by the use of bisoxazoline–copper (BOX–Cu) complexes as chiral catalysts, thus constituting the first example of asymmetric azide-alkyne

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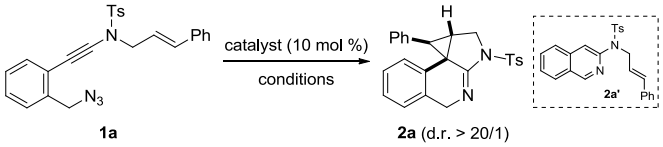
cyclization. In this article, we wish to report the results of our detailed investigations of this copper-catalyzed azide-ynamide cyclization, including substrate scope, synthetic applications, and mechanistic studies.

Results and Discussion

The *N*-styryl benzyl-tethered (azido)ynamide **1a** was chosen as the model substrate to optimize the reaction conditions, and selected results are listed in Table 1.[16] Based on our previous work on the Cu(I)-catalyzed cascade cyclization of ynamides,[14a,c] the Cu(I) catalysts were first investigated. To our delight, the desired tetracyclic heterocycle product **2a** could be obtained in 18% yield by employing 10 mol % of CuOTf as catalyst in DCE at 80 °C, albeit together with a significant amount of undesired isoquinoline product **2a′** (entry 1). We then examined other Cu(I) catalysts (entries 2–5) and were delighted to find that $Cu(CH_3CN)_4BF_4$ gave the best result, affording the desired product **2a** in 86% yield (entry 5). Of note, the use of $Cu(OTf)_2$ as catalyst led to a significantly decreased yield (entry 6). Other Lewis acids such as $Zn(OTf)_2$ and $Sc(OTf)_3$ and Brønsted acids such as CF_3CO_2H and MsOH were investigated as well, but the isoquinoline **2a′** was formed as main product(entries 7–10). In addition, the reaction proved to be less efficient when performed at 60 °C (entry 11) or in other solvents such as toluene and PhCl (entries 12 and 13). The reaction failed to give even a trace of **2a** in the absence of the catalyst, and isoquinoline **2a′** was obtained in 62% yield (entry 14). Finally, it should be mentioned that no triazole formation via azide−ynamide cycloaddition was observed in all cases.[17] Especially, no triazole formation was detected even when ynamide **1a** was subjected to Huang's reaction conditions.[16,17] Instead, **2a** was formed in 49% yield.

Table 1. Optimization of reaction conditions for the cascade cyclization of *N*-styryl (azido)ynamide **1a**.[a]



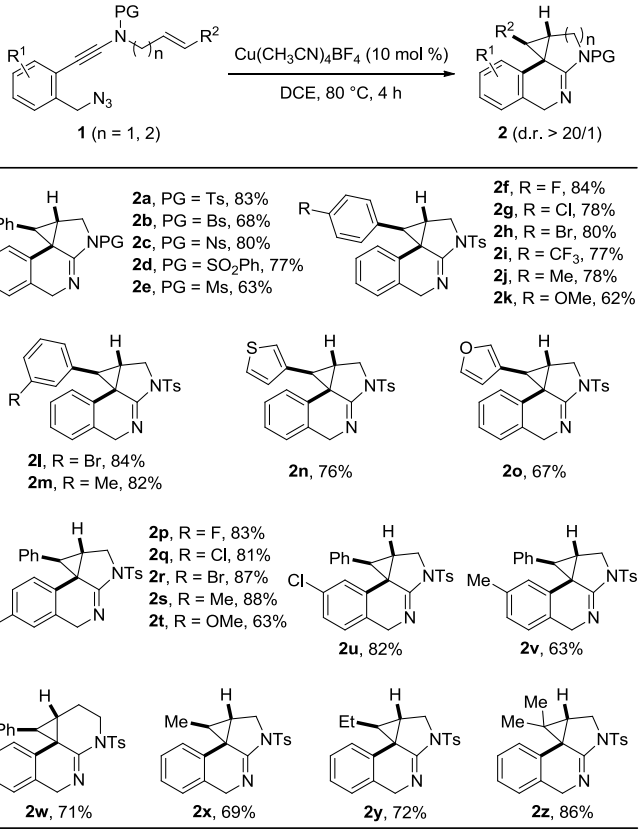
1a **2a** (d.r. > 20/1)

Entry	Catalyst	Reaction conditions	Yield [%][b]
1	CuOTf	DCE, 80 °C, 4 h	18 (54)
2	CuI	DCE, 80 °C, 4 h	21 (50)
3	CuCl	DCE, 80 °C, 4 h	74 (8)
4	$Cu(CH_3CN)_4PF_6$	DCE, 80 °C, 4 h	82 (5)
5	**$Cu(CH_3CN)_4BF_4$**	**DCE, 80 °C, 4 h**	**86 (<5)**
6	$Cu(OTf)_2$	DCE, 80 °C, 16 h	32 (30)
7	$Zn(OTf)_2$	DCE, 80 °C, 3 h	<1 (67)
8	$Sc(OTf)_3$	DCE, 80 °C, 3 h	<1 (71)
9	CF_3CO_2H	DCE, 80 °C, 2 h	<1 (55)
10	MsOH	DCE, 80 °C, 2 h	10 (78)
11	$Cu(CH_3CN)_4BF_4$	DCE, 60 °C, 27 h	75 (7)
12	$Cu(CH_3CN)_4BF_4$	toluene, 80 °C, 6 h	25 (35)
13	$Cu(CH_3CN)_4BF_4$	PhCl, 80 °C, 5 h	41 (24)
14	none	DCE, 80 °C, 5 h	<1 (62)

[a] Reaction conditions: **1a** (0.1 mmol), catalyst (0.01 mmol), solvent (2 mL), 60 °C to 80 °C, 2-27 h, in vials. [b] Measured by ^{1}H NMR using 2,6-dimethoxytoluene as the internal standard. The yield of **2a′** given within parentheses. DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.

With the optimal reaction conditions in hand (Table 1, entry 5), the scope of this copper-catalyzed cascade cyclization was then explored, as summarized in Table 2. Initially, different *N*-protecting groups of the ynamides were investigated and the reaction could proceed smoothly with Ts-, Bs-, Ns-, SO_2Ph- and Ms-protected (azido)ynamides **1**, affording the desired tetracyclic heterocycles **2a**–**2e** in 63–83% yields. In addition, various aryl-substituted benzyl-tethered (azido)ynamides bearing both electron-withdrawing and electron-donating groups were well tolerated in this reaction, leading to the corresponding cyclopropanation products **2f**–**2m** in generally good yields. The reaction was also extended to the thienyl- and furanyl-substituted (azido)ynamides to furnish **2n** and **2o** in 76% and 67% yields, respectively. Different substituents such as F, Cl, Br, Me, and OMe on the phenyl ring were also examined and the expected products **2p**–**2v** could be formed in 63–88% yields. Interestingly, the reaction was also viable for the construction of piperidine-fused tetracyclic heterocycle **2w** in 71% yield. Moreover, methyl-, ethyl- and even dimethyl-substituted *N*- allyl (azido)ynamides

Table 2. Reaction scope of the cascade cyclization of *N*-allyl (azido)ynamides **1**.[a]



[a] Reaction conditions: **1** (0.2 mmol), $Cu(CH_3CN)_4BF_4$ (0.02 mmol), DCE (4 mL), 80 °C, 4 h, in vials; isolated yields are reported. PG = protecting group, Bs = 4-bromobenzenesulfonyl, Ns = 4-nitrobenzenesulfonyl.

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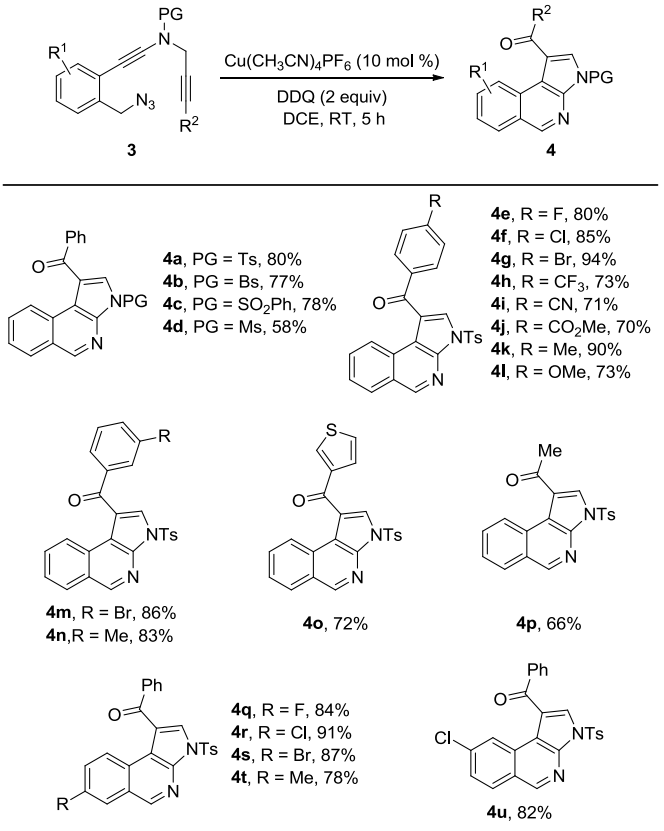
were also suitable substrates for this cascade cyclization, delivering products **2x**–**2z** in 69–86% yields. Of note, excellent diastereoselectivities (d.r. > 20/1) were achieved in all cases. The molecular structure of **2k** was confirmed by X-ray diffraction.[18]

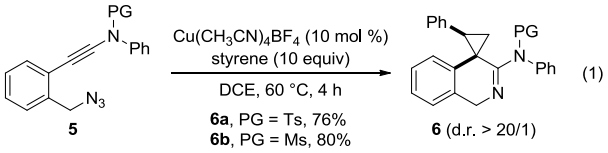
In addition to *N*-allyl benzyl-tethered (azido)ynamides, this copper-catalyzed cascade cyclization also occurred efficiently with *N*-propargyl benzyl-tethered (azido)ynamides[11d,14c,19] at room temperature by employing 10 mol % of $Cu(CH_3CN)_4PF_6$ as catalyst and 2 equiv of DDQ as oxidant,[16] thus allowing the synthesis of 3*H*-pyrrolo[2,3-*c*]isoquinolines **4**. Notably, the background formation of pyrrole-fused indenes via C−H insertion into copper carbenes was not detected.[14c] As shown in Table 3, initial investigation of *N*-protecting groups of the ynamides **3** demonstrated that the reaction could proceed smoothly with different sulfonyl groups, affording the desired tricyclic heterocycles **4a**–**4d** in 58–80% yields. In addition, a series of different aryl-substituted *N*-propargyl (azido)ynamides were also examined, and the corresponding pyrrole-fused isoquinoline products **4e**–**4n** were formed in 70–94% yields. Moreover, thienyl- and methyl-substituted *N*-propargyl (azido)ynamides were readily tolerated to produce the desired products **4o** and **4p** in 72% and 66% yields, respectively. This cascade cyclization also occurred efficiently for various phenyl rings bearing both electron-withdrawing and -donating groups, and products **4q**–**4u** were obtained in 78–91% yields. The molecular structure of **4m** was confirmed by X-ray diffraction.[18] Thus, this cascade cyclization provides a highly convenient and practical route for preparation of useful 3*H*-pyrrolo[2,3-*c*]isoquinolines.[20]

Table 3. Reaction scope of the cascade cyclization of *N*-propargyl (azido)ynamides **3**.[a]



[a] Reaction conditions: **3** (0.2 mmol), DDQ (0.4 mmol), $Cu(CH_3CN)_4PF_6$ (0.02 mmol), DCE (4 mL), RT, 5 h, in vials; isolated yields are reported. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Besides intramolecular trapping of the presumable α-imino copper carbenes by the alkene and alkyne moieties, this copper-catalyzed tandem reaction could also be applicable to intermolecular trapping by olefins. As shown in Eq. (1), the treatment of azide-ynamides **5** with 10 equiv of styrene at 60 °C by employing 10 mol % of $Cu(CH_3CN)_4BF_4$ as catalyst led to the efficient formation of spiro-cyclopropane products **6a**–**6b** in 76–80% yields with excellent diastereoselectivities (d.r. > 20/1). Importantly, this result further supports that the α-imino copper carbene intermediate is involved in this cascade cyclization. The molecular structure of **6a** was confirmed by X-ray diffraction.[18] It is notable that no intramolecular *ortho*-aryl C–H insertion was observed, and in particular, this insertion product was not detected even in the absence of styrene.[16]



After establishing a general and reliable method for this copper-catalyzed tandem reaction of azide-ynamides, we focused on the development of a chiral copper complex-catalyzed enantioselective version. That is, the catalytic asymmetric cascade cyclization of *N*-allyl (azido)ynamides **1** may lead to the synthesis of chiral cyclopropanation products **2** with three contiguous stereocenters. Although the use of chiral phosphine ligands failed to give the satisfactory enantioselectivity, high enantioselectivity could be achieved by employing chiral BOX ligands, as summarized in Table 4. In the presence of 10 mol % of $Cu(CH_3CN)_4PF_6$ and 12 mol % of BOX ligand **L1** in DCE at 50°C, the cascade cyclization of (azido)ynamide **1a** could afford the desired chiral cyclopropanation product **(-)-2a** in 63% yield with the e.r. of 77:23 (entry 1). Other typical BOX ligands **L2**−**L4** were then examined, but no significant improved enantioselectivity was achieved (entries 2–4). To our delight, increasing the steric hindrance of the ligands had a significant improvement on the enantioselectivities of product **(-)-2a** (entries 5–9), and an e.r. of 90.5:9.5 was achieved by using **L7** as chiral ligand (entry 7).[21] Other solvents such as DCM and $CHCl_3$ were also investigated, but failed to improve the enantioselectivity (entries 10 and 11). The use of $NaBAr^F{}_4$ (12 mol %) as additive or $Cu(CH_3CN)_4BF_4$ (10 mol %) as catalyst led to slightly decreased enantioselectivities (entries 12 and 13). Gratifyingly, the yield could be improved to 85% by increasing the loading of copper complex, and the e.r. was almost unchanged (entry 14).

The scope of this asymmetric cascade cyclization was next examined under the optimal reaction conditions (Table 4, entry 14). As depicted in Table 5, this asymmetric cyclization was also viable for the construction of chiral piperidine-fused tetracyclic heterocycle **(-)-2w** in 51% yield with the e.r. of 96:4. Different alkyl substituents at the terminal alkene moiety were then investigated. To our delight, the methyl- and ethyl-substituted (azido)ynamides led to a significantly improved enantioselectivities, affording the desired chiral tetracyclic heterocycle product **(-)-2x** (65%, e.r. of 95.5:4.5) and **(-)-2y** (68%, e.r. of 96.5:3.5), respectively. The reaction also proceeded smoothly with other substrates such as ^{n}Pr-, ^{i}Pr-, ^{n}Bu- and Cy-substituted (azido)ynamides to produce thedesired products **(-)-2aa**–**(-)-2ad** in 57–68% yields with the e.r. of 90:10–93:7. Of note, terminal alkene substituted (azido)ynamide was also suitable substrate to deliver the corresponding product **(-)-2ae** in 41% yield and e.r. of 90:10. Considering that the methyl substituted substrates could be prepared from readily available crotyl alcohol, we chose this kind

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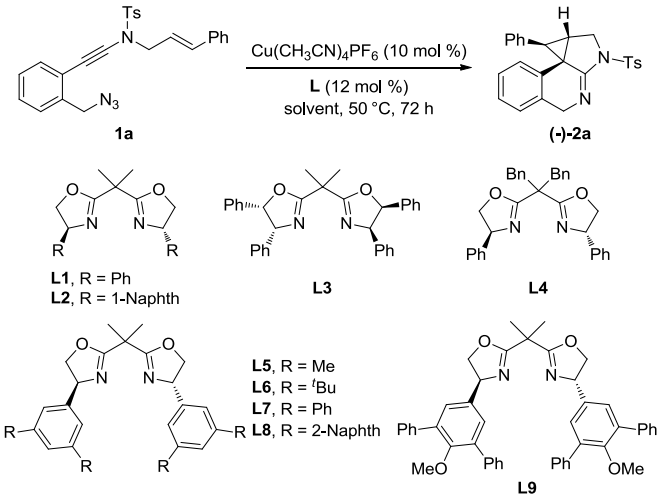
Table 4. Optimization of reaction conditions for the asymmetric cascade cyclization of *N*-styryl (azido)ynamide **1a**.[a]

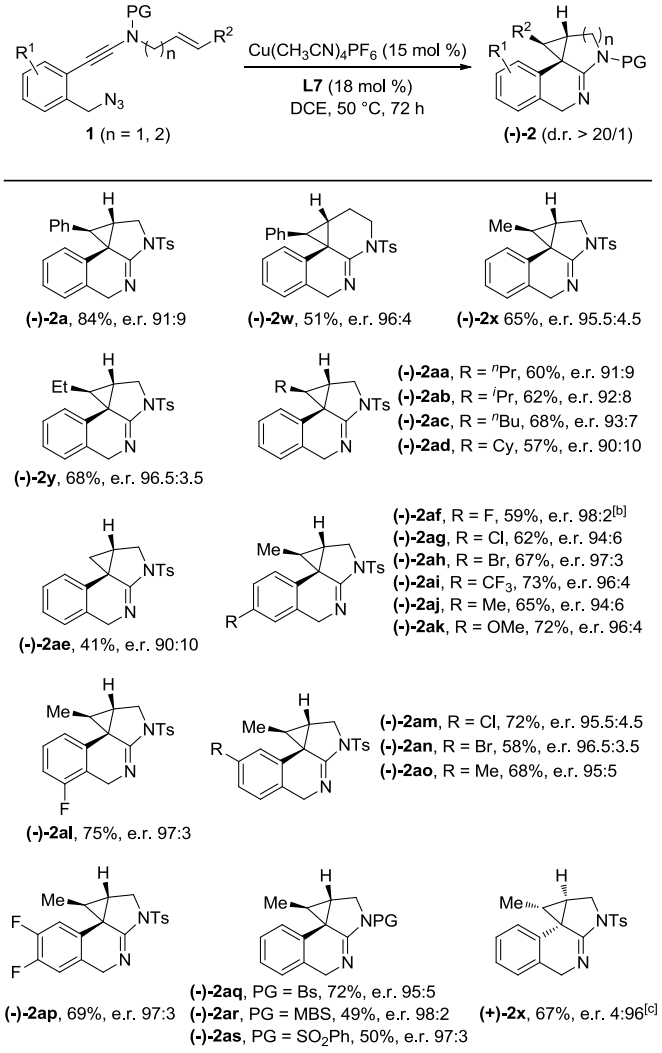


Entry	L	Solvent	Yield [%][b]	E.r.[c]
1	**L1**	DCE	63	77:23
2	**L2**	DCE	67	77.5:22.5
3	**L3**	DCE	62	79:21
4	**L4**	DCE	25	73:27
5	**L5**	DCE	44	86:14
6	**L6**	DCE	57	89:11
7	**L7**	DCE	56	90.5:9.5
8	**L8**	DCE	32	84:16
9	**L9**	DCE	55	88:12
10	**L7**	DCM	60	87:13
11	**L7**	$CHCl_3$	65	62:38
12[d]	**L7**	DCE	59	88.5:11.5
13[e]	**L7**	DCE	65	85:15
14[f]	**L7**	**DCE**	**85**	**91:9**

[a] Reaction conditions: **1a** (0.05 mmol), $Cu(CH_3CN)_4PF_6$ (0.005 mmol), L (0.006 mmol), DCE (1 mL), 50 °C, 72 h, in Schlenk tubes. [b] Measured by ^1H NMR using 2,6-dimethoxytoluene as the internal standard. [c] Determined by HPLC analysis. [d] $NaBAr^F_4$ (12 mol %) was employed as additive. [e] $Cu(CH_3CN)_4BF_4$ (0.005 mmol) was used as catalyst. [f] $Cu(CH_3CN)_4PF_6$ (15 mol %), **L7** (18 mol %). $NaBAr^F_4$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate.

of substrates for further reaction scope studies. Then, a wide array of (azido)ynamides bearing electron-withdrawing and -donating substituents at different positions of the phenyl group could be smoothly transformed into the expected chiral products **(-)-2af–(-)-2ap** in moderate to good yields (58–75%) and high enantioselectivities (e.r. of 94:6–98:2). Besides the Ts-protected ynamide **1a**, (azido)ynamides bearing various *N*-protected groups such as Bs-, MBS- and SO_2Ph were also tolerated, and the desired products **(-)-2aq** (72%, e.r. of 95:5), **(-)-2ar** (49%, e.r. of 98:2), **(-)-2as** (50%, e.r. of 97:3) were obtained, respectively. By employing BOX ligand **L7** with opposite configuration, the reaction also occurred smoothly to produce the desired **(+)-2x** in 67% yield and e.r. of 4:96 with the opposite enantioselectivity. Once again, excellent diastereoselectivities (d.r. > 20/1) were achieved in all cases. Attempts to expand this asymmetric catalysis to an intermolecular reaction with styrene have been unsuccessful as yet.

Table 5. Reaction scope of the asymmetric cascade cyclization of *N*-allyl (azido)ynamides **1**.[a]



[a] Reaction conditions: **1** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (0.015 mmol), **L7** (0.018 mmol), DCE (1 mL), 50 °C, 72 h, in Schlenk tubes; isolated yields are reported; e.r.'s are determined by HPLC analysis. [b] $Cu(CH_3CN)_4PF_6$ (20 mol %), **L7** (24 mol %). [c] **L7** with opposite configuration was employed as chiral ligand. MBS = 4-methoxybenzenesulfonyl.

Further synthetic transformations of the as-synthesized polycyclic N-heterocycles were then explored (Scheme 2). First, a gram-scale reaction of 1.11 g of (azido)ynamide **1a** was carried out under standard conditions, and 0.79 g of the desired product **2a** was furnished in 76% yield, demonstrating the reliability of the protocol. Then, facile deprotection of **2a** by $LiAlH_4$ in MTBE (methyl *t*-butyl ether) led to the formation of the desired product **2at** in 86% yield. Of note, some compounds bearing this core

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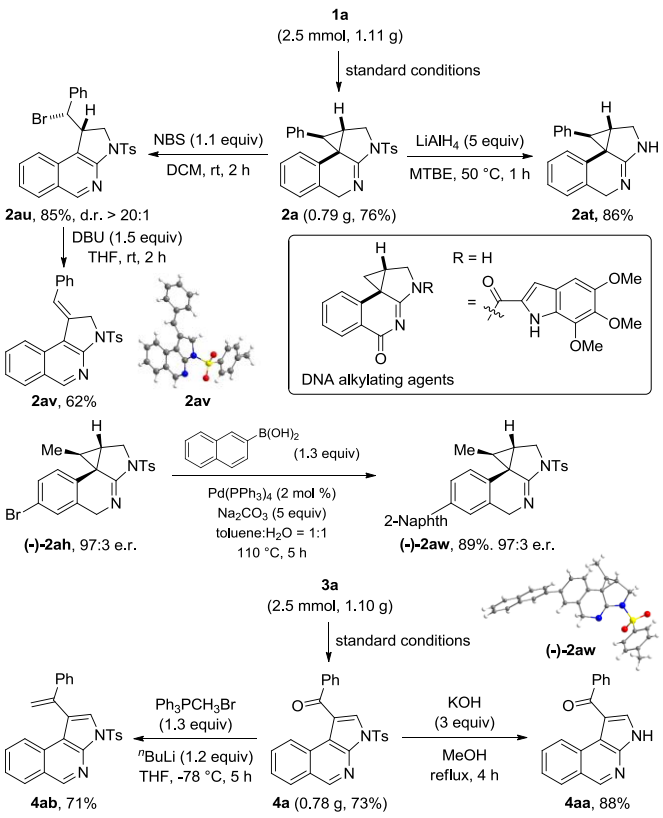
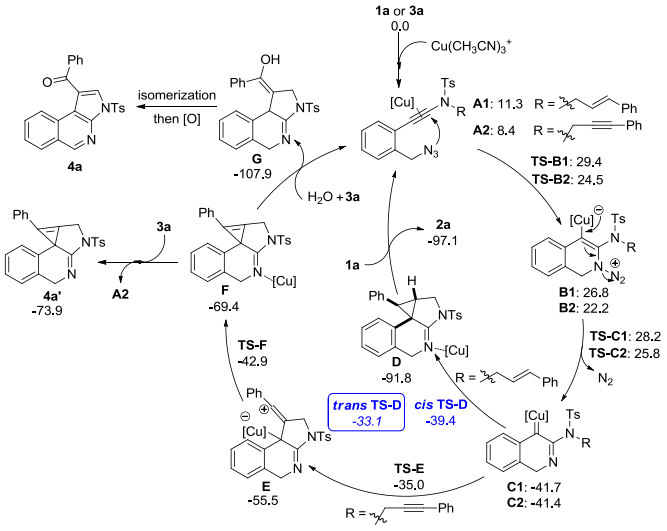
structure have been demonstrated as potent DNA alkylating agents.[22,23] Interestingly, the treatment of **2a** with NBS could led to diastereoselective ring opening to form the brominated isoquinoline **2au** in 85% yield (d.r. > 20/1).[10c] Subsequent β-elimination under basic conditions delivered the final tricyclic isoquinoline **2av** bearing exclusive *Z* configuration of the double bond in 62% yield, and its structure was confirmed by X-ray diffraction.[18] In addition, Suzuki coupling of chiral **(-)-2ah** with arylboronic acid produced the corresponding product **(-)-2aw** in 89% yield with well-maintained enantioselectivity. The molecular absolute configuration of **(-)-2aw** was confirmed by X-ray diffraction analysis,[18] which also determined the absolute configuration of the above chiral tetracyclic products **(-)-2**. Finally, some derivatizations of the tricyclic heterocycle **4a** were also carried out. The treatment of **4a**, also synthesized on a gram scale in 73% yield, with KOH and phosphorus ylide could afford the corresponding deprotection product **4aa** in 88% yield and alkenylation product **4ab** in 71% yield, respectively.



Scheme 2. Gram-scale reaction and synthetic transformations.

On the basis of the above experimental results, previous protocols on the azide-alkyne cyclization[2,12] and density functional theory (DFT) calculations, a plausible mechanism for the synthesis of polycyclic N-heterocycles **2a** and **4a** is depicted in Scheme 3. Initially, intramolecular nucleophilic attack of azido group to the copper-activated ynamide moiety via the six-membered ring transition state **TS-B** affords the vinyl copper intermediate **B**, followed by elimination of N_2, generating the α-imino copper carbene intermediate **C**. This copper carbene species is likely highly electrophilic,[24] and can be further trapped by different nucleophilic moieties. In the case of *N*-allyl (azido)ynamide **1a** as substrate, intramolecular highly diastereoselective cyclopropanation occurs to deliver the desired product **2a** and regenerate the copper catalyst. Of note, the activation barrier for the *trans*-isomer is higher than the desired *cis*-isomer by 6.3 kcal/mol. In the case of *N*-propargyl (azido)ynamide **3a**, intermediate **C** would be trapped by the *N*-propargyl group, leading to the formation of the vinyl cation intermediate **E**, which can be converted into the thermodynamically favorable cyclopropene intermediate **F**. Subsequent ring opening of cyclopropene intermediate **F** by trace water in the reaction system, followed by tautomerism/dehydrogenative oxidation[11d] furnishes the final product **4a**. In the cases where chiral copper complexes are employed, the reaction undergoes asymmetric cyclopropanation with high stereoselectivity to eventually furnish the chiral tetracyclic N-heterocycles **2**. Finally, it is notable that the reaction pathway involving the triazole formation via azide-alkyne cycloaddition[17] is less likely as the reaction would not afford the desired products by this way.[16]



Scheme 3. Plausible reaction mechanism. The relative free energies are given in kcal/mol.

Conclusions

In summary, we have developed an efficient copper-catalyzed cascade cyclization of azide-ynamides via α-imino copper carbene intermediates, which represents the first generation of α-imino copper carbenes directly from alkynes. This protocol enables the practical and divergent synthesis of an array of polycyclic N-heterocycles in generally good to excellent yields with broad substrate scope and excellent diastereoselectivities. Moreover, such an asymmetric azide-ynamide cyclization has been achieved with high enantioselectivities (up to 98:2 e.r.) by employing BOX-Cu complexes as chiral catalysts. Thus, this protocol constitutes the first example of asymmetric azide-alkyne cyclization. It is worth noting that this process begins from an acyclic precursor with no stereocenters and assembles a new tricyclic backbone containing three new stereocenters with high stereospecificity in one step under mild conditions. In addition, the proposed mechanistic rationale for this cascade cyclization is also strongly supported by theoretical calculations.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · metal carbene · alkynes · cyclization · heterocycles

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Asymmetric Catalysis

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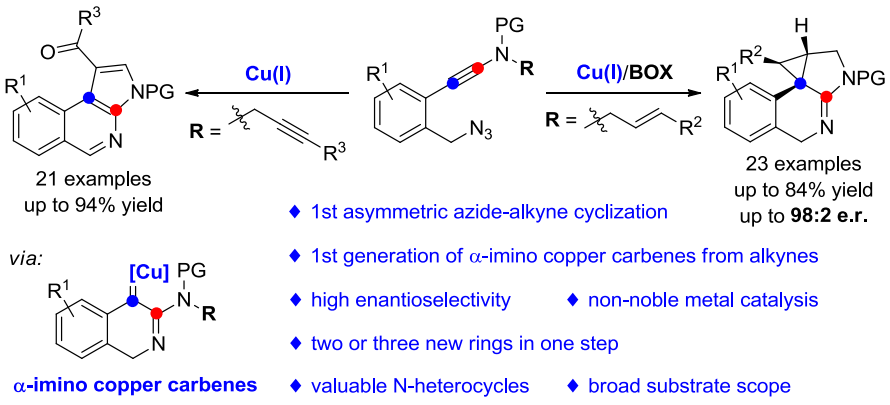
Copper-Catalyzed Azide-Ynamide Cyclization for Generation of α-Imino Copper Carbenes: Divergent and Enantioselective Access to Polycyclic N-Heterocycles



An efficient copper-catalyzed cascade cyclization of azide-ynamides via α-imino copper carbene intermediates is disclosed, enabling divergent synthesis of polycyclic N-heterocycles in generally good to excellent yields with broad substrate scope and excellent diastereoselectivities (d.r. > 20/1), which represents the first generation of α-imino copper carbenes directly from alkynes. Moreover, such an asymmetric azide-ynamide cyclization has been achieved with high enantioselectivities (up to 98:2 e.r.), which constitutes the first asymmetric azide-alkyne cyclization.