

Letter

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Acyl Fluorides as Efficient Electrophiles for the Copper-Catalyzed Boroacylation of Allenes

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ABSTRACT: The copper-catalyzed reaction of allenes with bis(pinacolato)diboron and acyl electrophiles is reported. In this transformation, acyl fluorides have been proven to be more efficient coupling partners than their chloride or carboxylate analogs. The optimized reaction conditions employed were shown to be compatible with a range of commonly used functional groups thus allowing the formation of a library of β -boryl β , γ -unsaturated ketones by varying the nature of the allene and acyl fluoride substrates.

KEYWORDS: Copper Catalysis - Allene - Acyl Fluoride - Boration - Vinylboron

The presence of contiguous carbon functionalization sites on allene motifs accounts for their use as versatile reactive intermediates in organic synthesis.¹ The possibility to functionalize allenes in a controlled manner by a 1,2-addition onto one of their C(sp)-C(sp²) unsaturations represents *a priori* a valuable synthetic tool for the straightforward elaboration of complex carbon skeletons. While such a type of reactivity can be accessed using standard synthetic methods, achieving regio- and stereoselective transformations is however generally problematic. Significant efforts have been recently directed towards the development of new strategies, based on the use of transition metal catalysis, in order to deal with these issues and allow the efficient and stereoselective functionalization of allenes.^{1,2}

During the last five years, the catalytic 1,2-addition of nucleophilic copper(I) species onto C(sp)-C(sp²) allene unsaturations has been the subject of many studies.^{2e} Efforts in this domain have demonstrated the efficiency of such an approach for the regiocontrolled formation of organocopper intermediates. Various catalytically generated Cu-B,3-5 Cu-Si,4g,1,6 Cu-H,3d,7 Cu-C,8 Cu-O9 and Cu-N10 species were shown as capable of delivering their nucleophilic moiety to the central carbon atom of allenic substrates thus producing intermediate allylcopper entities." Their subsequent electrophilic trapping in the presence of a protic source,^{3,6a,b,f} an aldehyde,^{4a,6a,d,9,10} a ketone,^{4a,k,6d,8,9,10} an imine,^{4g,h,m,7a} a Michael acceptor,^{4j,6e} an allylic species,^{4c,d,7b} an aryl halide,^{4e} a cyano group⁴ⁱ or even carbon dioxide^{6c} allowed for the preparation of a large range of synthetically valuable building blocks. It is however interesting to note that despite the variety of transformations developed so far, those involving the use of an acylating reagent as the

electrophilic coupling partner remain rare (Scheme 1, top part).

Scheme 1. Previous reports on the catalytic acylation/formylation of organocopper(I) species and our approach to the boroacylation of allenes

Trapping of Cu(I) intermediate with acylating or formylating reagents

D- Boroacylation of allenes, this work -



This is also true when one considers the field of coppercatalyzed nucleophilic transfers in general. To the best of our knowledge, only three groups previously reported the acylation of a catalytically generated organocopper species. In 2013, our group described a procedure for the synthesis of acylsilanes which involves a copper-catalyzed silylation of anhydrides (Scheme 1-A).12 The first extension to a threecomponent transformation was developed by Buchwald and co-workers with the enantioselective reductive coupling of styrenes with anhydrides (Scheme 1-B).¹³ This year, the group of Fujihara and Tsuji reported the copper-catalyzed boro- and silaformylation of alkyl-substituted allenes using hexyl formate as an acylating agent (Scheme 1-C).41 This elegant approach allowed the preparation of vinylboron derivatives containing a versatile formyl group. Whereas the formate ester appeared to be reactive enough to be employed as an electrophile in this transformation, no extension to the use of other acyl derivatives has been reported in the literature.¹⁴ In this context and following our continuous interest in Cu-catalyzed reactions, we envisioned to use acyl fluorides as alternative reagents to other acid derivatives for the trapping of catalytically generated copper species.15 We report herein our investigations in this field which have led to the development of a Cu-catalyzed regioselective boroacylation of allenes using acyl fluorides as electrophilic partners to generate β-boryl β ,y-unsaturated ketones possessing a quaternary center (Scheme 1-D).

We started our studies by attempting to react allene 3a, with $B_2Pin_2 a$ and benzoyl fluoride (1, X = F) in the presence of a catalytic amount of a copper species (see Table 1, top part).

Preliminary tests (not presented in Table 1) showed that the presence of an additive, whose role may be to activate the boron reagent, was crucial to obtain the desired product 4a in significant amount. Tetrabutylammonium difluorotriphenyl-silicate (TBAT) and lithium tert-butoxide (LiOtBu) were found to be poorly effective, whereas sodium trimethylsilanoate (TMSONa) allowed the formation of the boroacylation adduct.¹⁶ With regard to the copper catalyst, a screening of various ligands showed that 1,1'bis(diphenylphosphino)ferrocene (dppf) was suitable for this transformation. On the basis of these preliminary observations, we started to optimize the other reaction parameters (Table 1). Several copper(I) sources were first screened in association with the dppf ligand. The use of the cationic [Cu(MeCN)₄]PF₆ complex furnished the desired product in 61% yield (entry 1) while copper(I) iodide was completely ineffective under the same conditions (entry 2). Reacting the substrates in the presence of the separately prepared and isolated (dppf)CuCl complex did not improve the yield of the reaction (entry 3). Finally, it was proven that copper(II) acetate (5 mol%) in combination with 6 mol% dppf was an effective catalytic system as 4a could be formed in 62% yield (entry 4). Consequently, it was decided to keep the commercially available and inexpensive Cu(OAc)₂ as the copper source to carry on the optimization. Reducing the reaction temperature from 20 °C to o °C led to an increase in the yield (87%, entry 5). Under

these conditions, product **4a** could be obtained in 80% yield after purification. As shown in entries 6 and 7, reducing the amount of TMSONa or simply suppressing it had a detrimental effect on the reactivity. Finally, the use of benzoyl chloride or benzoyl anhydride as an alternative acyl source was evaluated (entry 8 and 9). No improvement could however be achieved.¹⁷

Table 1. Optimization of the reaction parameters^a

Ph X	PinB-BPin 2 + Ph \rightarrow Ph 3a	[Cu] source dppf (6 TMSONa (THF,	(5 mol%) mol%) ∕n equiv.) 3 h.	Ph	BPin Me Ph 4a
Entry	[Cu] Source	T (°C)	X	n	Yield (%) ^b
1	[Cu(NCCH ₃) ₄]PF ₆	^c 20	F	1.2	61
2	Cul ^c	20	F	1.2	< 3
3	(dppf)CuCl ^d	20	F	1.2	55
4	Cu(OAc) ₂	20	F	1.2	62
5	Cu(OAc) ₂	0	F	1.2	87 (80) ^e
6	Cu(OAc) ₂	0	F	0.2	11
7	Cu(OAc) ₂	0	F	0	< 3
8	Cu(OAc) ₂	0	CI	1.2	10
9	Cu(OAc) ₂	0	OBz	1.2	44

^aReaction conditions: [Cu] source (0.015 mmol, 5 mol%), dppf (0.018 mmol, 6 mol%), TMSONa (see Table), B_2Pin_2 (0.36 mmol, 1.2 equiv), **3a** (0.3 mmol), **1** (0.45 mmol, 1.5 equiv), **3** h. ^bDetermined by ¹H NMR spectroscopy analysis using an internal standard. ^c5 mol% of ligand was used. ^dNo additional dppf ligand was used. ^eIsolated yield in parenthesis for a 0.5 mmol scale reaction.

With optimized reaction conditions in hand, we then started to investigate the scope of the transformation by first varying the structure of the allene partner (Table 2). Simple 1,1-alkyl disubstituted allenes 3a-c were readily converted into the corresponding products 4a-c (72-80%). The presence of an aryl halide group on one of the aliphatic chains did not alter the reactivity and the corresponding boroacylation product 4d could be isolated in 79% yield. To our delight, aromatic substituted allenes 3e-h were also suitable partners in this reaction, allowing the formation of 4e-h in moderate to good yields. While fluoride ions are released during the coupling process, this did not affect the reactivity of the silvlether substituted allene **3i** which was converted into 4i in 58% yield, without any observable trace of desilylation product. A carbamate functionality was also tolerated as exemplified by the reaction of allene 3j which features a protected proline moiety. The reaction was less effective but delivered the desired boroacylation product in an acceptable 43% yield. The transformation was attempted with the monosubstituted allene 3k. The reaction appeared to be particularly efficient in this case and the corresponding product 4k was formed in an excellent 97% yield, as determined by 'H NMR analysis of the crude reaction mixture.¹⁸ A similar reactivity was observed with allene **3l** that could be cleanly converted into boroacylation product **4l**. In this case, a subsequent *in situ* oxidation was performed thus allowing the isolation of the corresponding 1,3-diketone (see also Scheme 2). Finally, the reaction was attempted with trisubstituted allene substrates as their use in catalytic borocupration/functionalization processes remains rare. Reacting allenes **3m** or **3n** under the optimized conditions led to low isolated yields of the corresponding boroacylation products, but interestingly, the reaction was shown to be highly regio- and stereoselective as only the *(E)* isomer of **4m** and **4n** could be detected.¹⁹

Table 2. Selected examples of boroacylation with var-iation of the allene



^aReaction conditions: Cu(OAc)₂ (0.025 mmol, 5 mol%), dppf (0.030 mmol, 6 mol%), TMSONa (0.6 mmol, 1.2 equiv), (BPin)₂ (0.6 mmol, 1.2 equiv), **3** (0.5 mmol), **1a** (0.75 mmol, 1.5 equiv), o °C, 3 h. Yields of isolated products are given. ^bNMR yield. ^cIsolated yield after oxidation of the vinylboron moiety into the corresponding ketone. See Scheme 2 and supporting information for more details.

We then turned our attention to the possibility to vary the nature of the acylation partner. As shown in Table 3, the transformation could be performed with the same efficiency in the presence of fluoroacyl derivatives 1b-i. Notably, the transformation tolerated the presence of electron rich and electron poor substituents on the aromatic moiety of benzoyl fluorides **1b-f**. In these cases, the corresponding boroacylation products 40-s were produced in yields ranging from 42 to 79%. Fluoroacyl derivatives 1g and 1h, featuring deactivating heteroaromatic groups, were found to be suitable coupling partners allowing the formation of product 4t and 4u, albeit in lower 39% and 46% yield. Finally, the reaction could also be performed in the presence of the structurally unusual ferrocene-based acyl fluoride 1i to produce for instance products 4v and 4w in 62% and 79% yield, respectively. A limit in reactivity was found with acyl fluoride derivatives possessing alkyl groups. In such a case and under the optimized experimental conditions, the formation of the corresponding boroacylation products could be observed but the reaction were poor yielding.²⁰

Table 3. Selected examples of boroacylation with variation of the acyl fluoride



^{*a*}Reaction conditions: Cu(OAc)₂ (0.025 mmol, 5 mol%), dppf (0.030 mmol, 6 mol%), TMSONa (0.6 mmol, 1.2 equiv), B_2Pin_2 (0.6 mmol, 1.2 equiv), **3** (0.5 mmol), **1** (0.75 mmol, 1.5 equiv), 0 °C to rt, 18 h. Yields of isolated products are given. ^{*b*}Reaction time: 3h (at 0 °C). ^c1.5 mmol scale.

We then rapidly investigated the reactivity of the boroacylation products **4** (Scheme **2**). For instance, the vinylboron moiety in **4** could be efficiently converted into an acetyl group under oxidative conditions, what led to the formation of **2**,**2**-disubstituted **1**,**3**-diketones of type **5**. The presence of the boronate moiety was also exploited in Pdcatalyzed cross-coupling reactions to produce functionalized styrene derivatives such as **6**.

Scheme 2. Reactivity of boroacylation products 4

Oxidative deborylation



On the basis of experimental results and literature precedents, a general mechanism that accounts for the observed formation of boroacylation products 4 is proposed in Scheme 3. The catalytically active Cu(I) species A could be initially produced by reduction of Cu(OAc)₂ in the presence of dppf and TMSONa.²¹ A subsequent σ-metathesis step between A and the activated diboron reagent B, generated in situ by interaction of B_2Pin_2 (2) with the TMSONa Lewis base, would lead to the formation of the Cu-B species C. A key regioselective insertion of C into allene 3 could then produce the allylcopper intermediate D. The observed regioselectivity could be tentatively explained by invoking some steric effects induced by the presence of the R¹ and R² substituents that would disfavour the interaction of reactive species C with the more substituted C-C bond in allene 3. Finally, the nucleophilic allylcopper D could react with the electrophilic acyl fluoride 1, via a potential highly organized six-membered ring transition state of type E,²² to furnish the boroacylation product 4 with regeneration of the catalytically active species A. The stereoselectivity observed with trisubstituted allenes 3m and 3n (see Table 2) can be rationalized by considering a transition state E in which the R^3 group $[(CH_2)_2OBn$ in **3m** and Ph in **3n**] would occupy a more favourable equatorial position.

Scheme 3 Proposed catalytic cycle for the boroacylation of allenes



In conclusion, we have developed a general procedure for the boroacylation of allenes in the presence of a catalytic amount of a copper complex. It was shown that acyl fluorides could be used as efficient electrophilic partners for the trapping of the allylcopper species intermediately formed during the process. The study of the reaction scope has shown that 1,1-disubstituted allenes were suitable substrates in this reaction allowing the generally efficient synthesis of various deconjugated enones featuring an interesting quaternary center. The reaction could be extended with great efficiency to the use of monosubstituted allenes but the isolation of the corresponding boroacylation compounds was found to be challenging. The optimized reactions conditions are mild and the transformation exhibits a wide functional group tolerance. Further extensions of this work including the development of an asymmetric version of this procedure, the in situ transformation of the boroacylation products and their valorization in synthesis are currently under way.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures, full spectroscopic data for all new compounds, and copies of ¹H NMR, ¹³ C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) When acyl chlorides were used as reacting partners, they were found unstable under the experimental conditions used and degraded. The use of acyl anhydride led to the formation of inhomogeneous mixtures and finally poor yields in boroacylation products.

(18) Product **4k** was not stable in the presence of silica or alumina gels. It could therefore not be purified in by traditional flash column chromatography procedures without a significative loss of yield.

(19) The experimental conditions were not optimized again for the reaction of trisubstituted allene **3m** and **3n**. This is currently under investigations.

(20) The boroacylation reaction was attempted using allene **3a** and several aliphatic acyl fluorides (See Supporting Information for more details). The trapping of the intermediate allyl copper appeared to be less efficient and the hydroboration products were observed either as the main products or in substantial amounts after workup of the reaction.

(21) Although the mechanism of the Cu(II)/Cu(I) reduction is not exactly known, the procedure involving the *in situ* generation of the copper(I) species from a copper(II) salt is admitted in the literature. See for example: Guzman-Martinez, A.; Hoveyda, A. H., *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637, and references 6c, 7a.

(22) Such a type of transition state has been previously postulated in related transformations. See for example: references 3e, 4a,f,g.

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