Letter

Copper-Catalyzed Hydroxyl-Directed Aminoarylation of Alkynes

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Copper-Catalyzed Hydroxyl-Directed Aminoarylation of Alkynes

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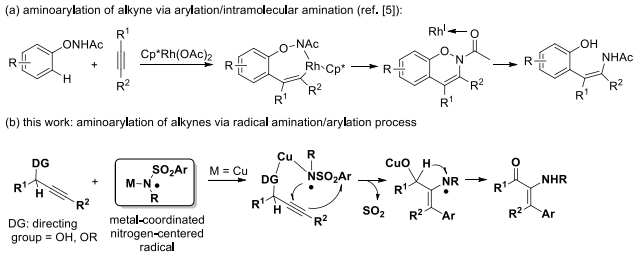
ABSTRACT: A facile, copper-catalyzed aminoarylation reaction of various aryl/alkyl alkynes was realized by utilizing *N*-fluoroarylsulfonimides (NFSI) as aminoarylation or amination reagent with hydroxyl as directing group. With this methodology, various α,β-unsaturated carbonyl compounds and indenones were efficiently constructed and the synthetic application for indole derivatives was also provided. The aminoarylation reactions operate via a regiospecific addition of copper coordinated nitrogen radical to C–C triple bond/C_{vinyl}–C_{aryl} bond formation followed by other series of radical processes.

Amines are ubiquitous functionality of overarching significance for a number of important research areas, including medicinal chemistry, total synthesis and material science.[1] Evolution of mild and highly selective C–N bond formation methods from readily available precursors is a long-standing goal of chemical research. Metal-catalyzed amino-difunctionalization reaction of alkynes represents a highly attractive amination method since various functional groups could be introduced to readily available starting materials besides the formation of a versatile enamine moiety.[2] Although metal-catalyzed hydroamination reaction of alkynes had made great achievement,[3] their amino-difunctionalization reactions have remained largely unexplored. Up to now, a reliable and predictable amino-difunctionalization methodology of internal alkynes to access tri-substituted enamine[3c] without forming N-heterocycles,[4] remains a formidable challenge.

Aminoarylation of alkynes can install nitrogen and aryl sources simultaneously to C–C triple bonds. To date, only one intermolecular aminoarylation example has been reported via rhodium-catalyzed alkyne arylation followed by intramolecular amination reaction (Scheme 1, a).[5] Recently, we realized an interesting amino-multi-functionalization reaction of alkynes for the synthesis of α-amino-α-aryl ketones,[6] although the regioselectivity for unsymmetric alkynes remains elusive in some examples. Based on the powerful selectivity control strategy utilizing directing group to coordinate with metal,[7] and our previous works of amination reaction based on nitrogen-centered radical,[8] we envision that by choosing a suitable directing group, the in-situ generated metal-coordinated nitrogen radical could be utilized to perform a highly regioselective amination reaction of unbiased alkynes (Scheme 1, b). In this communication, a novel hydroxyl group directed aminoarylation of alkynes with *N*-fluoroarylsulfonimides (NFSI) initiated by regiospecific addition of nitrogen radical to C–C triple bond, followed by radical C_{vinyl}–C_{aryl} bond formation to provide α,β-unsaturated carbonyl compounds was realized (Scheme 1, b). Notably, although amination based on metal-coordinated nitrogen radical has attracted much attention and some significant progress has been made,[9] so far, to our knowledge, amination reaction utilizing the double role of metal to coordinate with both nitrogen radical and directing group for site selectivity has never been demonstrated.



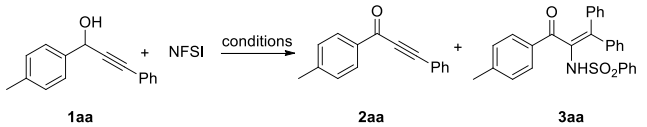
Scheme 1. Metal Catalyzed Aminoarylation of Alkynes

Radical reaction could be efficiently directed by alcohols and masked alcohols,[10] therefore, propargylic alcohols, which are among the most useful bifunctional building blocks available to the synthetic chemists,[11] are chosen for our synthetic design (Scheme 1, b). Initially, the reaction of propargylic alcohol **1aa** (0.3 mmol) with NFSI (1.2 equiv.) was investigated in the presence of CuCN (10 mol%). When the reaction was performed at 40 ^{o}C for 24 hours with anhydrous dichloromethane (DCM) as the solvent, only oxidation product **2aa** (11%) was formed and 82% of **1aa** was recovered (Table 1, entry 1). When 1.5 equiv. of pyridine was added to the above reaction, aminoarylation product **3aa**, containing an enamine moiety, was generated in 35%, along with 56% yield of **2aa** (Table 1, entry 2). There are some interesting features for above reactions: 1) a well known Meyer-Schuster rearrangement of propargylic alcohols through hydroxyl group migration[11a,11d] could also afford α,β–unsaturated carbonyl compounds, however, carbonyl group in **3aa** was formed by direct oxidation; 2) the common substitution reaction of hydroxyl group to form propargylic amide was not observed;[12] 3) the reaction of oxidation product **2aa** and NFSI under the same conditions (Table 1, entry 2) did not afford **3aa**.[13]

Further carefully investigation of the amazing aminoarylation reaction was next performed (to see Table S1). The yield of **3aa** could be increased to 53% under nitrogen atmosphere (Table 1, entry 3). With Et_3N or DBU as the additive, no desired aminoarylation product **3aa** was detected (Table 1, entries 4 and 5). In the absence of the copper catalyst, no reaction occurred (Table 1, entry 6). Other copper salts, such as CuCl and CuOTf did not improve the yields of **3aa** (Table 1, entries 7 and 8). Solvent screening showed that reactions in chloroform and dichloroethane (DCE) gave **3aa** in 30% and 35% yields, respectively (Table 1, entries 9 and 10); while no

desired **3aa** was detected in CH_3CN (Table 1, entry 11). To our delight, upon adding 0.3 g 4Å molecular sieves to the reaction, 83% of **3aa** was isolated (Table 1, entry 12). It should be noted that this aminoarylation reaction provides a facile and efficient access to enamides which are widely encountered in the scaffolds of natural products and functional materials.[14]

Table 1. Optimization of Reaction Conditions of 1aa with NFSI[a]



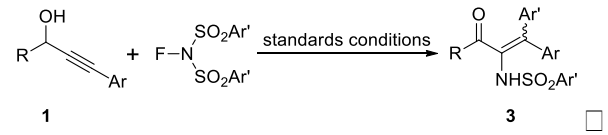
1aa **2aa** **3aa**

Entry	Catalyst	Additive	Solvent	**2aa** (%)	**3aa** (%)
1[b]	CuCN	None	DCM	11	0
2[b]	CuCN	Py	DCM	56	35
3	CuCN	Py	DCM	28	53
4	CuCN	Et_3N	DCM	0	0
5	CuCN	DBU	DCM	0	0
6	None	Py	DCM	0	0
7	CuCl	Py	DCM	0	46
8	CuOTf	Py	DCM	0	20
9	CuCN	Py	$CHCl_3$	0	30
10	CuCN	Py	DCE	0	35
11	CuCN	Py	CH_3CN	0	0
12[c]	**CuCN**	**Py**	**DCM**	**0**	**83**

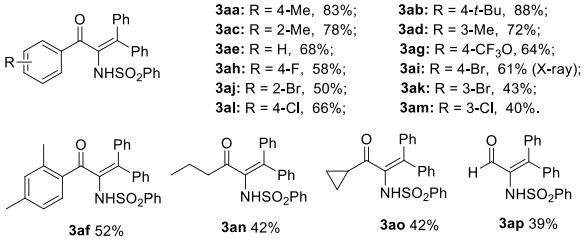
[a]General reaction conditions: **1aa** (0.3 mmol), NFSI (1.2 equiv.), catalyst (10 mol%), additive (1.5 equiv.), solvent (3 mL), 40 °C for 24 h under nitrogen atmosphere. Yields were determined after isolation of products by column chromatography. [b]The reaction was conducted under air. [c]0.3 g 4Å Molecular sieves were used.

With the optimized reaction conditions in hand (Table 1, entry 12), we turned to examine the generality of this alkyne aminoarylation reaction. As shown in Table 2, the tested 3-phenyl propargylic alcohol derivatives **1aa-am** with electron-donating group or electron-withdrawing group on aromatic ring reacted smoothly with NFSI to afford **3aa-am** in moderate to good yields. The structure of **3ai** was confirmed by X-ray diffraction analysis.[15] Aliphatic groups at C1 of propargylic alcohols, such as *n*-butyl (**1an**) and cyclopropyl (**1ao**) were compatible and the corresponding α-amino-β-aryl enones **3an** and **3ao** were obtained in a same yield. We also found that a primary propargylic alcohol (**1ap**) also proceeded under the optimal conditions to give the corresponding α,β-unsaturated aldehyde **3ap** in a reasonable yield (39%). Starting from 3-aryl substituted propargylic alcohols **1ba-bj**, the desired aminoarylative products **3ba-bj** were smoothly formed. In addition, we found that *E/Z*-isomerization of the C–C double bond in **3ba-bj** readily takes place,[16] even at room temperature in $CDCl_3$. The isomeric mixtures of **3ba-bj** in ratios ranging from 1:1 to 1:6.7 were obtained in total yields of 51-91%. Electron-rich aromatic substituted propargylic alcohols **1ba-be** and **1bj** gave much higher yields than electron-deficient aryl substituted **1bf-bh**. Aryl substituted **1bk** and **1bl** with strong electron-withdrawing group on the aromatic ring could not form the desired products. In addition, some other NFSI derivatives were used instead of NFSI to further explore the scope of this alkyne aminoarylation reaction. For NFR1 (*N*-fluoro-4-methyl-*N*-tosylbenzenesulfonamide) and NFR2 (*N*-fluoro-4-tert-butyl-*N*-tosylbenzenesulfonamide), the desired aminoaylation products **3ca** and **3cb** were obtained in 73% and 94% yields, respectively. For NFR3 (4-chloro-*N*-((4-chlorophenyl)sulfonyl)-*N*-fluorobenzenesulfonamide), product **3cc** was formed in a yield of 65%. These results showed that the transformation is more efficient for electron-rich aromatic rings than electron-poor ones in NFSI derivatives. In addition, the reaction between a masked alcohol, propargylic ether **1b** and NFSI provided aminoaylation product **3ap** in 29% yield (eq. 1). Under the same conditions, starting from propargylic ester **1c**, only a trace amount of **3ap** was detected (eq. 1).

Table 2. The Synthesis of α-Amino-β-aryl Unsaturated Carbonyl Compounds 3[a]

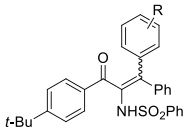


1 **3**

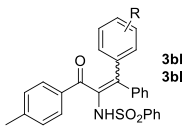


3aa: R = 4-Me, 83%; **3ab:** R = 4-*t*-Bu, 88%;
3ac: R = 2-Me, 78%; **3ad:** R = 3-Me, 72%;
3ae: R = H, 68%; **3ag:** R = 4-CF_3O, 64%;
3ah: R = 4-F, 58%; **3ai:** R = 4-Br, 61% (X-ray);
3aj: R = 2-Br, 50%; **3ak:** R = 3-Br, 43%;
3al: R = 4-Cl, 66%; **3am:** R = 3-Cl, 40%.

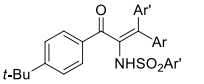
3af 52% **3an** 42% **3ao** 42% **3ap** 39%



3ba: R = 4-Me, 91%, (1:1)[b]; **3bb:** R = 3-Me, 82%, (1:1.2)[b];
3bc: R = 2-Me, 75%, (1:1.5)[b]; **3bd:** R = 4-MeO, 76%, (1:3)[b];
3be: R = 4-*t*-Bu, 61%, (1:2)[b]; **3bf:** R = 4-Br, 57%, (1:3)[b];
3bg: R = 4-Cl, 56%, (1:1.5)[b]; **3bh:** R = 4-F, 59%, (1:1)[b];
3bi: R = 4-phenyl, 51%, (1:6.7)[b];
3bj: R = 3,4-dimethyl, 80%, (1:1.4)[b].

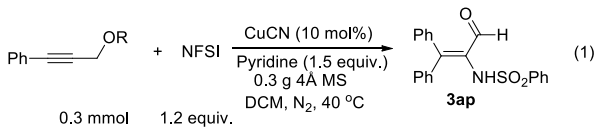


3bk: R = 4-Ac, 0%;
3bl: R = 4-COOMe, 0%.



3ca: Ar = Ar' = 4-MeC_6H_5, 73%;
3cb: Ar = Ar' = 4-*t*-BuC_6H_5, 94%;
3cc: Ar = Ar' = 4-ClC_6H_5, 65%.

[a]Conditions: **1** (0.3 mmol), NFSI (1.2 equiv.), CuCN (10 mol%), pyridine (1.5 equiv.), DCM (3 mL), 40 °C for 24 h under nitrogen atmosphere. Yields were determined after isolation of products by column chromatography. The ration of isomers was determined by ^1H NMR analysis. NFSI: Ar' = C_6H_5, NFR1: Ar' = 4-MeC_6H_4, NFR2: Ar' = 4-*t*-BuC_6H_4, NFR3: Ar' = 4-ClC_6H_4. [b]The ratio of isomers in parentheses.

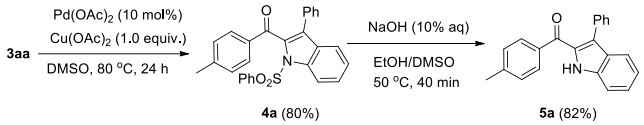


(1)

1b: R = Et, **3ap**: 29%; **1c**: R = OAc, **3ap**: trace

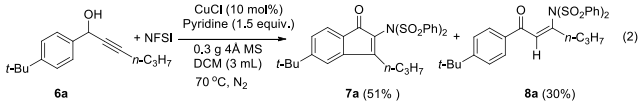
Given that the α-amino-β-aryl enone **3** contains enamine motif, we assumed that intramolecular dehydrogen cross coupling between C–H and N–H bonds of **3** might provide 2,3-disubsituted indoles (Scheme 2), a frequently encountered moiety in various natural products that exhibit a broad spectrum of biological activities.[17] To our delight, in the presence of $Pd(OAc)_2$ (10 mol%) and $Cu(OAc)_2$ (1.0 equiv.), the reaction of **3aa** afforded *N*-phenylsulfonyl-2,3-disubstituted indole

4a (80%), which gave *N*-free indole **5a** through hydrolysis in 82% yield.



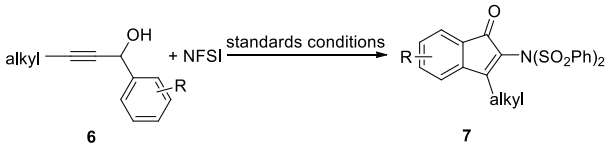
Scheme 2. Application of α-Amino-β-aryl Enone 3aa for Synthesizing 2,3-Disubstituted Indoles 4a and 5a

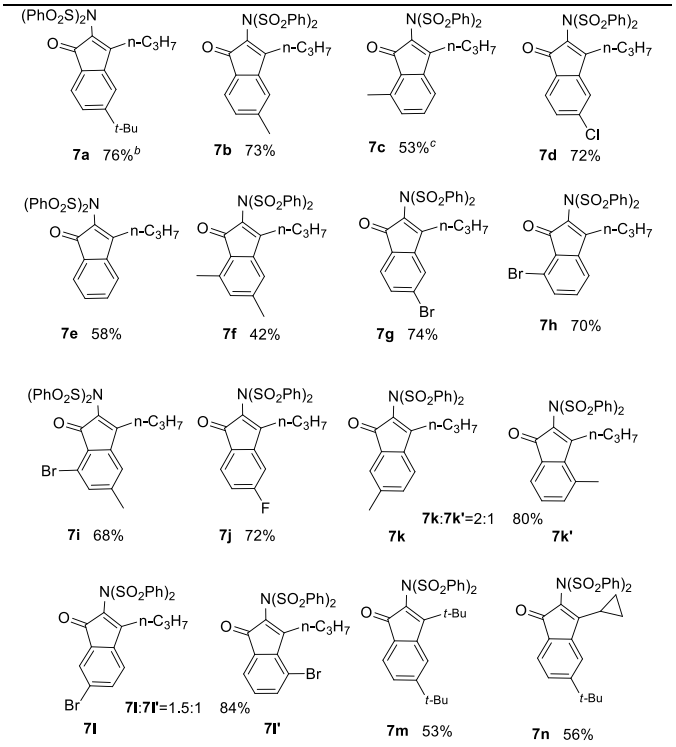
In order to expand the scope of alkynes aminoarylation, the reaction of 3-alkyl substituted propargylic alcohol **6a** (0.3 mmol) and NFSI (2.0 equiv.) was performed. Interestingly, a aminoarylation cyclization reaction occurred, providing indenone product 2-amino-1*H*-inden-1-one **7a** in 51% yield, along with hydroamination product **8a** in 30% yield (eq. 2). Notably, aminoarylation and hydroamination showed opposite regioselectivity. In the absence of pyridine, the reaction of **6a** and NFSI only formed hydroamination product **8a** in 53% yield. Without adding CuCl and pyridine, **8a** could also be obtained in 58% yield, albeit at a slightly higher temperature (90 °C). These results might indicate that for hydroamination reaction, OH group did not play as a directing group. As a result, different regio-selectivity from employing OH as directing group was observed in the aminoarylation cyclization reaction. Indeones exist in a number of naturally occurring compounds[18] and synthetic materials,[19] whose efficient synthetic methods are highly desirable. Therefore, we paid attention to the aminoarylation cyclization reaction for their construction. After scanning the reaction conditions carefully (to see Table S2), we were pleased to find that 76% of **7a** was obtained with 1.5 equiv 4-acetylpridine and 10 mol% $ZnCl_2$ as additives (SI Table S2, entry 21).[20]



To investigate the scope of this aminoarylation cyclization, the reaction of NFSI with various 1-aryl-3-alkyl propargylic alcohols were subsequently conducted. As summarized in Table 3, the *ortho*- and *para*-substituted 1-aryl-3-alkyl propargylic alcohols afforded the desired 2-amino-1*H*-inden-1-ones **7a-j** in moderate to good yields (42-74%). For *meta*-substituted substrates **6k** and **6l**, the isomeric mixture (*ortho*- and *meta*-cyclization) **7k**/**7k'** and **7l**/**7l'** were obtained in a total yields of 80% (**7k**:**7k'**=2:1) and 84% (**7l**:**7l'**=1.5:1), respectively. Halo-substituted propargylic alcohols were tolerated in the aminoarylation reaction, thus affording the corresponding products (**7d**, **7g-j**, **7l** and **7l'**) in good yields, which could be used for additional transformations. Other alkyl groups at C3-position, especially *tetra*-butyl (**6m**) and cyclopropyl (**6n**) group were intact during this transformation and the 2-amino-1*H*-inden-1-ones **7m** and **7n** were formed in 53% and 56% yields, respectively. Recently, Rh-catalyzed aminoarylation cyclization of alkyne has become a useful strategy for constructing nitrogen-containing cyclic compounds.[21] On the other hand, instead of the formation of nitrogen-containing cyclic compounds, this copper-catalyzed aminoarylation reaction provides a facile access to amino-substituted indenone derivatives.

Table 3. The Synthesis of 2-Amino-1*H*-Inden-1-one 7 [a]

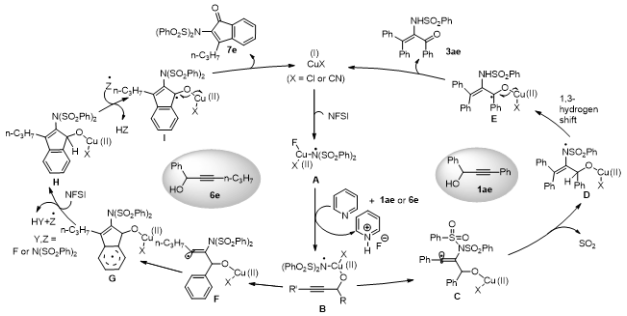




[a]General reaction conditions: **6** (0.3 mmol), NFSI (2.0 equiv.), CuCl (10 mol%), 4-acetyl pyridine (1.5 equiv.), $ZnCl_2$ (10 mol%), DCM (3 mL), 70 °C for 24 h under nitrogen atmosphere. Yields of isolated products. The ratio of isomerization was determined by ^{1}H NMR analysis. [b]**8a** was isolated in 10% yield. [c]**8c** was isolated in 11% yield.

Taking the present experimental results together,[22] and based on our previous works,[5,8,23] a possible mechanism was proposed as depicted in Scheme 3. Initially, the oxidation of Cu(I) with NFSI provided a copper(II)-coordinated benzenesulfonimide radical **A**. In the presence of pyridine, a Cu–O complex intermediate **B** was formed, releasing HF which is captured by pyridine. Next, the intramolecular regiospecific addition of nitrogen radical to alkyne took place, producing vinyl radical, whose geometry depends on the substitutent. For substrate **1ae** with aryl substituent, the in-situ generated vinyl radical intermediate **C** prefered a sp like linear configuration.[22] The following sequential 1,4-aryl migration /desulfonylation/1,3-hydrogen shift produced carbon radical **E**. Finally, the homolysis of Cu(II)–O bond furnished α-amino-β-aryl enones **3ae**, regenerating Cu(I) species for the next catalytic cycle. For **6e**, the vinyl radical **F** took a sp^2 bent configuration.[24] The highly reactive σ radical **F** was quickly trapped by aryl groups of substrates to construct carbon cyclic intermediate **G**. The following oxidation/hydrogen atom abstract/homolysis of Cu(II)–O bond finally provided 2-amino-1*H*-inden-1-one **7e**. As we can see here, engaging directing groups could grant access to regiosepecific alkyne aminoarylation. The rare radical nature of the aminoarylation reaction of

propargylic alcohol exhibits complementary reactivity pattern to its traditional ion type reaction.[11]



Scheme 3. The Possible Mechanism of Aminoarylation Reaction

In summary, utilizing NFSI as aminoarylation or amination reagent, we have developed a mild, copper-catalyzed aminoarylation reaction of various aryl/alkyl alkynes with hydroxyl as directing group. The protocol for direct conversion of internal alkynes to tetrasubstituted simple alkenes with a versatile enamide moiety is especially notable. With this methodology, various α,β-unsaturated carbonyl compounds and indenones were efficiently constructed and the synthetic application for indole derivatives was also provided. The aminoarylation reactions operate via a regiospecific addition of copper coordinated nitrogen radical to C–C triple bond/C_{vinyl}–C_{aryl} bond formation followed by other series of radical processes. We anticipate that this novel aminoarylation strategy of alkynes will play an important role for designing more types of aminodifunctionalization reaction of internal alkynes, and motivate rapid development of radical amination reaction.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral data for new compounds, and crystallographic data for **3ai** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Dewick, P. M. *Medicinal Natural Products; A Biosynthetic Approach* 3rd edn (Wiley, **2008**).

(2) Rappoport, Z. *The Chemistry of Enamines* (Wiley: New York, **1994**).

(3) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004,** *104*, 3079-3159. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008,** *108*, 3795-3892. (c) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015,** *115*, 2596-2697. (d) Shi, S.-L.; Buchwald, S. L. *Nature Chem*. **2015,** *7*, 38-44.

(4) (a) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011,** *133*, 8482-8485. (b) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett*. **2011,** *13*, 2395-2397. (c) Wang, W.; Shen, Y.; Meng, X.; Zhao, M.; Chen, Y.; Chen, B. *Org. Lett*. **2011,** *13*, 4514-4517. (d) Zeng, J.; Tan, Y. J.; Leow, M. L.; Liu, X.-W. *Org. Lett*. **2012,** *14*, 4386-4389. (e) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2012,** *51*, 5170-5174. (f) Xiao, D.; Han, L.; Sun, Q.; Chen, Q.; Gong, N.; Lv, Y.; Suzenet, F.; Guillaumet, G.; Chenga, T.; Li, R. *RSC Advances*, **2012,** *2*, 5054-5057. (g) Toh, K. K.; Sanjaya, S.; Sahnoun, S.; Chong, S. Y.; Chiba, S. *Org. Lett*. **2012,** *14*, 2290-2292. (h) Li, X.; Huang, L.; Chen, H.; Wu, W.; Huang H.; Jiang, H. *Chem. Sci*. **2012,** *3*, 3463-3467. (i) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. *J. Am. Chem. Soc*. **2012,** *134*, 17412-17415. (j) Li, J.; Neuville, L. *Org. Lett*. **2013,** *15*, 1752-1755. (k) Mohan, D. C.; Rao, S. N.; Adimurthy, S. *J. Org. Chem*. **2013,** *78*, 1266-1272.

(5) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. *Angew. Chem. Int. Ed*. **2013,** *52*, 6033-6037.

(6) Zheng, G.; Li, Y.; Han, J.; Xiong, T.; Zhang, Q. *Nat. Commun.* **2015,** *6*, 7011 doi: 10.1038/ncomms8011.

(7) (a) Labinger, J. A.; Bercaw, J. E. *Nature*, **2002,** *417*, 507 -514. (b) Godula, K.; Sames, D. *Science*, **2006,** *312*, 67-72. (c) Lyons, T.W.; Sanford, M. S. *Chem. Rev.* **2010,** *110*, 1147-1169.

(8) (a) Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q. *Angew. Chem. Int. Ed*. **2013,** *52*, 2529-2533. (b) Zhang, H.; Song, Y.; Zhao, J.; Zhang, J.; Zhang, Q. *Angew. Chem. Int. Ed*. **2014,** *53*, 11079-11083. (c) Zhang, G.; Xiong, T.; Wang, Z.; Xu, G.; Wang, X.; Zhang, Q. *Angew. Chem. Int. Ed.* **2015,** *54*, 12649-12653.

(9) Suarez, A. I. O.; Lyaskovskyy, V.; Reek, J. N. H.; van der Vlugt, J. I.; de Bruin, B. *Angew. Chem. Int. Ed.* **2013,** *52*, 12510-12529.

(10) Mo, F.; Tabor, J. R.; Dong, G. *Chem. Lett*. **2014,** *43*, 264-271.

(11) (a) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007,** *46*, 3410-3449. (b) Chinchilla, R.; Carman N. *Chem. Soc. Rev*. **2011,** *40*, 5084-5121. (c) Bauer, E. B. *Synthesis* **2012**, 1131-1151. (d) Zhu, Y.; Sun. L.; Lu, P.; Wang, Y. *ACS Catal*. **2014,** *4*, 1911-1925.

(12) (a) Liu, P.; Deng, C.-L.; Lei, X.; Lin, G.-Q. *Eur. J. Org. Chem*. **2011,** 7308-7316. (b) Biannic, B.; Aponick, A. *Eur. J. Org. Chem*. **2011,** 6605-6617. (c) Han, F.; Yang, L.; Li, Z.; Xia, C. *Adv. Synth. Catal*. **2012,** *354*, 1052-1060.

(13) Crisp, G. T.; Millan, M. J. *Tetrahedron* **1998,** *54*, 637-648.

(14) Carbery, D. R. *Org. Biomol. Chem*. **2008,** *6*, 3455-3460.

(15) The crystal structure of **3ai** see CCDC 1412400.

(16) Traven, V. F.; Ivanov, I. V.; Lebedev, V. S.; Chibisova, T. A.; Milevskii, B. G.; Soloveva, N.P.; Polshakov, V. I.; Alexandrov, G. G.; Kazheva, O. N.; Dyachenko, O. A. *Russ. Chem. Bull.* **2010,** *59*, 1605-1611.

(17) (a) Robinson, B. *Chem. Rev.* **1963,** *63*, 373-401. (b) Saxton, J. E. *Nat. Prod. Rep*. **1997,** *14*, 559-590.

(18) Russell, M. A.; Chai, C. L. L.; Wardlaw, J. H.; Elix, J. A. *J. Nat. Prod*. **2000,** *63*, 129-131.

(19) Kitani, Y.; Morita, A.; Kumamoto, T.; Ishikawa, T. *Helv. Chim. Acta*. **2002,** *85*, 1186-1195.

(20) $ZnCl_2$ might act as a Lewis acid to stabilize nitrogen-centered radicals. See Kundu, S.; Farquhar, E.; Miceli, E.; Pfaff, F. F.; Kuhlmann, U.; Hildebrandt, P.; Braun, B.; Greco, C.; Ray, K. *J.*

Am. Chem. Soc. **2012**, *134*, 14710-14713. Also see 8(b).

(21) (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012,** *41*, 3651-3678. (b) Ackermann, L. *Acc. Chem. Res*. **2014,** *47*, 281-295.

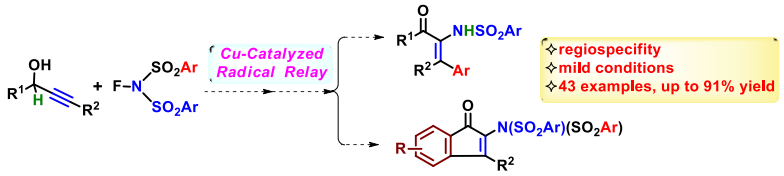
(22) When radical scavengers (1.5 equiv. of TEMPO (2,2,4,4-tetramethyl-1-piperidinyloxy), BHT (2,6-di-*tert*-butyl-4-methylphenol) or DPE (1,1-diphenylethylene)) were added to the reaction, no desired aminoarylation products. The details, please see SI.

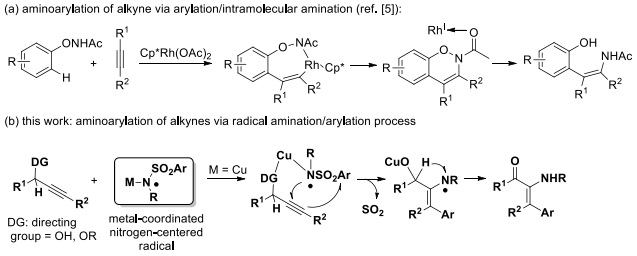
(23) (a) Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. *Angew. Chem. Int. Ed*. **2012,** *51*, 1244-1247. (b) Zhang, Q.; Lv,Y.; Li, Y.; Xiong, T.; Zhang, Q. *Acta Chim. Sinica*. **2014,** *72*, 1139-1143. (c) Sun, K., Li, Y.; Zhang, Q. *Sci. China Chem*. **2015,** *58*, 1354-1358.

(24) Galli, C.; Rappoport Z. *Acc. Chem. Res.* **2003,** *36*, 580-587.

Copper-Catalyzed Hydroxyl-Directed Aminoarylation of Alkynes

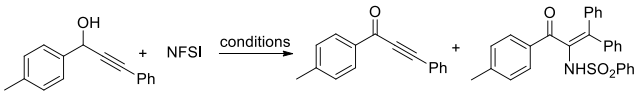
Jiaqiong Sun, Guangfan Zheng, Tao Xiong, Qiao Zhang, Jinbo Zhao, Yan Li* and Qian Zhang





Scheme 1. Metal Catalyzed Aminoarylation of Alkynes

Table 1. Optimization of Reaction Conditions of 1aa with NFSI[a]

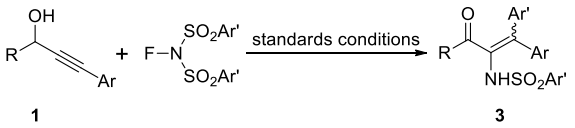


1aa **2aa** **3aa**

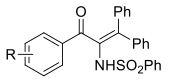
Entry	Catalyst	Additive	Solvent	**2aa** (%)	**3aa** (%)
1[b]	CuCN	None	DCM	11	0
2[b]	CuCN	Py	DCM	56	35
3	CuCN	Py	DCM	28	53
4	CuCN	Et_3N	DCM	0	0
5	CuCN	DBU	DCM	0	0
6	None	Py	DCM	0	0
7	CuCl	Py	DCM	0	46
8	CuOTf	Py	DCM	0	20
9	CuCN	Py	$CHCl_3$	0	30
10	CuCN	Py	DCE	0	35
11	CuCN	Py	CH_3CN	0	0
12[c]	**CuCN**	**Py**	**DCM**	**0**	**83**

[a]General reaction conditions: **1aa** (0.3 mmol), NFSI (1.2 equiv.), catalyst (10 mol%), additive (1.5 equiv.), solvent (3 mL), 40 °C for 24 h under nitrogen atmosphere. Yields were determined after isolation of products by column chromatography. [b]The reaction was conducted under air. [c]0.3 g 4Å Molecular sieves were used.

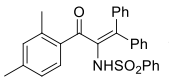
Table 2. The Synthesis of α-Amino-β-aryl Unsaturated Carbonyl Compounds 3[a]



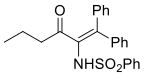
1 3



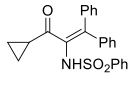
3aa: R = 4-Me, 83%; **3ab:** R = 4-*t*-Bu, 88%;
3ac: R = 2-Me, 78%; **3ad:** R = 3-Me, 72%;
3ae: R = H, 68%; **3ag:** R = 4-CF_3O, 64%;
3ah: R = 4-F, 58%; **3ai:** R = 4-Br, 61% (X-ray);
3aj: R = 2-Br, 50%; **3ak:** R = 3-Br, 43%;
3al: R = 4-Cl, 66%; **3am:** R = 3-Cl, 40%.



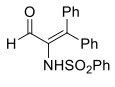
3af 52%



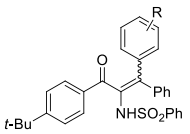
3an 42%



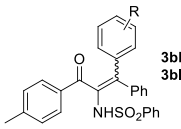
3ao 42%



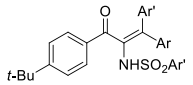
3ap 39%



3ba: R = 4-Me, 91%, (1:1)[b]; **3bb:** R = 3-Me, 82%, (1:1.2)[b];
3bc: R = 2-Me, 75%, (1:1.5)[b]; **3bd:** R = 4-MeO, 76%, (1:3)[b];
3be: R = 4-*t*-Bu, 61%, (1:2)[b]; **3bf:** R = 4-Br, 57%, (1:3)[b];
3bg: R = 4-Cl, 56%, (1:1.5)[b]; **3bh:** R = 4-F, 59%, (1:1)[b];
3bi: R = 4-phenyl, 51%, (1:6.7)[b];
3bj: R = 3,4-dimethyl, 80%, (1:1.4)[b].

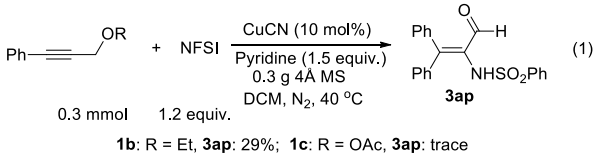


3bk: R = 4-Ac, 0%;
3bl: R = 4-COOMe, 0%.



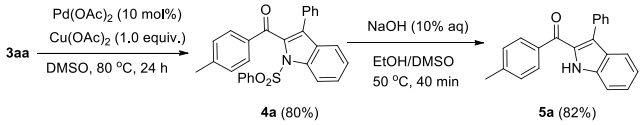
3ca: Ar = Ar' = 4-MeC_6H_5, 73%;
3cb: Ar = Ar' = 4-*t*-BuC_6H_5, 94%;
3cc: Ar = Ar' = 4-ClC_6H_5, 65%.

[a]Conditions: **1** (0.3 mmol), NFSI (1.2 equiv.), CuCN (10 mol%), pyridine (1.5 equiv.), DCM (3 mL), 40 °C for 24 h under nitrogen atmosphere. Yields were determined after isolation of products by column chromatography. The ration of isomers was determined by ^{1}H NMR analysis. NFSI: Ar' = C_6H_5, NFR1: Ar' = 4-MeC_6H_4, NFR2: Ar' = 4-*t*-BuC_6H_4, NFR3: Ar' = 4-ClC_6H_4. [b]The ratio of isomers in parentheses.



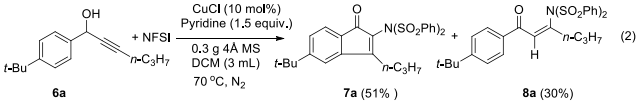
(1)

1b: R = Et, **3ap**: 29%; **1c**: R = OAc, **3ap**: trace



4a (80%) **5a** (82%)

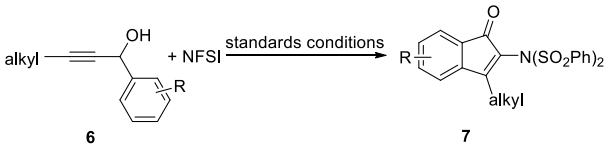
Scheme 2. Application of α-Amino-β-aryl Enone 3aa for Synthesizing 2,3-Disubstituted Indoles 4a and 5a



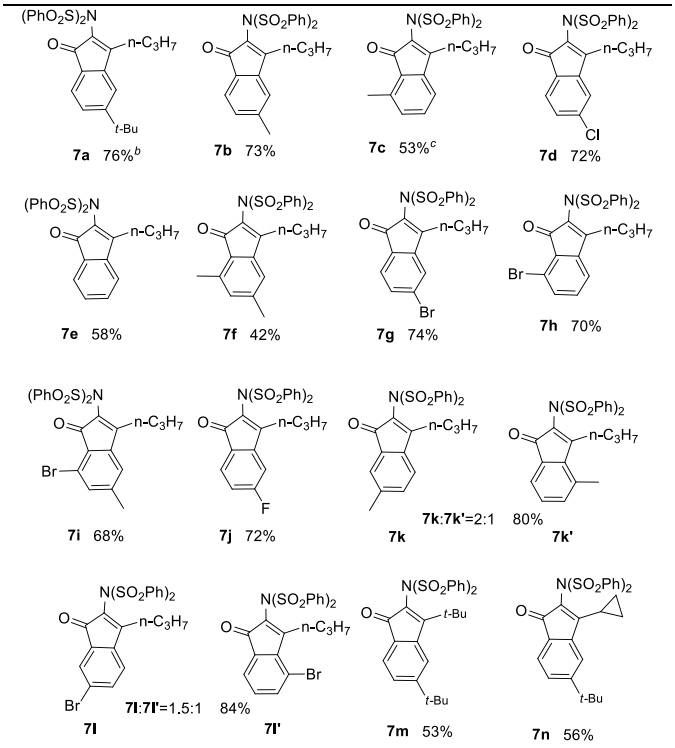
(2)

6a **7a** (51%) **8a** (30%)

Table 3. The Synthesis of 2-Amino-1*H*-Inden-1-one 7 [a]



6 7



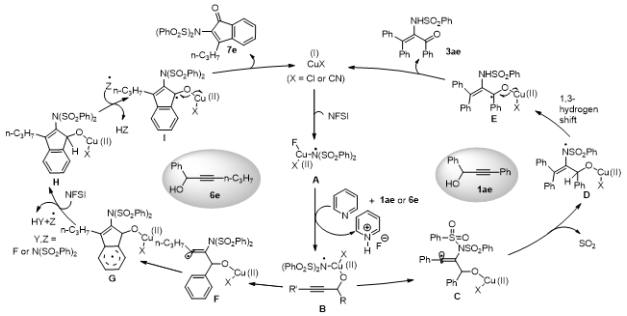
7a 76%[b] **7b** 73% **7c** 53%[c] **7d** 72%

7e 58% **7f** 42% **7g** 74% **7h** 70%

7i 68% **7j** 72% **7k** **7k**:**7k'**=2:1 80% **7k'**

7l **7l**:**7l'**=1.5:1 84% **7l'** **7m** 53% **7n** 56%

[a]General reaction conditions: **6** (0.3 mmol), NFSI (2.0 equiv.), CuCl (10 mol%), 4-acetyl pyridine (1.5 equiv.), $ZnCl_2$ (10 mol%), DCM (3 mL), 70 °C for 24 h under nitrogen atmosphere. Yields of isolated products. The ratio of isomerization was determined by ^{1}H NMR analysis. [b]**8a** was isolated in 10% yield. [c]**8c** was isolated in 11% yield.



Scheme 3. The Possible Mechanism of Aminoarylation Reaction

Copper-Catalyzed Hydroxyl-Directed Aminoarylation of Alkynes

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