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Copper-catalyzed tandem *cis*-carbometallation/cyclization of imine-ynamides with arylboronic acids

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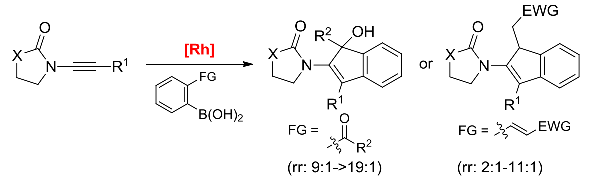
An efficient copper-catalyzed tandem regioselective *cis*-carbometallation/cyclization of imine-ynamides with arylboronic acids has been developed. This method leads to facile and practical synthesis of valuable 2,3-disubstituted indolines in moderate to excellent yields and features a broad substrate scope and wide functional group tolerance. Other significant features of this protocol include the use of readily available starting materials, high flexibility, simple procedure and mild reaction conditions.

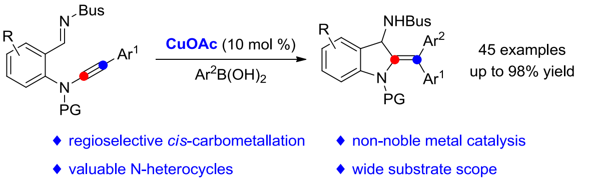
Transition-metal catalyzed tandem carbometallation/cyclization of alkynes by organoboronic acids with unsaturated moieties is a powerful method for the rapid assembly of structurally complex heterocycles and carbocycles.[1-6] However, compared with the carbonyl moieties,[2] transition-metal catalyzed arylative cyclization of alkynes with imine moieties has been far less exploited,[6] and these arylative cyclizations have been mostly limited to noble metal catalysts such as rhodium and palladium or special substrates such as 2-iminoarylboronic acids[6a,c] and dimethyl-tethered imine-alkynes due to Thorpe-Ingold effect.[6b] A likely reason for this paucity is that organoboronic acids may attack the highly electrophilic imine moieties directly.

Ynamides have proven to be powerful and versatile reagents in organic synthesis, and various efficient synthetic methods have been established in the past decade.[7] Despite these significant achievements, the above mentioned arylative cyclization based on ynamides has seldom been explored.[8,9] The only example was reported by Lam and co-workers for the synthesis of 2-amidoindenols or 2-amidoindenes through rhodium-catalyzed annulation of ynamides with arylboronic acids or esters containing an electrophilic functional group.[8a] Notable is that the reaction substrates are restricted to imidazolidinone- and oxazolidinone-derived ynamides as the carbonyls of these substrates provide coordination with metal catalyst to achieve the good regioselectivity (Scheme 1a). As a continuation of our work on developing ynamide chemistry for heterocycle synthesis,[10] we herein report an efficient copper-catalyzed highly regioselective arylative cyclization of imine-ynamides with arylboronic acids (Scheme 1b).[11] This protocol enables facile and practical synthesis of valuable 2,3-disubstituted indolines[12] in moderate to excellent yields and features a broad substrate scope and wide functional group tolerance.

a) Rh-catalyzed carbometallation/cyclization of ynamides with 2-acylarylboronic acids



b) Cu-catalyzed carbometallation/cyclization of imine-ynamides with arylboronic acids (this work)



Scheme 1 Tandem carbometallation/cyclization of ynamides with arylboronic acids.

At the outset, Bus-protected imine-ynamide **1a** and phenylboronic acid **2a** were used as the model substrates, and selected results are outlined in Table 1. We were delighted to find that the desired 2,3-disubstituted indoline **3a** could be formed in 50% yield in the presence of 10 mol % of CuOTf as catalyst and MeOH as solvent at 50 °C (Table 1, entry 1). Other typical copper(I) catalysts such as CuI and $Cu(MeCN)_4PF_6$ were not effective (Table 1, entries 2 and 3), and significant formation of hydrolyzed byproduct **3a′** was observed in the former case (Table 1, entry 2). Gratifyingly, 90% yield of product **3a** was achieved by employing CuOAc as catalyst (Table 1, entry 4). It is notable that the use of $Cu(OAc)_2$ as catalyst or the reaction at room temperature led to poor results (Table 1, entries 5 and 6). When 1.5 equiv of **2a** was employed, the yield of

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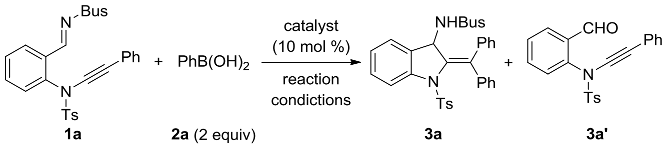
3a significantly decreased (Table 1, entry 7). Finally, it was found that **3a′** was obtained as the main product in case of using EtOH as solvent (Table 1, entry 8) or Ts-protected imine ynamide **1a′** as substrate.[13]

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Reaction Conditions	Yield[b] (%) 3a	3a'
1	CuOTf	MeOH, 50 °C, 19 h	50	<1
2	CuI	MeOH, 50 °C, 48 h	20	28
3	$Cu(MeCN)_4PF_6$	MeOH, 50 °C, 44 h	14	<1
4	**CuOAc**	**MeOH, 50 °C, 0.5 h**	**90**	**<1**
5	$Cu(OAc)_2$	MeOH, 50 °C, 98 h	19	12
6[c]	CuOAc	MeOH, rt, 120 h	28	20
7[d]	CuOAc	MeOH, 50 °C, 0.5 h	44	7
8	CuOAc	EtOH, 50 °C, 15 h	17	42

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (0.01 mmol), solvent (0.25 mL), rt–50 °C, 0.5–120 h, in Schlenk tubes. [b] Measured by ^1H NMR using diethyl phthalate as the internal standard. [c] 22% of **1a** remained unreacted. [d] 1.5 equiv of **2a** was used. Bus = *tert*-butylsulfonyl.

Under the optimal reaction conditions (Table 1, entry 4), the scope of the copper-catalyzed carbometallation-cyclization was examined. As shown in Table 2, a wide range of arylboronic acids with electron-withdrawing substituents such as F, Cl, Br, I on para-position and F, Cl, Br, CHO on meta-position were suitable substrates, delivering the corresponding 2,3-disubstituted indolines **3b–3h** and **3o–3r** in 44–98% yields. In addition, arylboronic acids bearing electron-donating substituents such as Me, OMe, SMe, phenyl on para-position and Me, OMe, OBn, CH_2OH on meta-position were also tolerated to produce the desired **3i–3n** and **3s–3v** in 53–90% yields. Moreover, the reaction was also extended to the disubstituted arylboronic acids, leading to the desired **3w–3z** in 58-76% yields. Finally, the reaction proceeded smoothly with 2-naphthyl and 5-indolyl boronic acids to afford the anticipated indolines **3aa** (68%), **3ab** (85%), respectively. The molecular structure of **3b** was confirmed by X-ray diffraction (Figure 1).[14]

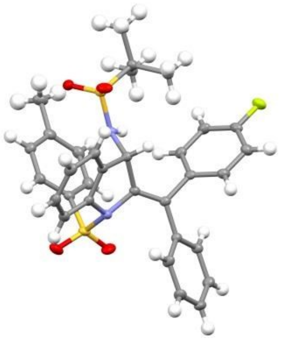
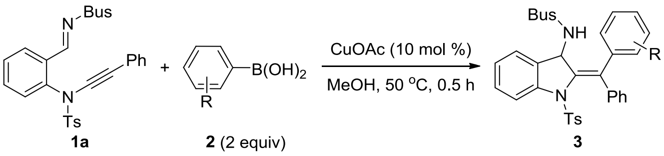
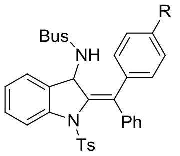


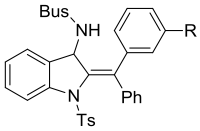
Figure 1 Structure of compound **3b** in its crystal. Thermal ellipsoids are shown at 50% probability.

Table 2 Copper-catalyzed reaction of imine-ynamide **1a** with different arylboronic acids **2**[a]

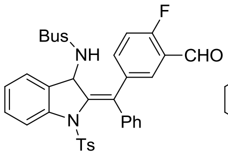




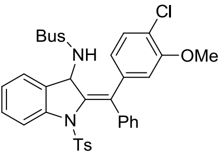
3a, R = H, 89%
3b, R = F, 70%
3c, R = Cl, 53%[b]
3d, R = Br, 53%
3e, R = I, 44%
3f, R = CO_2Me, 96%
3g, R = Ac, 98%
3h, R = CF_3, 64%
3i, R = Me, 62%[c]
3j, R = OMe, 53%[b]
3k, R = OCF_3, 64%
3l, R = SMe. 78%[b]
3m, R = Ph, 63%[b]
3n, R = TMS, 90%



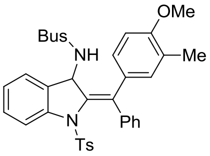
3o, R = F, 64%
3p, R = Cl, 80%
3q, R = Br, 70%
3r, R = CHO, 90%
3s, R = Me, 68%
3t, R = OMe, 66%
3u, R = OBn, 81%
3v, R = CH_2OH, 68%



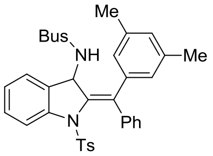
3w, 61%



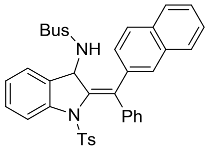
3x, 64%



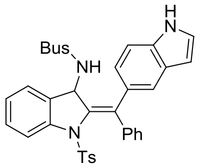
3y, 76%



3z, 58%



3aa, 68%



3ab, 85%

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), CuOAc (0.02 mmol), MeOH (0.5 mL), 50 °C, 0.5 h, in Schlenk tubes; isolated yields are reported. [b] 1 h. [c] 3 equiv of **2** was used.

The treatment of phenylboronic acid **2a** with different imine-ynamides **1** was then explored under the above copper catalysis. As depicted in Table 3, different *N*-protection groups such as MBS, SO_2Ph, Bs and Ms were compatible with this cyclization to produce the corresponding 2,3-disubstituted indolines **3ac–3af** in 52–82% yields. The cascade reaction also occurred smoothly with various ynamides bearing electron-withdrawing groups on both meta- and para-positions and electron-donating groups, leading to the desired products **3ag–3an** in good to excellent yields. In addition, different substituents such as F, Cl, and Me on the phenyl ring were also examined and the expected products **3ao–3as** were formed in 61–98% yields. Of note, attempts to extend the reaction to the alkyl-substituted and terminal ynamides or the styrylboronic acid only led to the formation of the corresponding products in low yields (<30%).[13] Thus, this method provides a highly efficient and practical route for the preparation of synthetically useful 2,3-disubstituted indolines.

Further synthetic transformations of the 2,3-disubstituted indolines were then explored, as shown in Scheme 2. First, indoline **3a** could be synthesized on a preparative scale in 81% yield under standard conditions, Interestingly, attempts to deprotect the *N*-Ts group in **3a** by the treatment with Na/naphthalene led to the formation of the 2-benzhydryl-1*H*-indole **4a** in 76% yield. In addition,

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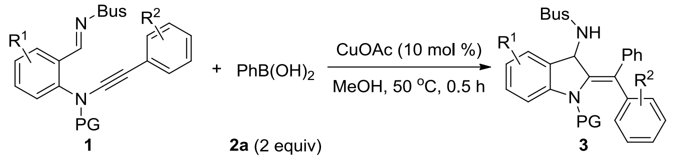
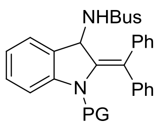
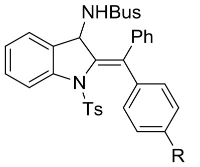
the treatment of **3a** with $AlCl_3$ and anisole afforded the corresponding 2-indolylmethanol **5a** in 57% yield, which may serve as a versatile building block in catalytic cycloadditions.[15] The molecular structure of **5a** was confirmed by X-ray diffraction (Figure 2).[14]

Table 3 Copper-catalyzed reaction of phenylboronic acid **2a** with different imine-ynamides **1**[a]

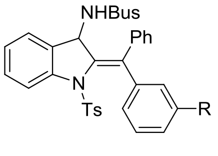




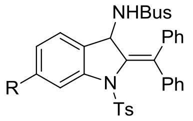
3ac, PG = MBS, 81%
3ad PG = SO_2Ph, 61%
3ae, PG = Bs, 52%
3af, PG = Ms, 82%



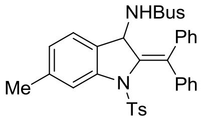
3ag, R = F, 87%
3ah, R = Cl, 78%
3ai, R = Br, 79%
3aj, R = CN, 77%
3ak, R = Me, 86%



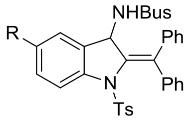
3al, R = F, 92%
3am, R = Br, 76%
3an, R = Me, 84%



3ao, R = F, 98%
3ap, R = Cl, 74%

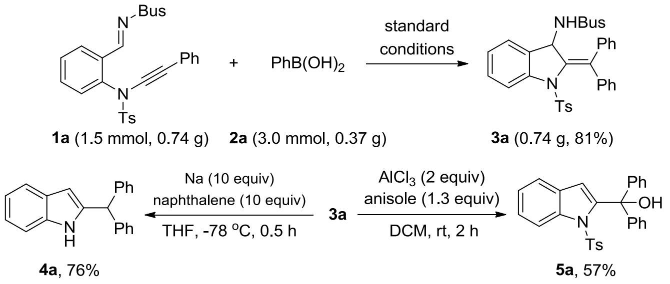


3aq, 76%



3ar, R = Cl, 61%
3as, R = Me, 93%

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), CuOAc (0.02 mmol), MeOH (0.5 mL), 50 °C, 0.5 h, in Schlenk tubes; isolated yields are reported. PG = protecting group, MBS = 4-methoxybenzenesulfonyl, Bs = 4-bromobenzenesulfonyl.



Scheme 2 Preparative-scale reaction and synthetic transformations.

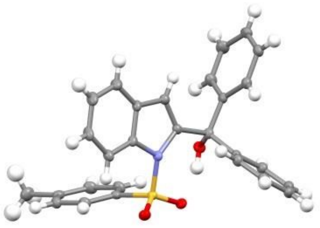
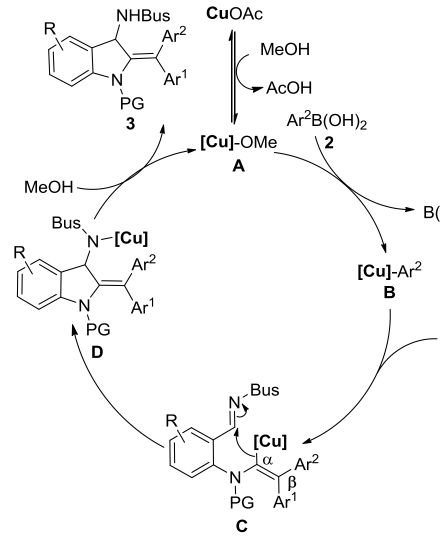


Figure 2 Structure of compound **5a** in its crystal. Thermal ellipsoids are shown at 50% probability.

Based on the above experimental observations and previous protocols on the transition-metal-catalyzed tandem carbometallation/cyclization of alkynes,[1-6] a plausible mechanism for the formation of 2,3-disubstituted indolines **3** is proposed (Scheme 3). Initially, the transmetallation between arylboronic acids **2** and copper(I) species **A** produces aryl copper intermediates **B**, which react with imine-ynamides **1** via regioselective *cis*-carbometallation, generating the vinyl copper intermediates **C**. Of note, previous nucleophilic addition to ynamides generally occurs on the α position of ynamides.[7a,9,16] Subsequent intramolecular cyclization leads to the *N*-copper intermediates **D**, which can be eventually transformed into the target products **3** upon protonation and regenerate the copper catalyst.



Scheme 3 Plausible reaction mechanism.

In summary, we have developed an efficient copper-catalyzed tandem *cis*-carbometallation/cyclization of imine-ynamides with arylboronic acids, where a unique regioselectivity is achieved. This method leads to facile and practical synthesis of valuable 2,3-disubstituted indolines in moderate to excellent yields and features a broad substrate scope and wide functional group tolerance. Other significant features of this protocol include the use of readily available starting materials, high flexibility, simple procedure and mild reaction conditions. Further investigations into the asymmetric version of the current protocol are in progress in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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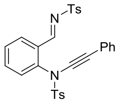
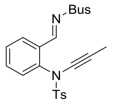
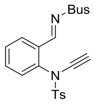


1a'



1s



1t

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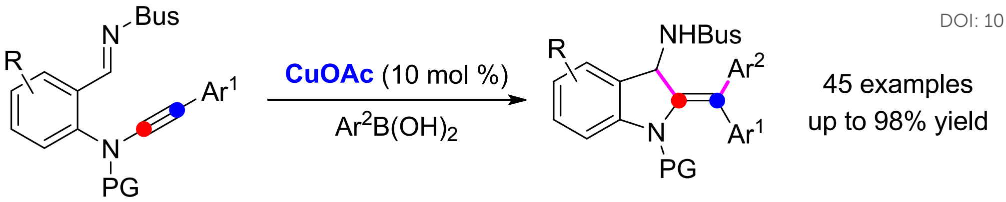

- ♦ regioselective *cis*-carbometallation
- ♦ non-noble metal catalysis
- ♦ valuable N-heterocycles
- ♦ wide substrate scope

An efficient copper-catalyzed regioselective *cis*-carbometallation/cyclization of imine-ynamides with arylboronic acids enables the facile and practical synthesis of valuable 2,3-disubstituted indolines.