Organic Syntheses

Discussion Addendum for:

Stereoselective Synthesis of 3-Arylacrylates by Copper-Catalyzed Syn Hydroarylation [(*E*)-Methyl 3-phenyloct-2-enoate]

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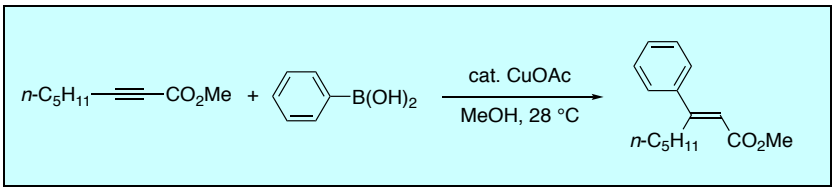

Conjugate arylation of alkynes activated by an electron-withdrawing group is a practical method to prepare substituted alkenes. Conventionally, arylcopper reagents have been employed for this purpose,[2] and the copper-catalyzed conjugate arylation using stoichiometric amounts of arylmagenesium halides has also been developed.[3] The *E*/*Z* stereoselectivity of the arylation products strongly depends on the structures of the alkyne substrates and arylmetal reagents as well as the reaction conditions. Moreover, nucleophilic arylmetal reagents used in the conventional methods have limited functional group compatibility. In striking contrast, the transition metal-catalyzed hydroarylations of alkynes with a broad substrate scope have recently been developed using bench-top stable arylboron reagents.[4] In particular, hydroarylation of activated alkynes generally afford products in which the aryl group is introduced at the carbon β to the electron-withdrawing group.

Although transition metal-catalyzed hydroarylations of alkynes are very useful, they require expensive rhodium or palladium catalysts, as well as additional ligands and/or additives. A few examples of catalysts based

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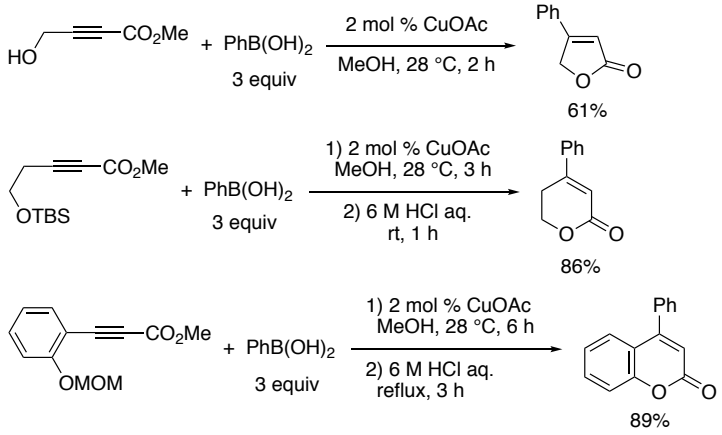
on inexpensive first-row transition metals, such as nickel and cobalt, have been reported, but they have seen limited development as compared to rhodium and palladium catalysts.[5] We have independently developed a hydroarylation of internal alkynoates with arylboronic acids using inexpensive copper catalysts, such as CuOAc or $Cu(OAc)_2$, in methanol at ambient temperature, which selectively afforded *syn*-hydroarylation products.[6] Furthermore, neither ligands nor additives are required in this reaction. Thus, the Cu-catalyzed hydroarylation of alkynoates provides easy access to synthetically valuable β,β-disubstituted acrylates.

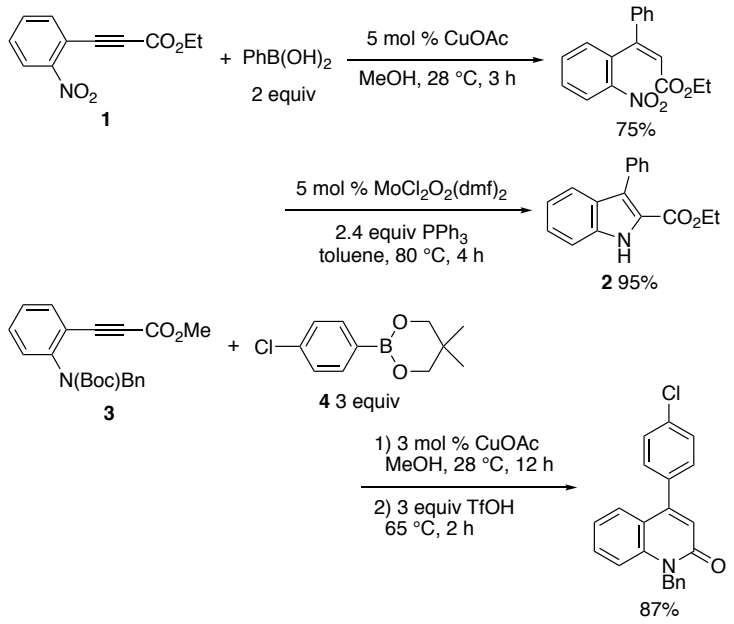
With the abovementioned features, the Cu-catalyzed hydroarylation of internal alkynoates has been applied to the synthesis of various heterocyclic motifs, which are found in natural products and pharmaceutically important compounds. For example, 4-arylbutenolides, 4-arylpentenolides, and 4-arylcoumarins have been synthesized from alkynoates having an alcohol or phenol moiety on the alkyne terminal *via* tandem Cu-catalyzed hydroarylation/lactonization processes.[7,8] Representative examples are shown in Scheme 1. Notably, hydroarylation/coumarin formation enabled the efficient synthesis of seven natural neoflavones.[7]



Scheme 1. Cu-catalyzed hydroarylation/lactonization

Nitrogen heterocycles have also been synthesized by Cu-catalyzed hydroarylation, as shown in Scheme 2.[9–11] The hydroarylation product derived from (*o*-nitrophenyl)alkynoate **1** was converted into 3-phenyl-indole-2-carboxylate **2** in high yield *via* Mo-catalyzed Cadogan cyclization.[9,12] Hydroarylation of the orthogonally protected (*o*-amino-

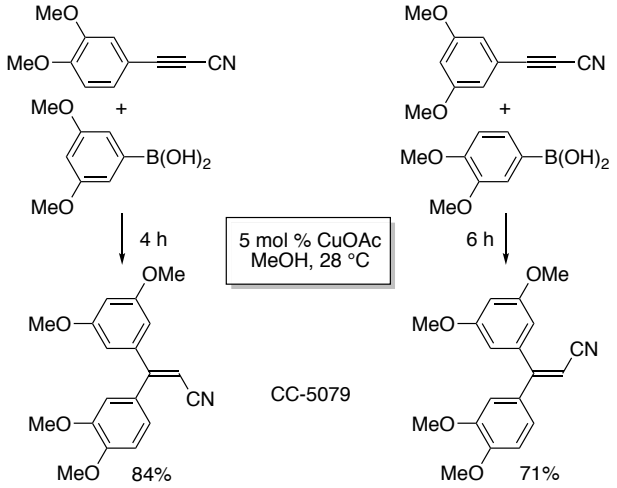
phenyl)alkynoate **3** could be performed under similar conditions to afford an *N*-benzyl-4-aryl-2-quinolone after acidic removal of the Boc group.[10] Because of the bulky protected *o*-aminophenyl moiety, protodeboration of the arylboronic acid proceeded faster than the desired hydroarylation. Thus, arylboronic acid 2,2-dimethyl-1,3-propanediol esters, such as **4**, should be used to suppress the undesired protodeboration. The use of a sterically more demanding pinacol ester retarded the reaction, thus diminishing the product yield. This tandem hydroarylation/lactamization process could be successfully applied to the synthesis of a natural alkaloid and relevant derivatives.[11]



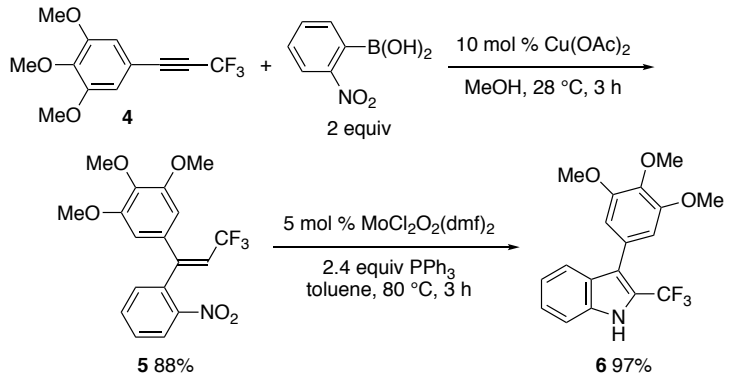
Scheme 2. *N*-Heterocycles synthesis via Cu-catalyzed hydroarylation

Besides alkynoates, other electron-deficient alkynes have also been used as substrates for Cu-catalyzed hydroarylation. The hydroarylation of 3-aryl-2-propynenitriles stereoselectively affords 3,3-diarylacrylonitriles,[13] and this method has been successfully extended to the synthesis of antitumor agent CC-5079 (Scheme 3).[14] Since the biological activity of CC-5079 strongly depends on its olefin geometry,[15] Cu-catalyzed hydroarylation is quite useful as it affords both stereoisomers in a stereospecific manner. Trifluoromethyl groups also function as electron-withdrawing groups, as

Cu-catalyzed hydroarylation efficiently proceeds with (trifluoromethyl)-alkynes, affording valuable tri-substituted (trifluoromethyl)alkenes.[16] Thus, the Cu-catalyzed hydroarylation of (trifluoromethyl)alkyne **4** with (*o*-nitro)phenylboronic acid stereoselectively furnished trisubstituted alkene **5**, which was further transformed into 3-aryl-2-(trifluoromethyl)indole **6** in high yield *via* the modified Cadogan cyclization (Scheme 4).[17]



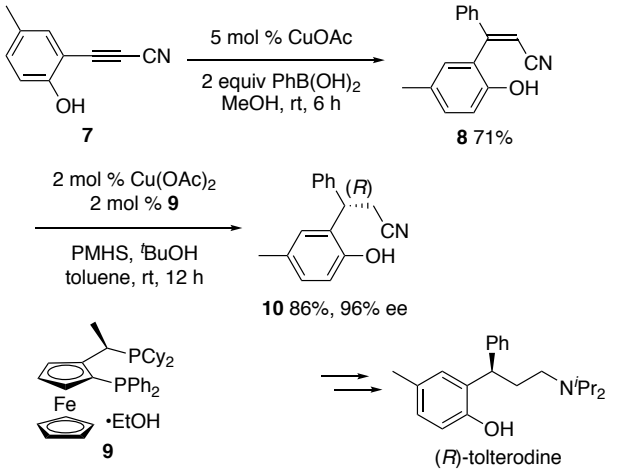
Scheme 3. Synthesis of CC-5079



Scheme 4. Synthesis of 3-aryl-2-(trifluoromethyl)indole

Enantioselective conjugate reduction of β,β-diaryl-α,β-unsaturated carbonyl compounds provides efficient access to chiral 1,1-diarylalkyl

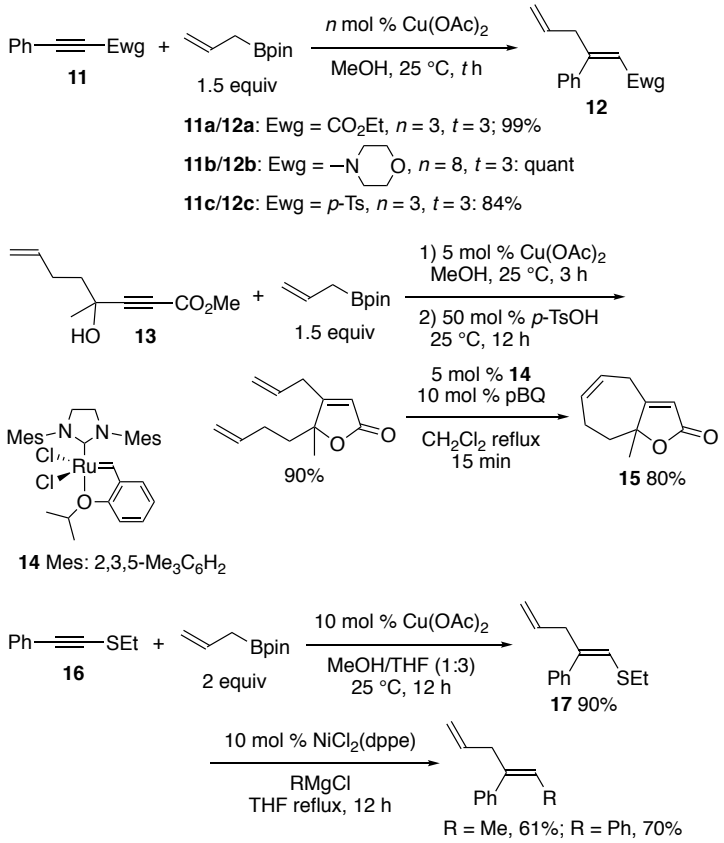
motifs, which are frequently found in bioactive molecules. Therefore, stereoselective construction of the required unsaturated carbonyl precursors is crucial, and Cu-catalyzed hydroarylation has been used for this purpose.[18] As a demonstration of this strategy, Yun and co-workers reported the enantioselective synthesis of (*R*)-tolterodine,[19] a potent muscarinic antagonist, *via* Cu-catalyzed asymmetric conjugate reduction of a 3,3-diarylacrylonitrile (Scheme 5).[20] The required acrylonitrile precursor **8** was obtained in 71% yield *via* Cu-catalyzed hydroarylation of cyanoalkyne **7** bearing an unprotected phenol moiety with phenylboronic acid. Subsequent asymmetric conjugate reduction of **8** with polymethylhydrosiloxane (PMHS) as the reducing agent was performed in the presence of 2 mol % $Cu(OAc)_2$ and 2 mol % chiral ligand **9** ((*R*)-(*S*)-Josiphos) in toluene at room temperature, affording the desired saturated 3,3-diarylpropanenitrile **10** in 86% yield and with 96% ee. Finally, **10** was transformed to (*R*)-tolterodine in 63% yield over two steps.



Scheme 5. Enantioselective synthesis of (*R*)-tolterodine

When allylboronate was used instead of arylboron reagents under the Cu-catalyzed hydroarylation conditions, hydroallylation products were obtained with high regio- and stereoselectivities. Notably, this mild Cu-catalyzed protocol selectively produced 1,4-dienes in good yields, although such a skipped diene tends to undergo isomerization to a more stable 1,3-diene (conjugate diene). Hydroallylation proceeded with alkynylamide **11b** and alkynylsulfone **11c**, in addition to alkynoates and cyanoalkynes

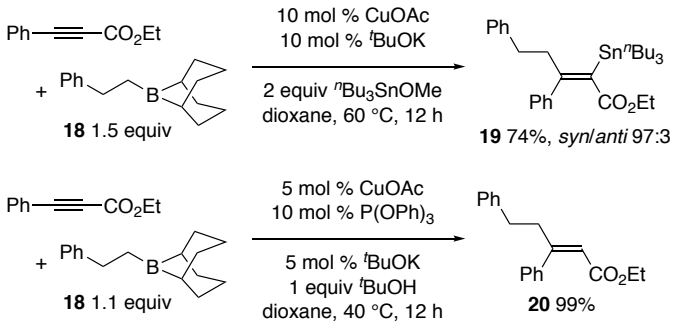
(Scheme 6).[21] The introduced allyl moiety could be employed as a synthetic handle for subsequent transformations, such as hydroboration/oxidation or hydroboration/Suzuki–Miyaura coupling. The interesting bicyclic butenolide **15** was also synthesized from 1,6-enynoate **13** *via* sequential hydroallylation/ring-closing metathesis.[22] Furthermore, Kong, Zhu, and co-workers reported the hydroallylation of thioalkynes, such as **16**.[23] In this case, modified conditions with a mixed solvent (MeOH/THF, 1:3) improved the product yield. The obtained product **17** could be used for nickel-catalyzed cross coupling with Grignard reagents *via* C–S bond cleavage.



Scheme 6. Cu-catalyzed hydroallylation of internal alkynes

A disadvantage of Cu-catalyzed hydroarylation and hydroallylation is that they are restricted to the synthesis of trisubstituted alkenes. Hence, an

alternative method to synthesize tetrasubstituted alkenes was developed by Sawamura, Ohmiya, and co-workers: the three-component coupling of an alkynoate, alkyl-9-BBN **18**, and $^{n}Bu_3SnOMe$ proceeded in the presence of catalytic amounts of CuOAc and $^{t}BuOK$ in dioxane at 60 °C, affording alkenylstannane **19** in 74% yield with a *syn*/*anti* ratio of 97:3 (Scheme 7).[24] The obtained product could be utilized as a substrate for various cross-coupling reactions. When adding $^{t}BuOH$ instead of $^{n}Bu_3SnOMe$ as the proton source, hydroalkylation product **20** was also obtained quantitatively.[25] In this case, the use of $P(OPh)_3$ as the ligand was necessary to achieve a complete *syn* selectivity.



Scheme 7. Cu-catalyzed stannylalkylation and hydroalkylation

In summary, Cu-catalyzed hydroarylation of electron-deficient alkynes with arylboron reagents has been developed as an efficient protocol for the regio- and stereoselective synthesis of valuable trisubstituted alkenes with a functional group under mild conditions. This method is also intriguing because inexpensive copper acetates act as catalysts, and neither ligands nor additives are required. The broad substrate scope of this Cu-catalyzed hydroarylation has been exploited for the synthesis of important heterocyclic compounds, including butenolides, pentenolides, coumarins, indoles, and 2-quinolones. Moreover, the protocol was extended to hydroallylation and hydroalkylation/stannylalkylation using allylboronates or alkylborons, respectively, instead of arylboron reagents. In the future, these methods are expected to find broad application in the synthesis of natural products, functional materials, and bioactive molecules.

References

1. Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan. Email: yamamoto-yoshi@ps.nagoya-u.ac.jp
2. Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631.
3. (a) Xie, M.; Huang, X. *Synlett* **2003**, 477–480. (b) Jennings, M. P.; Swant, K. B. *Eur. J. Org. Chem.* **2004**, 3201–3204. (c) Mueller, A. J.; Jennings, M. P. *Org. Lett.* **2007**, *9*, 5327–5329.
4. Yamamoto, Y. *Catalytic Alkyne Hydroarylation Using Arylboron Reagents, Aryl Halides, and congeners*, in *Catalytic Hydroarylation of Carbon–Carbon Multiple Bonds* (Eds.: L. Ackermann, T. B. Gunnoe, L. G. Habgood), Wiley-VCH, Weinheim, **2017**, Chap. 1.7, pp. 305-359.
5. (a) Shirakawa, E.; Takahashi, G.; Tsuchimoto, T.; Kawakami, Y. *Chem. Commun.* **2001**, 2688–2689. (b) Robbins, D. W.; Hartwig, J. F. *Science* **2011**, *333*, 1423–1427. (c) Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chem. Eur. J.* **2008**, *14*, 11296–11299.
6. Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008**, 2010–2012.
7. Yamamoto, Y.; Kirai, N. *Org. Lett.* **2008**, *10*, 5513–5516.
8. Yamamoto, Y.; Kirai, N. *Hetrocycles* **2010**, *80*, 269–279.
9. Yamamoto, Y.; Yamada, S.; Nishiyama, H. *Adv. Synth. Catal.* **2011**, *353*, 701–706.
10. Murayama, T.; Shibuya, M.; Yamamoto, Y. *Adv. Synth. Catal.* **2016**, *358*, 166–171.
11. Murayama, T.; Shibuya, M.; Yamamoto, Y. *J. Org. Chem.* **2016**, *81*, 11940–11949.
12. Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnáiz, F. J. *Adv. Synth. Catal.* **2007**, *349*, 713–718.
13. Yamamoto, Y.; Asatani, T.; Kirai, N. *Adv. Synth. Catal.* **2009**, *351*, 1243–1249.
14. Zhang, L.-H.; Wu, L.; Raymon, H. K.; Chen, R. S.; Corral, L.; Shirley, M. A.; Narla, R. K.; Gomez, J.; Muller, G. W.; Stirling, D. I.; Bartlett, J. B.; Schafer, P. H.; Payvandi, F. *Cancer Res.* **2006**, *66*, 951–959.
15. Fang, Z.; Song, Y.; Sarkar, T.; Hamel, E.; Fogler, W. E.; Agoston, G. E.; Fanwick, P. E.; Cushman, M. *J. Org. Chem.* **2008**, *73*, 4241–4244.
16. Yamamoto, Y.; Ohkubo, E.; Shibuya, M. *Green Chem.* **2016**, *18*, 4628–4632.

17. Yamamoto, Y.; Ohkubo, E.; Shibuya, M. *Adv. Synth. Catal.* **2017**, *359*, 1747–1751.
18. (a) Yoo, K.; Kim, H.; Yun, J. *Chem. Eur. J.* **2009**, *15*, 11134–11138; (b) Ebner, C.; Pfaltz, A. *Tetrahdron* **2011**, *67*, 10287–10290. (c) Itoh, K.; Tsuruta, A.; Ito, J.; Yamamoto, Y.; Nishiyama, H. *J. Org. Chem.* **2012**, *77*, 10914–10919. (d) Li, Y.; Dong, K.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 6748–6752.
19. Nilvebrant, L. *Rev. Contemp. Pharmacother.* **2000**, *11*, 13–27.
20. Yoo, K.; Kim, H.; Yun, J. *J. Org. Chem.* **2009**, *74*, 4232–4235.
21. Yamamoto, Y.; Yamamda, S.; Nishiyama, H. *Chem. Eur. J.* **2012**, *18*, 3153–3156.
22. Yamamoto, Y.; Shibano, S.; Kurohara, T.; Shibuya, M. *J. Org. Chem.* **2014**, *79*, 4503–4511. Also see, ref. 11a.
23. Kong, W.; Che, C.; Kong, L.; Zhu, G. *Tetrahedron Lett.* **2015**, *56*, 2780–2782.
24. Wakamatsu, T.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11620–11623.
25. Wakamatsu, T.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Beilstein J. Org. Chem.* **2015**, *11*, 2444–2450.

Professor Yoshihiko Yamamoto received his Ph.D. degree in 1996 from Nagoya University, where he was appointed Assistant Professor in 1996, promoted to Associate Professor in 2003. He moved to Tokyo Institute of Technology in 2006, and returned to Nagoya University in 2009. He began his independent career at the current position in 2012. His research interests are focused on organometallic catalysts and their application to the synthesis of biologically important molecules.