Organic Letters

Copper-Catalyzed Cascade Reaction via Intramolecular Hydroamination Cyclization of Homopropargylic Amines and Intermolecular Povarov Reaction with Imines

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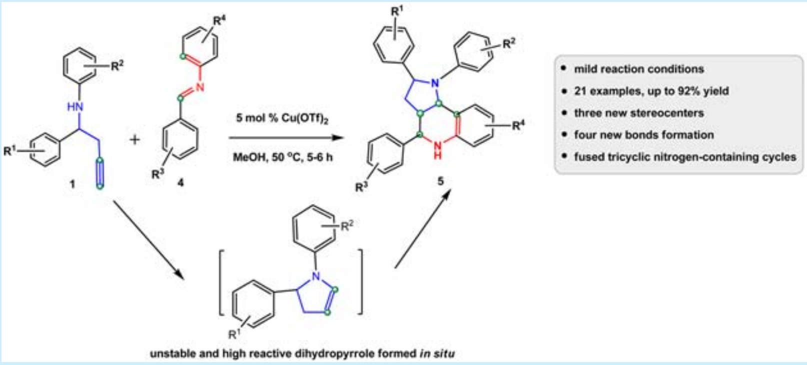
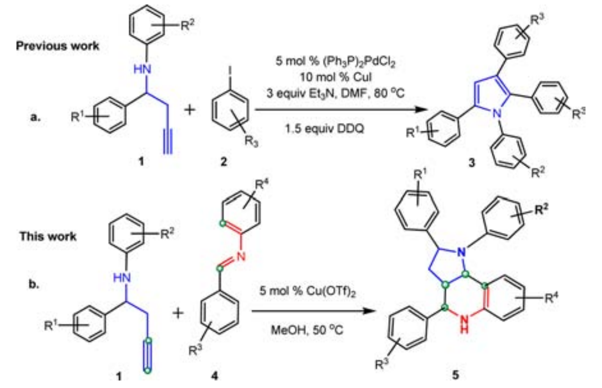
Supporting Information



ABSTRACT: A new one-pot cascade reaction of homopropargylic amines with simple imines is developed in the presence of $Cu(OTf)_2$ and affords a series of hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline derivatives in good to high yields. This reaction proceeds through an intramolecular hydroamination cyclization of homopropargylic amine to generate a highly reactive dihydropyrrole intermediate in situ. It subsequently reacts with imine via an intermolecular inverse-electron-demand aza-Diels−Alder reaction and a 1,3-H shift to give the fused pyrroloquinoline structures, forming two new C−C bonds and one C−N bond and one N−H bond.

Homopropargylic amine is a *β*-amino alkyne that contains two functional groups, an amino group and a triple bond. Taking full advantage of these two functional groups at the same time results in an elegant reaction: metal-catalyzed intramolecular 5-*endo-dig* cyclization of homopropargylic amines for the synthesis of five-membered *N*-containing heterocyclic compounds.[1] This cyclization usually involves the formation of a sp^2 C−M bond, and trapping of this sp^2 C−M bond by a proton occurs in most cases.[2] Recently, some examples of exploration of this sp^2 C−M bond to generate a C−C bond have been reported.[3] For example, we have developed a tandem reaction of homopropargylic amine **1** to construct a series of multisubstituted pyrrole derivatives **3** by reacting it with aryl iodides **2** (Scheme 1, a).[4] As a part of our continuous program aimed at exploring the diverse reactivity of homopropargylic amine in organic synthesis, we envisioned that the cyclization of homopropargylic amines in the presence of triple bond activators will produce a highly reactive dihydropyrrole, an enamine, which might be further applied to other transformations. Therefore, the typical Povarov reaction, an inverse-electron-demand aza-Diels−Alder reaction (IEDDA reaction) between 2-azadienes and electron-rich olefins, was chosen to investigate the reactivity of enamine formed in situ, which may act as electron-rich olefin dienophile.[5] To our delight, the cascade hydroamination cyclization−Povarov reaction was expectedly realized between homopropargylic amine **1** and imine **4** in the presence of

Scheme 1. Possible Reactions of Homopropargylic Amines



Received: March 19, 2016
Published: April 29, 2016

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DOI: 10.1021/acs.orglett.6b00804
Org. Lett. 2016, 18, 2367−2370

copper triflate (Scheme 1, b). Through this strategy, an arsenal of pyrroloquinoline derivatives **5** can be facilely and highly efficiently constructed in one pot, which would offer a new avenue to fabricate substituted nitrogen-containing fused polyheterocyclic compounds. The hexahydropyrrolo[3,2-*c*]-quinoline motif is a unique nitrogen-containing heterocycle. It can be found in the alkaloids of *Martinella iquitosensis*, such as martinellic acid (**6a**) and martinelline (**6b**), which exhibit interesting biological activity (Figure 1).[6] Additionally, it is worth noting that this reaction renders several distinguishing features: (1) a fused tricyclic pyrroloquinoline, which has one more nitrogen-containing heterocycle than that of elegant Povarov reaction of imine and electron-rich olefin, is generated in this reaction, and (2) the cyclic enamine formed in situ without a special protecting group, an unstable dihydropyrrole which is difficult to prepare in advance, is suggested to be reactive in the Povarov reaction, as it expands previous limited *N*-protected (*N*-Ts, *N*-Boc, or *N*-Cbz) dihydropyrroles.[7]

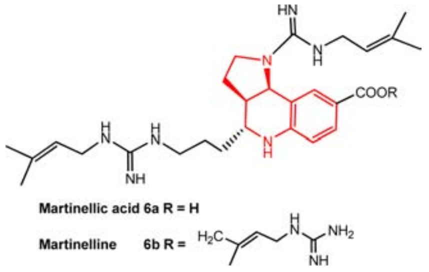
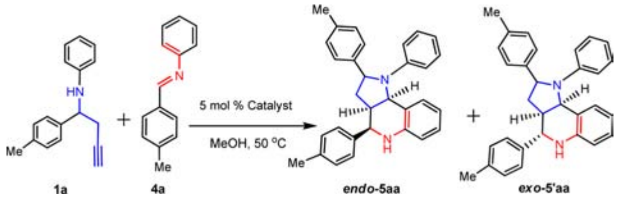


Figure 1. Natural products from the roots of the Amazonian plant *Martinella iquitosensis.*

This interesting cascade sequence intrigued us and prompted us to investigate the reaction parameters in greater detail to evaluate their impact on the outcome of the reaction. The homopropargylic amine (**1a**) and imine (**4a**) were selected as model substrates. π-Acidic metal catalysts, Au/Ag and $PtCl_2$, were first employed to catalyze this reaction. However, the starting material remained untouched in these two cases (Table 1, entries 1 and 2). Copper(II) trifluoromethanesulfonate, $Cu(OTf)_2$, was then used as a metal catalyst in the reaction of homopropargylic amine and imine. Gratifyingly, this reaction gave high total yields of pyrroloquinoline **5** and **5′** (*endo-* and *exo-*) in MeOH at 50 °C (entry 3). The absolute configuration of *exo*-**5′aa** was unambiguously determined by a single-crystal X-ray diffraction (Figure S1).[8] Other metal triflates, such as $Fe(OTf)_3$, were screened, but no obvious improved result was obtained (entry 4). In the presence of $Zn(OTf)_2$ or $Hg(OTf)_2$, no reaction occurred (entries 5 and 6). Using CuCl, this reaction could also proceed smoothly in MeOH at 50 °C and deliver the corresponding pyrroloquinoline in good total yields (entry 7). In addition, the protic acid catalysts were also examined. However, both TfOH and PhCOOH have no effect on this reaction (entries 8 and 9). When PhCOOH was combined with $Cu(OTf)_2$, the reaction gave a result similar to that using only $Cu(OTf)_2$ (entry 10). On the basis of these outcomes, $Cu(OTf)_2$ was considered as the optimal catalyst. Other experimental parameters, such as solvent, the ratio of homopropargylic amine **1a** and imine **4a**, and the amount of catalyst as well as the system concentration, were then examined as shown in Tables S1–S3. It was found that the optimal reaction conditions were a 1.2:1 ratio of **1a**/**4a**, 5 mol % of $Cu(OTf)_2$, 0.1 M MeOH, 50 °C, in air.

Table 1. Screening of Catalysts in the Cascade Reaction of Homopropargylic Amine and Imine[a]

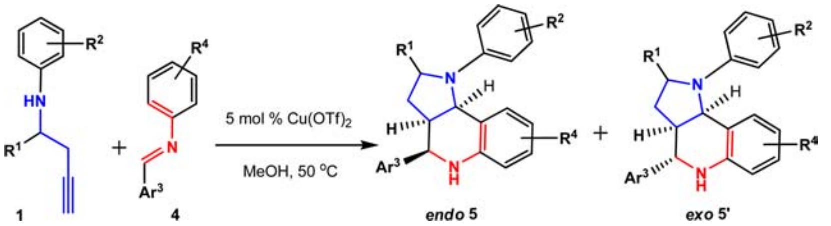


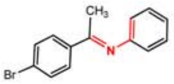
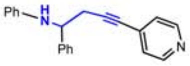
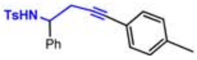
entry	catalyst	dr (*endo*/*exo*)[b]	total yield[c] (%)
1	$PPh_3AuCl/AgNTf_2$		
2	$PtCl_2$		
3	$Cu(OTf)_2$	62:38	92
4	$Fe(OTf)_3$	58:42	82
5	$Zn(OTf)_2$		
6	$Hg(OTf)_2$		
7	CuCl	63:37	79
8	TfOH (10 mol %)		
9	PhCOOH (10 mol %)		
10	$Cu(OTf)_2$ (5 mol %), PhCOOH (10 mol %)	56:44	86

[a]Reaction conditions: **1a** (0.24 mmol, 1.2 equiv), **4a** (0.2 mmol, 1.0 equiv), 5 mol % of catalyst, and MeOH (2 mL) were sequentially added into a tube. The reaction was carried out under the given reaction conditions, and the products were subsequently detected by TLC. [b]The diastereomeric ratios were determined on the basis of NMR analysis of the crude products. [c]Isolated yield.

With the optimal reaction conditions in hand, various homopropargylic amines and imines were then investigated to diversify the general pyrroloquinoline (Table 2). Remarkably, all substrates were competent in this cascade reaction and produced multiaryl-substituted pyrroloquinoline derivatives in good or high yields. For instance, regarding the 4-methylphenyl or 4-methoxyphenyl (R^1) homopropargylic amine substrates **1a** (R^2 = H) and **1c** (R^2 = Me), both electron-rich and electron-deficient substituents on two different aryl rings of imines (**4a**–**e**) could be smoothly converted to the desired products (Table 2, entries 1–5 and 7–9). For the nonsubstituted phenyl homopropargylic amine (**1e**), only the imines with electron-donating substituents could react smoothly and give the fused pyrroloquinolines (entries 11–13). In the case of homopropargylic amines bearing 4-F (**1d**) and 4-Br substituents (**1f**), the reactions delivered the corresponding products in good yields under the optimal reaction conditions with imine **4a**, respectively (Table 2, entries 10 and 14). Interestingly, when R^1 = H, R^2 = 4-$HOCH_2CH_2$, namely **1g**, the amine could also react with imines **4a** and **4i**, which even bears heteroaryl group, to efficiently produce the target compounds (entries 15 and 16). Unfortunately, when using the imines with aryl group bearing electron-withdrawing substituents (4-NO_2, **4i** and 4-Br, **4j**) on the *N* terminal, only trace of target compounds were obtained by ^1H NMR with most materials left (entries 17–18). Additionally, no reaction occurred in three cases, such as employing ketimine **4k** or homopropargylic amines **1h** or **1i** with internal alkyne (entries 19–21). The reason may be ascribed to the low activity and steric hindrance of ketimine **4k** and the large steric hindrance and electron effect of internal alkynes **1h** and **1i**. Notably, most reactions of homopropargylic amines and imines afforded diastereoisomers with *endo-* and *exo*-configured pyrroloquinolines. In particular, the imines **4e** and **4f** with 2-BrC_6H_4 (Ar^3) and 3-CN C_6H_4 (Ar^3) gave a single

Table 2. Scope of Homopropargylic Amines and Imines[a]



entry	R^1	R^2	1	Ar^3	R^4	4	*dr* (endo:exo)[b]	product 5	total yield (%)[c]
1	4-MeC$_6$H$_4$	H	**1a**	4-MeC$_6$H$_4$	H	**4a**	62:38	**5aa/5'aa**	92
2	4-MeC$_6$H$_4$	H	**1a**	4-MeC$_6$H$_4$	4-Me	**4b**	57:43	**5ab/5'ab**	73
3	4-MeC$_6$H$_4$	H	**1a**	Ph	4-OMe	**4c**	70:30	**5ac/5'ac**	67
4	4-MeC$_6$H$_4$	H	**1a**	4-NO$_2$C$_6$H$_4$	H	**4d**	52:48	**5ad/5'ad**	83
5	4-MeC$_6$H$_4$	H	**1a**	2-BrC$_6$H$_4$	H	**4e**	100:0	**5ae**	56
6	4-MeC$_6$H$_4$	4-Me	**1b**	4-MeC$_6$H$_4$	H	**4a**	55:45	**5ba/5'ba**	73
7	4-MeOC$_6$H$_4$	4-Me	**1c**	4-MeC$_6$H$_4$	H	**4a**	56:44	**5ca/5'ca**	77
8	4-MeOC$_6$H$_4$	4-Me	**1c**	4-MeC$_6$H$_4$	4-Me	**4b**	43:57	**5cb/5'cb**	72
9	4-MeOC$_6$H$_4$	4-Me	**1c**	3-CNC$_6$H$_4$	2-Me	**4f**	0:100	**5'cf**	52
10	4-MeOC$_6$H$_4$	4-F	**1d**	4-MeC$_6$H$_4$	H	**4a**	88:12	**5da/5'da**	80
11	Ph	H	**1e**	4-MeC$_6$H$_4$	H	**4a**	54:46	**5ea/5'ea**	82
12	Ph	H	**1e**	4-MeC$_6$H$_4$	4-Me	**4b**	46:54	**5eb/5'eb**	77
13	Ph	H	**1e**	4-MeC$_6$H$_4$	4-OMe	**4g**	40:60	**5eg/5'eg**	79
14	Ph	4-Br	**1f**	4-MeC$_6$H$_4$	H	**4a**	53:47	**5fa/5'fa**	71
15	H	4-HOCH$_2$CH$_2$	**1g**	4-MeC$_6$H$_4$	H	**4a**	53:47	**5ga/5'ga**	48
16	H	4-HOCH$_2$CH$_2$	**1g**	thiophene	4-Me	**4h**	50:50	**5gh/5'gh**	68
17	4-MeC$_6$H$_4$	H	**1a**	Ph	4-NO$_2$	**4i**	--	--	trace
18	Ph	H	**1e**	Ph	4-Br	**4j**	--	--	trace
19[d]	4-MeC$_6$H$_4$	H	**1a**			**4k**	--	--	--
20[e]			**1h**	4-MeC$_6$H$_4$	H	**4a**	--	--	--
21[e]			**1i**	4-MeC$_6$H$_4$	H	**4a**	--	--	--

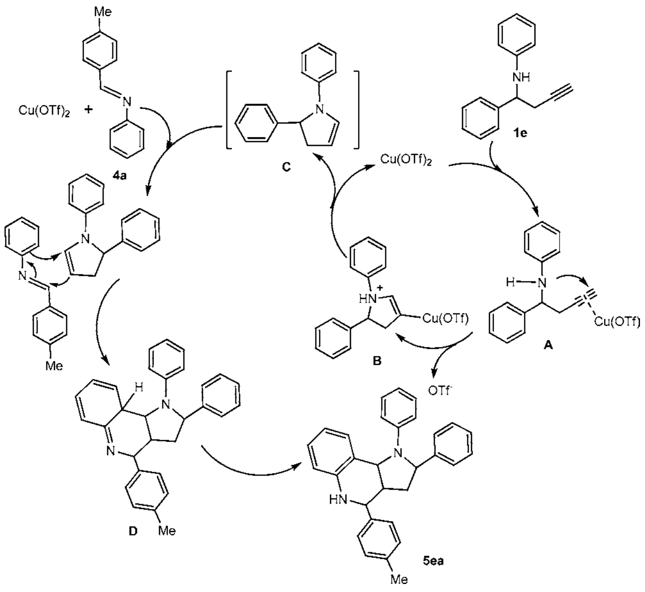
[a] Reaction conditions: **1** (0.24 mmol, 1.2 equiv), **4** (0.2 mmol, 1.0 equiv), 5 mol % of Cu(OTf)$_2$, and MeOH (2 mL) were sequentially added into a tube. The reaction was carried out at 50 °C in the air for 5−6 h, and the products were subsequently detected by TLC. [b] The diastereomeric ratios were determined based upon NMR analysis of the crude products. [c] Isolated yield. [d] Using ketimine derived from 4-bromoacetophenone. [e] The substrates were homopropagylic amines with internal alkyne.

endo- and *exo*-product in moderate yields, respectively (entries 5 and 9). Moreover, due to three new stereocenters formed in the products, some *endo*- or *exo*-configurational pyrroloquinolines have additional diastereoisomers. All products were racemic.

With the scope of this method established, the reaction mechanism was considered. The key intermediate is the formation of dihydropyrrole intermediate. A possible mechanism was proposed as shown in Scheme 2. The dihydropyrrole **C** was generated via a typical intramolecular hydroamination cyclization of terminal alkyne activated by Cu(OTf)$_2$. Subsequently, the formed unstable enamine attacked the imine **4a**, which was activated by Lewis acid Cu(OTf)$_2$, to render the intermediate **D**, followed by a 1,3-H shift to give the final product pyrroloquinoline **5ea** (Scheme 2).

In summary, we have established a simple, rapid, and high-yielding synthesis of diverse polyaryl-substituted hexahydropyrrolo[3,2-*c*]quinolines from simple homopropargylic amines and imines. Two main diastereomers, *endo*- and *exo*-, were obtained with the formation of five σ-bonds (C−N(1), C−H(1), C−C(2), N−H(1)) and three new stereogenic centers in a one-pot, sequential transformation. It should be noted that the highly reactive dihydropyrrole was formed in situ through intramolecular hydroamination cyclization of the homopropargylic amine and then subtly used as a dienophile in a subsequent Povarov reaction with imine. This strategy

Scheme 2. Possible Cascade Reaction Mechanism of Homopropargylic Amine and Imine



expands previous limited *N*-protected dihypyrroles in the Povarov reaction and provides a new route for the synthesis of diverse pyrroloquinoline derivatives. We believe that this intramolecular hydroamination cyclization of alkyne constitutes a particularly striking example of a one-pot reaction for the rapid assembly of molecular complexity, which should prove highly valuable in the context of the diversity-oriented synthesis. Our ongoing studies focus on an asymmetric variant and its extension toward the synthesis of other heterocyclic scaffolds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00804.

Procedures for the synthesis of homopropargylic amines and cascade reaction; NMR and HR-MS spectra of all pyrroloquinoline derivatives (PDF)
Characterization data (PDF)
X-ray data of compound *exo*-**5′aa** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (Grant No. 21372120) for this work. We also acknowledge support from the Collaborative Innovation Center of Chemical Science and Engineering (Tianjin).

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(8) Crystal data for the compound **5′aa**: $C_{31}H_{30}N_2$, MW) 430.58, triclinic, *P*-1; final *R* indices [$I > 2\sigma(I)$], R1 = 0.0448, wR2 = 0.1318, *R* indices (all data), R1 = 0.0637, wR2 = 0.1449, a = 10.116(2) Å, b = 10.554(2) Å, c = 11.501(2) Å, V = 1172.5(4) Å^3, T = 113 (2) K, Z = 2. Reflections collected/unique: 11808/5502 [R(int) 0.0285], number of observations [$I > 2\sigma(I)$] 5502, parameters) 300, goodness-of-fit on F_2) 1.005. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 1441746.