

3,3'-Disubstituted Oxindoles Formation via Copper-Catalyzed Arylboration and Arylsilylation of Alkenes

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oxindoles are obtained in moderate to excellent yields. The reaction is proposed to proceed via a domino sequence involving intermolecular olefin borylcupration or silylcupration followed by intramolecular coupling of an alkyl-Cu intermediate with aryl iodide.

ransition-metal-catalyzed olefin difunctionalization represents an efficient strategy for rapid assembly of complex molecules by forming two chemical bonds in one single step. Among, 1,2-carboboration of alkenes² is particularly attractive as the resulting organoboranes allow further transformations to access functional molecules, such as oxidation to form alcohols and Suzuki-Miyaura cross-coupling to create new C-C bonds. Currently, 1,2-arylboration of olefin with B₂pin₂ and arylhalides relied on the use notable palladium catalyst (for Heck/borylation domino reactions),³ nickel catalyst,⁴ and Pd/ Cu-5 or Ni/Cu-6 cocatalysts. In the latter case, alkyl-Cu species, generated by olefin borylcupration,⁷ acts as an organometallic reagent to couple with arylhalides in the presence of Pd- or Ni-based catalysts (Scheme 1a). Whereas in 2014, Brown and co-workers demonstrated in an elegant copper-catalyzed diarylation of alkenes with arylborates and aryl iodides that the alkyl-Cu species could directly couple with

Scheme 1. Arylboration and Arylsilylation of Alkenes Involving Cu-Based Catalyst

a) Olefin arylboration with Cu/Pd or Cu/Ni co-catalysts



copper as sole catalyst

√functional oxindole formation

√C-B and C-Si bond formation

iodoarene to form a new C–C bond (Scheme 1b).⁸ Inspired by this result, we envisioned that the use of copper as a sole catalyst might enable olefin 1,2-arylboration through couplings of alkenes, aryl iodides, and borates. If true, it would avoid the use of notable Pd-catalyst or dual-metal catalysis in the olefin 1,2-arylboration reaction.

3,3'-Disubstituted oxindole represents a privileged building block that frequently occurred in natural products, pharmaceuticals, and bioactive molecules.⁹ A number of synthetic transformations have been developed toward the construction of such a unique structural unit.¹⁰ Nevertheless, it is still highly desirable to develop efficient methods to install functionalities (e.g., boryl or silyl) possessing potential transformations to the oxindole core. We herein communicate an efficient arylboration reaction of N-(2-iodoaryl)acrylamide with B₂pin₂ by using simple CuOAc as the sole catalyst, which achieves a number of borylated 3,3'-disubstituted oxindoles in moderate to excellent yields with a high reaction rate (Scheme 1c). It is noted that the same transformation has been realized by the group of Vachhani and Eycken using Pd-catalyst under microwave.^{3f} Gratifyingly, the present process is further extended to 1,2arylsilylation¹¹ with PhMe₂Si-Bpin, delivering a range of silvlated 3,3'-disubstituted oxindoles in good yields.

We commenced the study of arylboration reaction by using N-(2-iodophenyl)-2-phenylacrylamide 1a and B₂pin₂ as model substrates. Initial testing found the reaction completed in 5 min by employing the complex CuI/1,10-Phen as a catalyst and KO^tBu as a base in toluene at 100 °C, which delivered oxindole 2a in 95% yield (Table 1, entry 1). The effect of the

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8 examples

52-90% yields

26 examples

24-97% yields

Α

Table 1. Optimization of the Reaction Conditions^a

		,Ph + B ₂ pin ₂	[Cu], Ligand Base Solvent, 100 °C	Ph Ph 2a Me	Bpin O
Entry	[Cu]	Ligand	Base	Solvent	Yield (%) ^b
1	CuI	1,10-Phen	KO ^t Bu	toluene	95
2	CuBr	1,10-Phen	KO ^t Bu	toluene	96
3	CuCl	1,10-Phen	KO ^t Bu	toluene	94
4	CuOAc	1,10-Phen	KO ^t Bu	toluene	97
5	$Cu(OTf)_2$	1,10-Phen	KO ^t Bu	toluene	90
6	CuOAc	1,10-Phen	NaO ^t Bu	toluene	90
7 ^c	CuOAc	1,10-Phen	LiO ^t Bu	toluene	50
8	CuOAc	1,10-Phen	KO ^t Bu	1,4-dioxane	96
9	CuOAc	1,10-Phen	KO ^t Bu	THF	78
10	CuOAc	2,2'-Bipy	KO ^t Bu	toluene	43
11 ^d	CuOAc	Pyridine	KO ^t Bu	toluene	35
12 ^d	CuOAc	PPh_3	KO ^t Bu	toluene	70
13	CuOAc	dppf	KO ^t Bu	toluene	63
14 ^e	CuOAc	1,10-Phen	KO ^t Bu	toluene	90
15 ^f	CuOAc	1,10-Phen	KO ^t Bu	toluene	85
16	-	1,10-Phen	KO ^t Bu	toluene	nd ^g
-		,			/

^{*a*}Reaction conditions: 1a (0.2 mmol), B_2pin_2 (0.3 mmol), [Cu] (10 mol %), ligand (10 mol %), base (1.5 equiv), and solvent (2.0 mL) at 100 °C (oil bath) for 5 min. ^{*b*}Isolated yields. ^{*c*}For 1 h. ^{*d*}Ligand (20 mol %). ^{*e*}At 80 °C. ^{*f*}CuOAc (5 mol %), 1,10-Phen (5 mol %). ^{*g*}Not detected.

copper salt was then investigated. CuBr and CuCl resulted in comparable yields (entries 2 and 3), while CuOAc proved to be the best choice to produce **2a** in 97% yield (entry 4). Changing the base to NaO'Bu or LiO'Bu diminished the yield to 90% or 50%, respectively (entries 6 and 7). The influence of the solvent was examined. Lower yields were observed in 1,4dioxane and THF (entries 8 and 9). Other solvents, such as DMF, NMP, or CH₃CN, failed to give the target product. Several other ligands, such as 2,2'-bipy, pyridine, PPh₃, and dppf, were also tested in this reaction, whereas all these ligands led to **2a** in moderate yields (entries 10–13). In addition, lowering the temperature to 80 °C and the catalyst loading to 5 mol % resulted in decreased yields (entries 14 and 15). Product **2a** was not detected in the absence of CuOAc, which implied a radical pathway is not likely (entry 16).¹²

With the optimal conditions in hand, the scope of the arylboration reaction was then investigated. A slightly lower yield of 94% was obtained in a 1.0-mmol-scale reaction of 2a. As shown in Scheme 2, a variety of N-(2-iodoaryl)acrylamides reacted smoothly with B₂pin₂ in the presence of the CuOAc catalyst, affording the corresponding oxindoles in moderate to excellent yields. Substituents attached at C4-C5 on the aniline ring, either electron-donating (2c, 2g, 2h) or electronwithdrawing (2d-2f, 2i-2k, 2m), were well tolerated, and the products were achieved in the yields ranging from 60% to 85%. Note that bromine can survive from the reaction to afford 2f and 2k in 65% and 85% yields, respectively. N-Benzyl and 6-Cl-substrates were also suitable for this reaction to give the products 2b and 2l in 94% and 88% yield. In addition, the aryl group attached on the alkene moiety was also investigated. Products 2n-2s having different aryl substituents were achieved in moderate to excellent yields. The para- and ortho-methyl groups on the benzene ring resulted in products 2n and 2s in lower yields. Moreover, a number of 2methylacrylamide derived substrates were treated to the

Scheme 2. Substrate Scope for the Arylboration Reaction^a



"Reaction conditions: 1 (0.2 mmol), B_2pin_2 (0.3 mmol), CuOAc (10 mol %), 1,10-Phen (10 mol %), and KO'Bu (1.5 equiv) in toluene (2.0 mL) at 100 °C (oil bath) for 5–35 min. ^b1.0 mmol scale.

reaction, which led to the desired products 2u-2z in 57– 87% yields. Acrylamide with no substituent (R'' = H) could also be converted to 3-monosubstituted oxindole 2t, albeit in a lower yield of 24%. It is noteworthy that all the reactions could complete in 5–35 min, showing a fast reaction rate for this Cucatalyzed arylboration process.

To our delight, this copper-catalyzed difunctionalization process was further extended to a 1,2-arylsilylation reaction. Therefore, a range of silylated 3,3'-disubstituted oxindoles were obtained by the reaction of acrylamides 1 with PhMe₂Si-Bpin. As displayed in Scheme 3, several substrates having substituents, such as -OMe, -F, -Cl, and -Br, attached at

Scheme 3. Substrate Scope for the Arylsilylation Reaction



"Reaction conditions: 1 (0.2 mmol), $PhMe_2Si-Bpin$ (0.6 mmol), CuOAc (10 mol %), 1,10-Phen (10 mol %), KO'Bu (1.2 equiv), and 4 Å MS (100 mg) in toluene (2.0 mL) at room temperature for 1 h.

C4–C6 on the aniline ring were examined. The desired silanecontaining 3,3'-disubstituted oxindoles 3a-3h were formed in 52-90% yields in the presence of CuOAc catalyst at room temperature.

A tentative reaction mechanism is depicted in Scheme 4. The active species CuO'Bu is first formed by the reaction of

Scheme 4. Proposed Mechanism



CuOAc with KO^tBu. Subsequently, organocopper intermediates of Cu^I-Bpin or Cu^I-SiMe₂Ph are generated through the transmetalation of CuO^tBu with B₂pin₂ or PhMe₂Si-Bpin. The following borylcupration or silylcupration via the insertion of the C=C bond to Cu^I-Bpin or Cu^I-SiMe₂Ph leads to alkyl-Cu species I. The intramolecular coupling of alkyl-Cu with the CAr-I bond affords either borylated or silylated 3,3'disubstituted oxindoles 2 or 3 and releases catalyst precursor CuI.⁸ Finally, the catalytic cycle is finished by the conversion of CuI to CuO^tBu through an anionic exchange. Two possible pathways are as follows: (1) the oxidative addition of alkyl-Cu to C_{Ar} -I followed by reductive elimination of the Cu(III) species generated and (2) the nucleophilic aromatic substitution of alkyl-Cu with iodoarene might account for the conversion of intermediate I to product. The detailed mechanism could not be concluded at this stage, although an oxidative addition/reductive elimination sequence is more likely.13

In summary, we have developed a highly efficient coppercatalyzed arylboration and arylsilylation reaction of alkenes. A range of borylated or silylated 3,3'-disubstituted oxindoles are obtained in moderate to excellent yields in the reaction of *N*-(2-iodoaryl)acrylamide with B₂pin₂ or PhMe₂Si-Bpin. The present protocol provides an alternative access to functionalized oxindoles, which featured high efficiency, a broad scope, and mild reaction conditions by using a simple copper salt as the sole catalyst.

ASSOCIATED CONTENT

9 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00999.

Experimental procedures, characterization data for all products, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For reviews: (a) Fu, X.; Zhao, W. Youji Huaxue 2019, 39, 625–647.
 (b) Yin, G.; Mu, X.; Liu, G. Acc. Chem. Res. 2016, 49, 2413–2423.
 (c) Schultz, D. M.; Wolfe, J. P. Synthesis 2012, 44, 351–361.
 (2) Liu, Z.; Gao, Y.; Zeng, T.; Engle, K. M. Isr. J. Chem. 2019, 59, DOI: 10.1002/ijch.201900087.

(3) For the Pd-catalyzed arylboration of alkenes: (a) Shen, C.; Zeidan, N.; Wu, Q.; Breuers, C. B. J.; Liu, R.-R.; Jia, Y.-X.; Lautens, M. *Chem. Sci.* **2019**, *10*, 3118–3122. (b) Liu, Z.; Chen, J.; Lu, H.-X.; Li, X.; Gao, Y.; Coombs, J. R.; Goldfogel, M. J.; Engle, K. M. Angew. *Chem., Int. Ed.* **2019**, *58*, 17068–17073. (c) Yang, K.; Song, Q. Org. *Lett.* **2016**, *18*, 5460–5463. (d) Wei, F.; Wei, L.; Zhou, L.; Tung, C.-H.; Ma, Y.; Xu, Z. Asian J. Org. Chem. **2016**, *5*, 971–975. (e) Yang, K.; Song, Q. Org. Lett. **2016**, *18*, 5460–5463. (f) Vachhani, D. D.; Butani, H. H.; Sharma, N.; Bhoya, U. C.; Shahb, A. K.; der Eycken, E. V. V. Chem. Commun. **2015**, *51*, 14862–14865.

(4) For the Ni-catalyzed arylboration of alkenes: (a) Wang, W.;
Ding, C.; Pang, H.; Yin, G. Org. Lett. 2019, 21, 3968-3971.
(b) Logan, K. M.; Sardini, S. R.; White, S. D.; Brown, M. K. J. Am. Chem. Soc. 2018, 140, 159-162.

(5) For the Pd/Cu-cocatalyzed arylboration of alkenes: (a) Bergmann, A. M.; Dorn, S. K.; Smith, K. B.; Logan, K. M.; Brown, M. K. Angew. Chem., Int. Ed. 2019, 58, 1719–1723. (b) Kuang, Z.; Li, B.; Song, Q. Chem. Commun. 2018, 54, 34–37. (c) Logan, K. M.; Brown, M. K. Angew. Chem., Int. Ed. 2017, 56, 851–855. (d) Sardini, S. R.; Brown, M. K. J. Am. Chem. Soc. 2017, 139, 9823–9826. (e) Smith, K. B.; Brown, M. K. J. Am. Chem. Soc. 2017, 139, 7721–7724. (f) Chen, B.; Cao, P.; Yin, X.; Liao, Y.; Jiang, L.; Ye, J.; Wang, M.; Liao, J. ACS Catal. 2017, 7, 2425–2429. (g) Chen, B.; Cao, P.; Yin, X.; Liao, Y.; Jiang, L.; Ye, J.; Wang, M.; Liao, J. ACS Catal. 2017, 7, 2425–2429. (h) Logan, K. M.; Smith, K. B.; Brown, M. K. Angew. Chem., Int. Ed.
2015, 54, 5228-5231. (i) Smith, K. B.; Logan, K. M.; You, W.;
Brown, M. K. Chem. - Eur. J. 2014, 20, 12032-12036. (j) Semba, K.;

Nakao, Y. J. Am. Chem. Soc. 2014, 136, 7567-7570. (6) For the Ni/Cu-cocatalyzed arylboration of alkenes: Semba, K.;

Ohtagaki, Y.; Nakao, Y. Org. Lett. **2016**, *18*, 3956–3959. (7) For a DFT study: Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B.

(7) For a DFT study. Dang, E., Zhao, H., Elli, Z., Warder, T. B. Organometallics 2007, 26, 2824–2832.

(8) (a) You, W.; Brown, M. K. J. Am. Chem. Soc. 2015, 137, 14578–14581.
(b) You, W.; Brown, M. K. J. Am. Chem. Soc. 2014, 136, 14730–14733.

(9) For selected examples: (a) Zhang, Z.; Zhang, W.; Kang, F.; Ip, F.
C. F.; Ip, N. Y.; Tong, R. J. Org. Chem. 2019, 84, 11359–11365.
(b) Bergonzini, G.; Melchiorre, P. Angew. Chem., Int. Ed. 2012, 51, 971–974. (c) Christensen, M. K.; Erichsen, K. D.; Trojel-Hansen, C.; Tjørnelund, J.; Nielsen, S. J.; Frydenvang, K.; Johansen, T. N.; Nielsen, B.; Sehested, M.; Jensen, P. B.; Ikaunieks, M.; Zaichenko, A.; Loza, E.; Kalvinsh, I.; Björkling, F. J. Med. Chem. 2010, 53, 7140–7145. (d) Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. Chem. - Eur. J. 2008, 14, 8079–8081.

(10) For reviews: (a) Cao, Z.-Y.; Zhou, F.; Zhou, J. Acc. Chem. Res. **2018**, 51, 1443–1454. (b) Dalpozzo, R. Org. Chem. Front. **2017**, 4, 2063–2078. (c) Dalpozzo, R. Adv. Synth. Catal. **2017**, 359, 1772–1810. (d) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. Org. Biomol. Chem. **2012**, 10, 5165–5181. (e) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. Chem. Soc. Rev. **2012**, 41, 7247–7290. (f) Zhou, F.; Liu, Y.-L.; Zhou, J. Adv. Synth. Catal. **2010**, 352, 1381–1407.

(11) For 1,2-arylsilylation of alkenes: (a) Xu, Y.; Liu, X.; Chen, W.; Deng, G.; Liang, Y.; Yang, Y. J. Org. Chem. 2018, 83, 13930–13939.
(b) Xiao, G.; Chen, L.; Deng, G.; Liu, J.; Liang, Y. Tetrahedron Lett. 2018, 59, 1836–1840. (c) Xiao, G.; Chen, L.; Zhou, B.; Deng, G.; Gong, J.; Liang, Y. Adv. Synth. Catal. 2018, 360, 3477–3481. (d) Lv, W.; Yu, J.; Ge, B.; Wen, S.; Cheng, G. J. Org. Chem. 2018, 83, 12683–12693.

(12) Shirakawa, E.; Itoh, K.; Higashino, T.; Hayashi, T. J. Am. Chem. Soc. 2010, 132, 15537–15539.

(13) (a) Thapa, S.; Basnet, P.; Giri, R. J. Am. Chem. Soc. 2017, 139, 5700–5703. (b) Shrestha, B.; Thapa, S.; Gurung, S. K.; Pike, R. A. S.; Giri, R. J. Org. Chem. 2016, 81, 787–802.