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Copper-Catalyzed Borylacylation of Activated Alkenes with Acid Chlorides

Yuan Huang, Kevin B. Smith, and M. Kevin Brown*

Brown Department of Chemistry, Indiana University 800 E. Kirkwood Avenue, Bloomington, IN 47401 (USA)

Abstract

A method for the copper-catalyzed borylacylation of activated alkenes is presented. The reaction involves borylcupration of the alkene, followed by capture of the generated alkyl–copper intermediate with an acid chloride. The reactions operated with low catalyst loading and generally occur within 15 min at room temperature for a range of activated alkenes. In the case of vinyl arenes, enantioselective borylacylation was possible.

Keywords

acid chlorides; alkenes; boron; copper; homogeneous catalysis

Cross-coupling reactions of acyl electrophiles and organometallic reagents represent a useful and well-established strategy for the synthesis of ketones (Scheme 1A).^[1] Such transformations have been shown to occur with a variety of acyl electrophiles (e.g., acid chlorides,^[2] thioesters,^[3] and activated amides^[4]) as well as organometallic reagents (e.g., Grignard,^[5] zinc,^[6] tin,^[7] and boron^[8]). More recent advances in this area have demonstrated that the coupling of acyl electrophiles and organohalides is possible in the presence of a reducing agent.^[9]

In recent years, copper-catalyzed carboboration reactions of alkenes have emerged as a useful strategy for chemical synthesis because the C–B bond can be converted into other groups with ease, thus allowing for carbofunctionalization.^[10] Over the last several years, our research group^[11] and others^[12,13] have developed methods for the arylboration of alkenes by Cu/Pd cooperative catalysis (Scheme 1B). In these reactions, an alkyl–copper intermediate is generated by catalytic borylcupration of an alkene, followed by palladium-catalyzed cross-coupling. This strategy has been shown to be effective for the functionalization of alkenyl arenes, 1,3-dienes, vinyl silanes, and strained alkenes.

To extend the utility of these reactions, we desired to develop a process in which acyl electrophiles could be employed (Scheme 1C).^[14] Such a process was viewed as a valuable strategy, as the products would be versatile entities for chemical synthesis and map onto

*Department of Chemistry, Indiana University 800 E. Kirkwood Avenue, Bloomington, IN 47401 (USA), brownmkb@indiana.edu.

Conflict of interest

The authors declare no conflict of interest.

molecules of biological interest (Scheme 1D).^[15] Though the direct formation of ketones through a carboboration process is unknown, the Popp group recently reported the borylcarboxylation of vinyl arenes to generate carboxylic acids.^[16] While this is a significant advance, in our view, the direct synthesis of ketones from simple and widely available precursors would be valuable to streamline synthesis. Furthermore, Buchwald and co-workers have developed a copper-catalyzed hydroacylation reaction of alkenyl arenes with anhydrides^[17] and more recently carboxylic acids.^[18] Herein, a method is presented for the borylacylation of a variety of activated alkenes with widely available acid chlorides (Scheme 1C).^[19]

Initial studies focused on the use of thioester-derived electrophiles in a Fukuyama-type cross-coupling.^[3] Under all conditions attempted, however, the desired borylacylation product was formed in less than 2% yield (Scheme 2A). We then turned our attention to the use of acid chlorides (e.g., **1**).^[2] In this case, the desired product **3** was observed, albeit in low yield. Further analysis of the reaction through control experiments revealed that the Pd catalyst was not necessary. It appears that the generated C(sp³)-Cu complex **5**^[20] can undergo direct reaction with an acid chloride according to the catalytic cycle shown in Scheme 2B.^[21,22]

From this result, the reaction was initially optimized to the conditions shown in Table 1, entry 1. Key to the reaction optimization was the identification of a solvent and base that minimized the background formation of PhCO₂*t*-Bu. This criterium was met with the combination of Et₂O and LiO*t*-Bu, in which the base has minimal solubility. Other activated carbonyl derivatives **7–10** were evaluated, but did not allow for product formation (Table 1, entries 2–5). As shown in Table 1, entries 6–8, the reaction is largely specific to the use of SIMesCuCl. Finally, it was observed that the yield of the reaction could be improved if 2.0 equivalents of the base were used (Table 1, entry 12). Furthermore, it was identified that the reaction could be carried out with only 1 mol% SIMes-CuCl and was complete after only 15 min (Table 1, entry 13). The reaction could also be carried out in air with nearly identical results to those observed for the reaction carried out under an inert atmosphere (Table 1, entry 14).

Under the optimized conditions, a range of vinyl arenes and acid chlorides were investigated (Scheme 3). Electron-rich (product **12**), electron-poor (products **14** and **16**), and sterically demanding vinyl arenes (products **13–16**) were tolerated. Furthermore, functional groups such as benzyl chlorides (product **11**), nitriles (product **14**), aryl chlorides (product **16**), ketones (product **18**), and esters (product **15**) did not inhibit product formation to any significant degree. At this time, attempted borylacylation of 1,2-disubstituted alkenyl arenes has only resulted in recovery of the starting material (not shown). With respect to the acid chloride component, besides aryl chlorides with various steric and electronic properties (products **19–21**), alkyl acid chlorides could also be used (products **22–27**).

A notable aspect of this study is that the borylacylation reaction can be extended to other classes of activated alkenes (Scheme 4). The reaction of 1-phenylbutadiene (**29**) under the standard conditions resulted in the formation of a mixture of 1,2- and 1,4-borylacylation products **30** and **31**, respectively.^[11d,e] The formation of the 1,4-borylacylation product

could be suppressed provided that an additional substituent was present, as in diene **32**. 2,3-Dimethylbutadiene (**34**) could also be used, and resulted in exclusive formation of the 1,2-borylacylation product **35**, which contains a quaternary carbon center. Finally, bicyclic strained alkenes could also be used in this reaction. All products **37–40** were generated as a single diastereomer in good yield.

The borylacylation reaction could also be carried out on a gram scale by an operationally simple procedure [Eqs. (1) and (2)].

The products of the borylacylation reaction are useful intermediates for chemical synthesis (Scheme 5). The primary alkyl-Bpin product **3** was subjected to cross-coupling conditions to provide **44** in 62% yield.^[23] Owing to the ring strain of bicyclic alkene **37**, ring-opening cross-metathesis with ethylene allowed for the formation of **45**. After oxidation of the Bpin unit of **9** to an alcohol, highly diastereoselective addition of a methyl Grignard generated **46**.^[24] Likewise, diastereoselective reduction of the oxidized product derived from **43** provided **47**, which could also be cyclized under copper catalysis to provide chromane derivative **48**.^[25]

Finally, we briefly investigated the enantioselective borylacylation of vinyl arenes (Scheme 6). We evaluated a series of catalysts and found that Cu complex **49**, which was readily prepared in two steps from commercially available materials, promoted the formation of (*R*)-**3** with 85:15 er. Additional studies showed that sterically demanding vinyl arenes enabled formation of the desired product with higher yield and enantioselectivity (products (*R*)-**13** and (*R*)-**17**). Borylacylation product (*R*)-**13** (which was prepared on a 1.0 mmol scale) could be recrystallized to afford the compound in 99:1 er and ultimately allowed for absolute structure determination by X-ray crystallography. The Bpin unit of (*R*)-**13** could also be oxidized to generate the corresponding alcohol without loss of enantiomeric purity.^[26]

In summary, we have described a method for the borylacylation of activated alkenes with acid chlorides. The method was shown to be compatible with vinyl arenes, 1,3-dienes, and strained bicyclic alkenes as well as acid chlorides with varying steric and electronic properties. Owing to the short reaction times and use of readily available starting materials, the method is straightforward and practical. Future efforts will focus on expanding the range of alkenes that can be utilized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A) Cross-Coupling with Acyl Electrophiles **B) Arylboration of Alkenes by Pd/Cu Cooperative Catalysis** **C) This Study** **D) Representative Molecules** **Scheme 1.**

Relevant precedent and current studies.

(BPin)₂ = bispinacolatodiboron.

Scheme 2.

Initial findings and proposed catalytic cycle. SIMes=*N,N'*-bis(2,4,6-trimethylphenyl)-2,5-imidazolin-2-ylidene.

Scheme 3.

Borylacylation of vinyl arenes and acid chlorides. Yields are for the isolated, purified product and reported as the average of at least two experiments. [a] The reaction was carried out for 30 min. [b] The reaction was carried out with 5 mol% SIMesCuCl in toluene and with 1.5 equivalents of LiOt-Bu for 2 h. Ts = *p*-toluenesulfonic acid.

Scheme 4.

Borylacylation of various activated alkenes. [a] Yields were determined by ^1H NMR analysis of the combined mixture of 1,2- and 1,4-borylacylation products with an internal standard. [b] Reaction time: 2 h. Reaction run in toluene. Bz= benzoyl.

Scheme 5.

Transformations of borylacylation products. dba = dibenzylideneacetone.

Scheme 6.
Enantioselective borylacylation of vinyl arenes.

Table 1

Reaction optimization.

Entry	Change from conditions in the scheme	Yield [%] ^[a]
1	no change	88
2	7 instead of benzoyl chloride (1)	<2
3	8 instead of benzoyl chloride (1)	<2
4	9 instead of benzoyl chloride (1)	<2
5	10 instead of benzoyl chloride (1)	<2
6	IMesCuCl instead of SIMesCuCl	56
7	dpppCuCl instead of SIMesCuCl	25
8	dppbzCuCl instead of SIMesCuCl	6
9	NaOt-Bu instead of LiOt-Bu	56
10	THF instead of Et ₂ O	13
11	toluene instead of Et ₂ O	54
12	2.0 equiv LiOt-Bu instead of 1.5 equiv LiOt-Bu	98
13 ^[b]	2.0 equiv LiOt-Bu instead of 1.5 equiv LiOt-Bu	98
14 ^[c]	2.0 equiv LiOt-Bu instead of 1.5 equiv LiOt-Bu	96

^[a]The yield was determined by GC analysis with a calibrated internal standard.

^[b]The reaction was carried out with 1 mol% SIMesCuCl for 15 min.

^[c]The reaction was carried out with 1 mol% SIMesCuCl for 15 min in air. Bn= benzyl, Boc=*N-tert*-butoxycarbonyl.