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(Hetero)arylboration of alkynes: a strategy for the synthesis of α,α -bis(hetero)arylketones†

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Abstract

A method for (hetero)arylboration of alkynes is presented. The reaction allows for the synthesis of densely functionalized tetrasubstituted alkenes with control of regioselectivity and diastereoselectivity. The conversion of the products to the corresponding α,α -bis(hetero)arylketones is also shown.

Alkyne carbofunctionalization reactions represent an important strategy for the synthesis of stereodefined alkenes.¹ In recent years, alkyne carboboration has been demonstrated to work with a variety of substrates to prepare tri- and tetrasubstituted stereodefined alkenes.^{2,3} These reactions are valuable as the generated C–B bond can be elaborated to other groups by application of established strategies. Of the several catalysts systems applied toward alkyne carboboration, Cu-catalyzed variants have been investigated most expansively.³ These reactions have been shown to operate by addition of Cu-Bpin to an alkyne followed by capture of the generated alkenyl Cu-complex with an electrophile. In 2014, our group reported the first Cu-catalyzed arylboration of alkynes with aryl iodides.^{4a} The reactions worked well across a broad range of substrates; however, the regioselectivities suffered for some cases. Furthermore, reactions with substrates other than diarylalkynes resulted in lower yields (Scheme 1A).

In 2015, Cazin reported a Cu/Pd-catalyzed arylboration of alkynes with aryl bromides. These reactions required the use of a Pd co-catalyst to activate the aryl bromide component.^{4b} More recently, Semba/Nakao have investigated a similar Cu/Pd-catalyzed arylboration of alkynes with primarily aryl chlorides (Scheme 1B).^{4c} These reactions likely operate by the catalytic cycles illustrated in Scheme 1C, in which an alkenyl-Cu-complex (**III**) is formed by borylcupration that then undergoes Pd-catalyzed cross coupling. This work is related to studies from the Semba/Nakao group as well as studies from our own lab towards Cu/Pd-catalyzed arylboration of activated alkenes.⁵ In this manuscript, we report our own efforts towards Cu/Pd-catalyzed arylboration of alkynes with aryl bromides to specifically demonstrate reaction with heterocyclic substrates, as well as showcase a strategy for the synthesis of α,α -bis(hetero)arylketones (Scheme 1C).

† Electronic supplementary information (ESI) available: Experimental procedures and copies of spectra. See DOI: 10.1039/c9ob00961b

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Conflicts of interest

There are no conflicts to declare.

Recently, our group reported the synthesis and use of Cu-pyridylidene complexes (*e.g.*, **5**) for heteroarylboration of heteroalkenylarenes.^{5h} These conditions were also found to function well in the arylboration of an alkyne in one example. As shown in Scheme 2, arylboration of alkyne **2** with arylbromide **1** in the presence of Cu-catalyst **5** and APhosPdG3 worked well to provide **3** in excellent yield as a single observable regioisomer.⁶ It should be noted that in this example, SIMesCuCl (**4**) was also a competent catalyst; however, we elected to employ the Cu-pyridylidene complex **5** to further highlight the utility of these catalysts.

With an optimized set of conditions in hand, we surveyed the scope of this transformation (Scheme 3). Internal alkynes that are substituted with aryl-, alkyl- and silyl-groups all function well. The regioselectivity of the reaction is established during the addition of Cu-Bpin, which occurs through a transition state to generate the more stable alkenyl-Cu-complex. The reaction was found to tolerate NHBoc and OTBDPS groups. In addition, heterocycles such as pyridines, furan, indoles and carbazoles can be utilized on both the arylbromide and/or alkyne components.

Prior studies have demonstrated the utility of the C–B bond towards the synthesis of all carbon, stereodefined, tetrasubstituted alkenes by cross coupling.^{2d} While oxidation of alkenylboronic esters has been demonstrated, use of this process to prepare α,α -bis(hetero)arylketones has not been shown. Thus simple treatment of the alkenylboronic esters with NaBO₃ allows for smooth conversion to the ketones **21–24** (Scheme 4). The strategy outlined here for synthesis of α,α -bis(hetero)arylketones represents an orthogonal approach to this class of molecules that may offer advantages in some cases. For example, use of the related cross coupling approach, α -arylation,⁷ to prepare **22–24** would be complicated due to poor regioselectivity of reaction at one of two similarly substituted benzyl positions.

Conclusions

In conclusion, our efforts towards the arylboration of alkynes is presented. We further demonstrate the utility of pyridylidene complexes in catalysis and showcase a strategy for the synthesis of α,α -bis(hetero)arylketones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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6. Control experiments confirmed that the Pd-catalyst is necessary for this reaction, see the ESI† for details.
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A) Previous Work: Cu-Catalyzed Arylboration: Brown 2014

B) Previous Work: Cu/Pd-Catalyzed Arylboration: Cazin 2015 and Semba/Nakao 2017

C) This Work: Cu/Pd-Catalyzed (Hetero)arylboration

Scheme 1.
Arylboration of alkynes.

Scheme 2.

Comparison of Cu-Catalysts. Yield determined by analysis of the unpurified reaction mixture by ¹H NMR with an internal standard.

Scheme 3.

Reaction scope. Yields are the isolated, purified product and are reported as the average of at least two experiments. ^a Yield determined by analysis of the unpurified reaction mixture with an internal standard. ^b Reaction run at 45 °C.

Scheme 4.

Synthesis of α,α -bis(hetero)arylketones. Yields are the isolated, purified product and are reported as the average of at least two experiments.