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Copper- or Nickel-Enabled Oxidative Cross-Coupling of Unreactive C(sp^3)–H Bonds with Azole C(sp^2)–H Bonds: Rapid Access to β-Azolyl Propanoic Acid Derivatives

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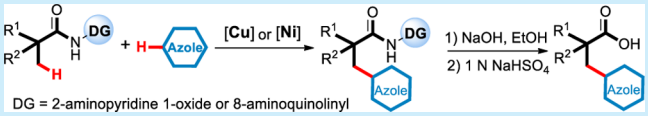
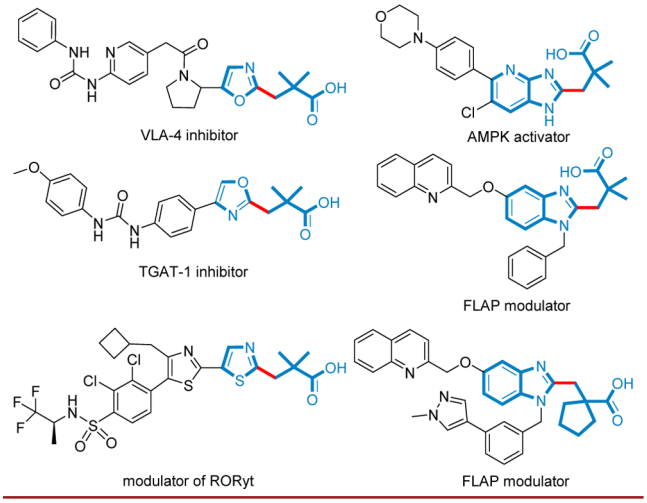
Supporting Information

ABSTRACT: β-Azolyl propanoic acid derivatives are frequently found in biologically active molecules and pharmaceuticals. Here, we report the oxidative heteroarylation of unactivated C(sp^3)–H bonds with azole C(sp^2)–H bonds via copper or nickel catalysis with the aid of removable bidentate auxiliary, which provides a rapid pathway to β-azolyl propanoic acid derivatives. A variety of azoles such as oxazole, benzoxazole, thiazole, benzothiazoles, benzimidazole, purine, and even [1,2,4]triazolo[1,5-*a*]pyrimidine could be engaged in this protocol.



β-Azolyl propanoic acid derivatives are frequently found in biologically active molecules and pharmaceuticals (Scheme 1).[1,2]

Scheme 1. Pharmaceutical and Biologically Active Molecules Containing β-Azolyl Propanoic Acid Derivatives



Traditional approaches to β-azolyl propanoic acid derivatives generally require multiple-step sequences and harsh reaction conditions.[2] Thus, it would be highly desirable to develop an innovative strategy for the synthesis of these structural motifs. Given that both propanoic acid derivatives and azoles are among the most prevalent scaffolds, we surmised that transition-metal-catalyzed oxidative C–H/C–H cross-coupling of propanoic acid derivatives with azoles would be a distinct, straightforward gateway to β-azolyl propanoic acid derivatives.

In recent years, transition-metal-catalyzed oxidative C(sp^2)–H/C(sp^2)–H cross-coupling reactions between a directing-group-containing (hetero)arene and a heteroarene have been well-demonstrated.[3−7] However, the oxidative heteroarylation of unreactive C(sp^3)–H bonds remains under-represented because of the high bond strengths of inert C(sp^3)–H bonds and low reactivity of metal–C(alkyl) species.[8] In 2015, Ge reported 8-aminoquinoline-assisted copper-promoted oxidative heteroarylation of unactivated C(sp^3)–H bonds with acidic polyfluoroarenes.[9] Very recently, Yin realized the nickel-catalyzed oxidative cross-coupling of unactivated C(sp^3)–H bonds with electron-rich heteroarenes such as thiophen and furan.[10] Recently, the Muria group and our group have individually demonstrated the copper-, cobalt-, or nickel-promoted/catalyzed heteroarylation of C(sp^2)–H bonds of (hetero)arene acid derivatives with azole C(sp^2)–H bonds with the help of 8-aminoquinoline auxiliary as a bidentate directing group (Scheme 2a).[5c,6,7] We envisaged that the bidentate-assisted strategy could enable the first row transition-metal-catalyzed oxidative cross-coupling of unactivated C(sp^3)–H bonds with azole C(sp^2)–H bonds. Herein, we reported the copper- or nickel-promoted/catalyzed oxidative cross-coupling of unreactive C(sp^3)–H bonds with azole C(sp^2)–H bonds, offering a rapid gateway to β-azolyl propanoic acid derivatives (Scheme 2b).

Our investigation commenced with the reaction between 2-pivalamidopyridine 1-oxide **1a** and benzoxazole **2a** (for detailed optimization, see Table S1). By employing 2.0 equiv of $Cu(OAc)_2·H_2O$ as the promoter and 0.5 equiv of PivOH as the additive in *o*-xylene at 140 °C under a N_2 atmosphere for 24 h, a deoxygenated product **3a** could be obtained in 36% yield (Table 1, entry 1). The addition of 2.0 equiv of K_2CO_3 improved the yield of **3a** to 56% (Table 1, entries 2−4). Other copper salts such as $Cu(OAc)_2$, $CuCl_2$, and $Cu(OTf)_2$ were less effective for the process (Table 1, entries 7−9). After the solvents were

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Scheme 2. First Row Transition-Metal-Catalyzed C−H Heteroarylation Assisted by Bidentate Auxiliary (DG: Directing Group)

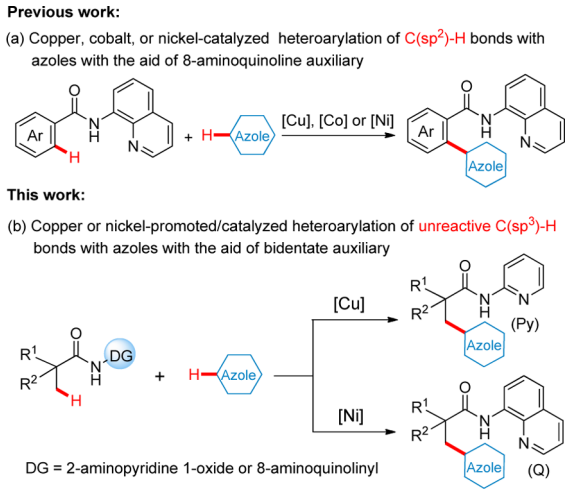
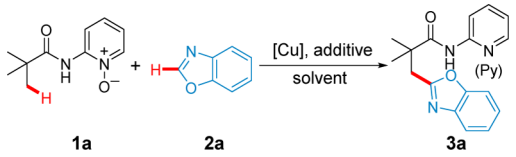


Table 1. Optimization of the Reaction Conditions[a,b]



1a 2a 3a

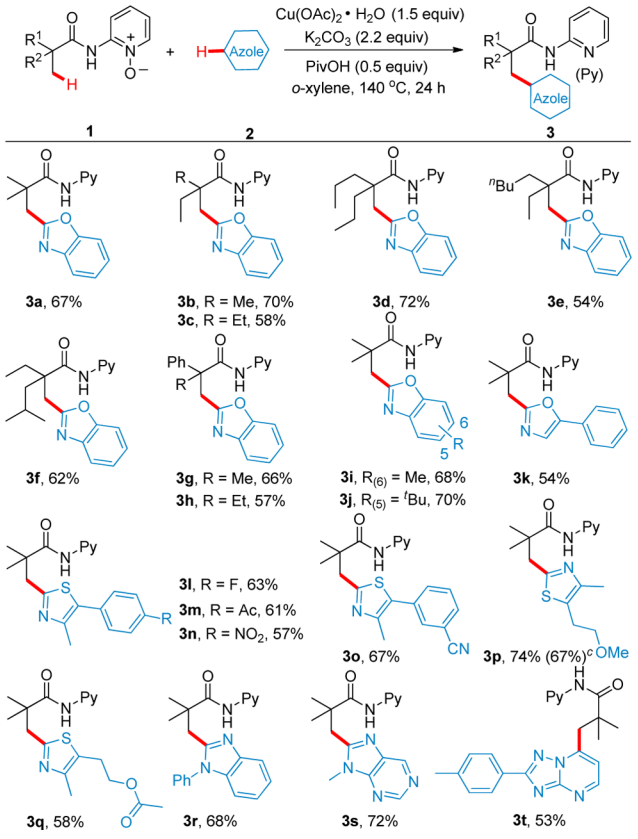
entry	copper salt	additive	solvent	**3a** (%)
1	$Cu(OAc)_2·H_2O$	PivOH	*o*-xylene	36
2	$Cu(OAc)_2·H_2O$	Na_2CO_3/PivOH	*o*-xylene	41
3	$Cu(OAc)_2·H_2O$	K_2CO_3/PivOH	*o*-xylene	56
4	$Cu(OAc)_2·H_2O$	K_2HPO_4/PivOH	*o*-xylene	27
5		K_2CO_3/PivOH	*o*-xylene	nr
6	$Cu(OAc)_2·H_2O$	K_2CO_3	*o*-xylene	26
7	$Cu(OAc)_2$	K_2CO_3/PivOH	*o*-xylene	53
8	$CuCl_2$	K_2CO_3/PivOH	*o*-xylene	49
9	$Cu(OTf)_2$	K_2CO_3/PivOH	*o*-xylene	trace
10	$Cu(OAc)_2·H_2O$	K_2CO_3/PivOH	toluene	47
11	$Cu(OAc)_2·H_2O$	K_2CO_3/PivOH	DCE	20
12	$Cu(OAc)_2·H_2O$	K_2CO_3/PivOH	DMSO	trace
13	$Cu(OAc)_2·H_2O$	K_2CO_3/AcOH	*o*-xylene	trace
14[c]	$Cu(OAc)_2·H_2O$	K_2CO_3/PivOH	*o*-xylene	62
15[c,d]	**$Cu(OAc)_2·H_2O$**	**K_2CO_3/PivOH**	***o*-xylene**	**67**
16[c,d,e]	$Cu(OAc)_2·H_2O$	K_2CO_3/PivOH	*o*-xylene	34

[a]Reaction conditions: 2-pivalamidopyridine 1-oxide **1a** (0.2 mmol), benzoxazole **2a** (0.4 mmol), $Cu(OAc)_2·H_2O$ (2.0 equiv), base (2.0 equiv), additive (50 mol %), and solvent (1.0 mL) at 140 °C under an N_2 atmosphere for 24 h. [b]Yields of isolated products. [c]2.2 equiv of K_2CO_3 was used. [d]1.5 equiv of $Cu(OAc)_2·H_2O$ was used. [e]At 120 °C; nr: no reaction.

examined, *o*-xylene proved to be superior to toluene, DCE, and DMSO (Table 1, entries 3 and 10−12). Either removal or replacement of PivOH with AcOH led to a reduced yield (Table 1, entries 6 and 13). Further optimization of the reaction parameters, such as the amounts of $Cu(OAc)_2·H_2O$ and K_2CO_3, and reaction temperature, improved the yield of **3a** to 67% yield (Table 1, entries 14−16). Notably, the diarylated product was not detected. To clarify whether the N−O bond plays a role of co-oxidant together with the Cu(II) oxidant, a control experiment for the dosage of $Cu(OAc)_2·H_2O$ was performed. As shown in Table S1 (entries 31−36), the yields of **3a** were progressively diminished along with the decrease of $Cu(OAc)_2·H_2O$, suggesting that the N−O bond might not act as a co-oxidant. In addition, only a trace amount of deoxidized byproduct **1aa** (*N*-(pyridin-2-yl)pivalamide) was observed in the absence of benzoxazole **2a**, implying that the deoxygenation of pyrinde *N*-oxide might mainly occur along with the formation of **3a** (for details, see Table S2, entries 1−3).

With the optimized conditions in hand, we explored the scope of propanoic acid derivatives and azoles. As shown in Scheme 3,

Scheme 3. Scope of Copper-Promoted Heteroarylation of Unreactive C(sp^3)−H Bonds with Azoles[a,b]



[a]Reactions were performed with **1** (0.2 mmol) and **2** (0.4 mmol) in 1.0 mL of *o*-xylene at 140 °C for 24 h under N_2. [b]Yields of isolated products. [c]67% yield was obtained from a 1.0 mmol scale reaction.

a series of 2,2-disubstituted propanamides bearing linear chains could react with benzoxazole **2a**, delivering the corresponding deoxygenated products in moderate to good yields (Scheme 3, **3a**−**3h**). Isobutyric acid and *n*-propanoic acid derivatives did not undergo this transformation. Moreover, benzoxazoles with methyl and *tert*-butyl and 5-phenyloxazole could be engaged in this reaction (Scheme 3, **3i**−**3k**). Phenylthiazoles and thiazoles were also compatible with this protocol (Scheme 3, **3l**−**3q**). Sensitive functional groups such as fluoro, acetyl, nitro, cyano, alkoxy, and even acetoxyl were well-tolerated under the optimized conditions. Other electron-deficient heteroarenes such as benzimidazole, purine, and [1,2,4]triazolo[1,5-*a*]pyrimidine could also couple with **1a** to give the desired products in satisfactory yields (Scheme 3, **3r**−**3t**).

Inspired by our previous nickel-catalyzed oxidative C−H/C−H cross-coupling between two heteroarenes with the aid of 8-aminoquinoline,[7] we investigated the reactivity of nickel in the heteroarylation of C(sp^3)−H by replacing 2-aminopyridine 1-oxide with

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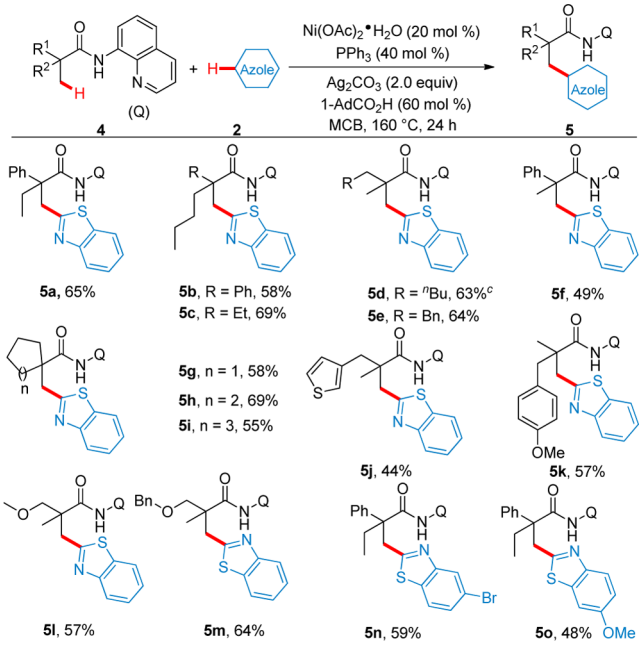
8-aminoquinoline as a bidentate directing group. After nickel salts, oxidants, ligands, additives, and solvents were screened, the best result was observed under a catalytic system comprising $Ni(OAc)_2 \cdot 4H_2O$ (20 mol %), Ag_2CO_3 (2.0 equiv), 1-$AdCO_2H$ (60 mol %), and PPh_3 (40 mol %) in chlorobenzene at 160 °C for 24 h (for detailed optimization, see Table S3). Given that PPh_3 could remarkably enhance the yield of **5a** (Table S3, entries 2 and 9), we speculated that PPh_3 might act as an efficient ligand.[7] As

Scheme 4. Scope of Nickel-Catalyzed Heteroarylation of Unreactive C(sp^3)−H Bonds with Azoles[a,b]



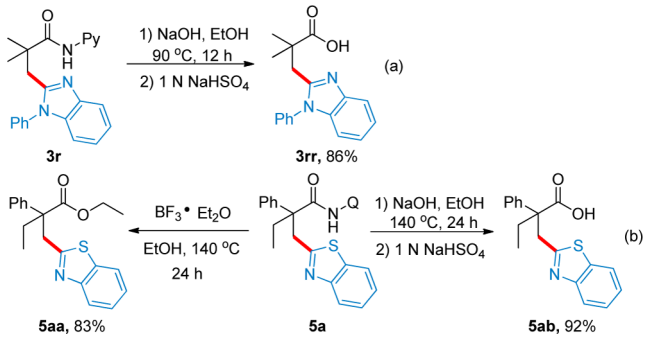
[a]Reactions were performed with **4** (0.2 mmol) and **2** (0.4 mmol) in 0.5 mL of chlorobenzene (MCB) at 160 °C for 24 h under N_2. [b]Yields of isolated products. [c]Azole **2** (0.6 mmol) was used.

summarized in Scheme 4, various 2,2-disubstituted propanamides bearing a linear or cyclic chain could smoothly react with benzothiazole **2n**, giving the *β*-azolyl propanamides **5** (Scheme 4, **5a**−**5i**). Isobutyric acid and *n*-propanoic acid derivatives could not be compatible with this protocol. Substrates with functional groups such as (hetero)aryl and alkoxy on the alkane skeletons were compatible with this reaction (Scheme 4, **5j**−**5m**). Benzothiazole with the electron-withdrawing (Br) or electron-donating (methoxy) groups underwent this coupling process in a moderate yield (Scheme 4, **5n**−**5o**). Note that the diarylated products were not observed.

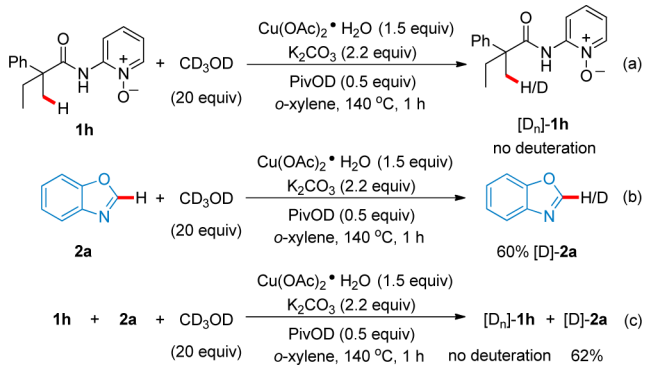
To further highlight the synthetic utility of our strategy, the hydrolysis of **3r** and the esterlysis and hydrolysis of **5a** were performed to remove the directing group, affording **3rr**, **5aa**, and **5ab** in 86, 83, and 92% yields, respectively (Scheme 5a,b).[11,12]

To gain some insights into the reaction mechanism, hydrogen/deuterium exchange experiments were performed for both coupling partners. Under the standard conditions, the reaction of 2-(2-methyl-2-phenylbutanamido)pyridine 1-oxide (**1h**) with 20 equiv of CD_3OD in the absence or presence of benzoxazole (**2a**) for 1 h did not lead to any deuterated [D_n]-**1h** (Scheme 6a,c), suggesting that the primary C(sp^3)−H bond cleavage could be an irreversible process. Whereas **2a** reacted with CD_3OD in the absence or presence of **1h**, the H/D exchange ratios of **2a** were approximately 60 and 62%,

Scheme 5. Removal of the Directing Groups of 3r and 5a



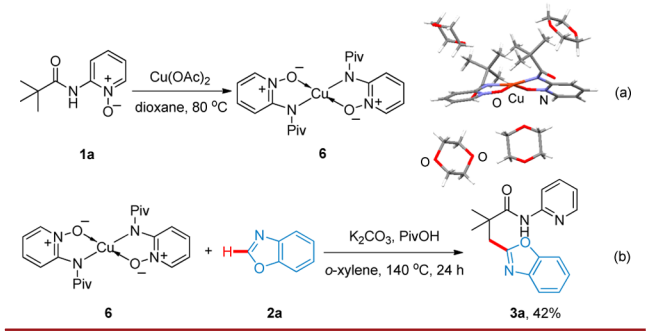
Scheme 6. Deuterium Labeling



respectively, implying that the cleavage of the C2−H bond of **2a** could be a reversible process (Scheme 6b,c).

Treatment of **1a** with 1.0 equiv of $Cu(OAc)_2$ in dioxane at 80 °C led to Cu^{II} complex **6** and its structure was established by X-ray crystallographic analysis (Scheme 7a). The in situ formed

Scheme 7. Preparation and Reactivity of Complex 6



complex **6** could react with benzoxazole **2a**, giving **3a** in 42% yield (Scheme 7b). This result suggested that a ligand exchange of 2-pivalamidopyridine 1-oxide **1a** with $Cu(OAc)_2 \cdot H_2O$ might occur initially in the mechanistic pathway, forming the intermediate **6**.

Based on the above results and previous copper-promoted C(sp^2)−H heteroarylation,[5] a plausible mechanistic pathway is proposed in Scheme 8. First, a ligand exchange of 2-pivalamidopyridine 1-oxide **1a** with $Cu(OAc)_2 \cdot H_2O$ forms the complex **6**. Next, the complex **6** reacts with benzoxazole **2a** to produce the intermediate **IM1**. Then, the C−H cupration of primary C(sp^3)−H bond forms the Cu^{III} complex **IM3** with the help of an additional $Cu(OAc)_2$ (disproportionation).[5c,13] Subsequently, **IM3** undergoes a reductive elimination[14] to give a Cu(I)-coordinated intermediate **IM4**. Finally, the N−O bond of **IM4** is fractured

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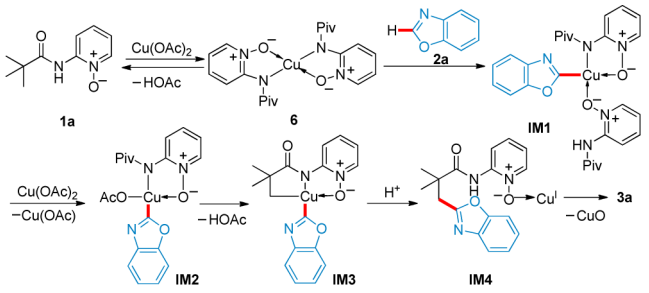
Scheme 8. Plausible Mechanistic Pathway



with the aid of reductive Cu(I) along with the release of **3a** and CuO (observed in the reaction mixture and tube wall). The formation of inert CuO also explains why a superstoichiometric $Cu(OAc)_2 \cdot H_2O$ is necessary for this transformation. Notably, at the present stage, another possible azolylcopper species generated from a ligand exchange of benzoxazole **2a** with $Cu(OAc)_2$ could not be excluded.[5c]

In summary, we have addressed a copper- or nickel-promoted/catalyzed oxidative cross-coupling of unreactive C(sp^3)−H bonds with azole C(sp^2)−H bonds. Azoles such as oxazole, benzoxazole, thiazole, benzothiazoles, benzimidazole, purine, and even [1,2,4]triazolo[1,5-*a*]pyrimidine can be engaged in this protocol. We believe that this method would provide a rapid route to *β*-azolyl propanoic acid derivatives in medical chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02265.

Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra of final products (PDF)
X-ray data for **6** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Chupak, L. S.; Duplantier, A. J.; Lau, W. F.; Milici, A. J. Patent Appl. WO 01/51487 A1, 2001. (b) Kojima, E.; Tonogaki, K.; Tanaka, N.; Katou, M.; Ino, A.; Iwatsu, M.; Fujioka, M.; Hinata, Y.; Ohyabu, N. Patent Appl. WO 2013/011932 A1, 2013.

(2) (a) Sharma, R.; Kadam, K. S.; Jadhav, R. D.; Kandre, S. S.; Gupte, A. Patent Appl. WO 2012/029032 A2, 2012. (b) Chai, W.; Deckhut, C.; Dvorak, C. A.; Eccles, W.; Edwards, J. P.; Goldberg, S. D.; Krawczuk, P. J.; Lebsack, A. D.; Liu, J.; Tanis, V. M.; Tarantino, K. T. Patent Appl. US 2014/0275028 A1, 2014. (c) Goldberg, S.; Steeneck, C.; Gege, C.; Kinzel, O.; Kleymann, G.; Hoffmann, T. Patent Appl. US 2016/0120850 A1, 2016.

(3) For selected examples of chelation-assisted rhodium-catalyzed heteroarylation of (hetero)arene C(sp^2)−H bonds, see: (a) Wencel-Delord, J.; Nimphius, C.; Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 13001. (b) Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 580. (c) Huang, Y.; Wu, D.; Huang, J.; Guo, Q.; Li, J.; You, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 12158. (d) Shang, Y.; Jie, X.; Zhao, H.; Hu, P.; Su, W. *Org. Lett.* **2014**, *16*, 416. (e) Qin, X.; Li, X.; Huang, Q.; Liu, H.; Wu, D.; Guo, Q.; Lan, J.; Wang, R.; You, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 7167. (f) Qin, D.; Wang, J.; Qin, X.; Wang, C.; Gao, G.; You, J. *Chem. Commun.* **2015**, *51*, 6190. (g) Deng, H.; Li, H.; Wang, L. *Org. Lett.* **2016**, *18*, 3110. (h) Hu, J.; Li, G.; Yuan, C.; Huang, Z.-B.; Shi, D.-Q.; Zhao, Y. *Org. Lett.* **2016**, *18*, 5998.

(4) For chelation-assisted palladium-catalyzed heteroarylation of (hetero)arene C(sp^2)−H bonds, see: Gao, D.-W.; Gu, Q.; You, S.-L. *J. Am. Chem. Soc.* **2016**, *138*, 2544.

(5) For chelation-assisted copper-catalyzed/mediated heteroarylation of (hetero)arene C(sp^2)−H bonds, see: (a) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (b) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 6993. (c) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4457. (d) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10784. (e) Zhao, S.; Yuan, J.; Li, Y.-C.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 12823.

(6) For chelation-assisted cobalt-catalyzed heteroarylation of (hetero) arene C(sp^2)−H bonds, see: Tan, G.; He, S.; Huang, X.; Liao, X.; Cheng, Y.; You, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 10414.

(7) For chelation-assisted nickel-catalyzed heteroarylation of (hetero) arene C(sp^2)−H bonds, see: Cheng, Y.; Wu, Y.; Tan, G.; You, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 12275.

(8) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541.

(9) Wu, X.; Zhao, Y.; Ge, H. *Chem. Sci.* **2015**, *6*, 5978.

(10) During the preparation of this paper, Yin's group reported the nickel-catalyzed oxidative cross-coupling of unactivated C(sp^3)−H bonds with electron-rich thiophen and furan with the aid of 8-aminoquinoline auxiliary. Notably, while the thiazole was employed as heteroarene partner, the transformation occurred at the electron-rich C5−H bond of thiazole. See: Wang, X.; Xie, P.; Qiu, R.; Zhu, L.; Liu, T.; Li, Y.; Iwasaki, T.; Au, C.-T.; Xu, X.; Xia, Y.; Yin, S.-F.; Kambe, N. *Chem. Commun.* **2017**, *53*, 8316.

(11) Li, M.; Yang, Y.; Zhou, D.; Wan, D.; You, J. *Org. Lett.* **2015**, *17*, 2546.

(12) Wang, X.; Qiu, R.; Yan, C.; Reddy, V. P.; Zhu, L.; Xu, X.; Yin, S.-F. *Org. Lett.* **2015**, *17*, 1970.

(13) Takamatsu, K.; Hirano, K.; Miura, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 5353.

(14) For the rapid reductive elimination reaction of some Cu^{III} intermediates, see: (a) Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386. (b) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3706.

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