

Catalytic Enantioselective Allylboration of Ketones

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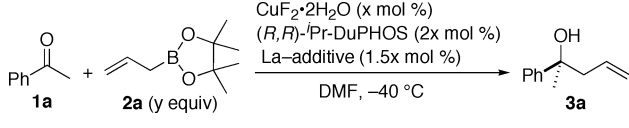
The allylation reaction is one of the most useful carbon–carbon bond-forming reactions in organic synthesis.¹ There are highly stereoselective (enantioselective and diastereoselective) catalytic allylation and crotylation reactions² using aldehydes as a substrate to produce chiral secondary homoallyl alcohols. There are far fewer successful examples, however, of targeting ketones as a substrate.³ Although high enantioselectivity is produced in some cases, only toxic allylstannanes can be used as an allylating reagent, and these reactions require high catalyst loading (10–30 mol %). In addition, there are no reports of catalytic enantioselective crotylation of ketones. Despite the importance of chiral tertiary homoallyl alcohols as a chiral building block for biologically significant compounds, there is little synthetic methodology available due to the attenuated reactivity of ketones and the lesser steric dissimilarity of the two substituents on the carbonyl carbon compared to aldehydes.⁴ We report herein the first catalytic enantioselective allylboration of ketones, which overcomes the above-mentioned hurdles in chiral tertiary homoallyl alcohol synthesis.

We reported a general catalytic allylation using CuCl and TBAT (tetrabutylammonium difluorotriphenylsilicate) as catalysts and allyltrimethoxysilane as an allylation reagent.⁵ This reaction was extended to a catalytic enantioselective allylation of ketones; however, only moderate enantioselectivity (up to 61% ee using tol-BINAP) was obtained using 15 mol % catalyst. To improve the efficiency, we investigated use of allylboronates instead of allyltrimethoxysilane, on the basis of recent important findings that allylboronates can be catalytically activated by a Lewis acid to achieve stereoselective allylation of aldehydes.⁶

First, we found that catalytic allylation of various ketones, including aromatic, heteroaromatic, α,β -unsaturated, and aliphatic ketones, proceeded smoothly at ambient temperature in THF, using 1–3 mol % of catalyst (CuCl-TBAT or CuF·3PPh₃·2EtOH⁷) and commercially available pinacol 2-propenylboronic ester (**2a**: 1.1–3 equiv).⁸ Enones gave the 1,2-adducts with complete regioselectivity. Therefore, allylboronates can be used with an efficiency comparable to that of allyltrimethoxysilane in the CuF-catalyzed allylation to ketones. The catalysis of CuF is due to an activation of the allylboronate (see below), as was the case with allyltrimethoxysilane.⁵

We then extended this newly developed catalytic allylboration of ketones to an enantioselective reaction. After intensive screening of chiral ligands and optimization of the catalyst preparation methods,⁹ the CuF catalyst prepared in situ from CuF₂·2H₂O (15 mol %) and *i*-Pr-DuPHOS (**4**: 30 mol %)¹⁰ gave the best enantioselectivity; the product **3a** was obtained from acetophenone (**1a**) in 42% yield with 79% ee at –40 °C for 20 h in DMF (Table 1, entry 1). Encouraged by the markedly improved enantioselectivity, we investigated additive effects, expecting that the addition of a catalytic amount of Lewis acid metal would improve both reactivity

Table 1. Lanthanide Effect on Catalytic Enantioselective Allylboration of Ketones



entry	catalyst (x mol %)	2a (y equiv)	La-additive	time (h)	yield ^a (%)	ee ^b (%)
1	15	3	–	20	42	79
2	15	3	La(O ^{<i>i</i>} Pr) ₃	3.5	95	77
3	3	1.2	La(O ^{<i>i</i>} Pr) ₃	1	94	82
4	15	3	(<i>R</i>)-BINOL-La(O ^{<i>i</i>} Pr) ₃	20	52	80
5	15	3	(<i>S</i>)-BINOL-La(O ^{<i>i</i>} Pr) ₃	20	48	79

^a Isolated yield. ^b Determined by chiral HPLC.

and enantioselectivity through dual activation of the allylboronate and the ketone by CuF and the additive Lewis acid, respectively.¹¹ Specifically, we focused on the effect of lanthanides, taking advantage of the dynamic coordinating nature of lanthanide metals.¹² The addition of 20 mol % of La(O^{*i*}Pr)₃ accelerated the reaction between **1a** and **2a** in the presence of 15 mol % CuF–**4** without changing the enantioselectivity, and the product **3a** was obtained in 95% yield with 77% ee in 3.5 h (entry 2).¹³ The high reaction rate allowed for a decrease in the catalyst loading; using 3 mol % CuF–**4** and 4.5 mol % La(O^{*i*}Pr)₃, the reaction was completed in 1 h, giving **3a** in 94% yield with improved 82% ee (entry 3). The addition of La(O^{*i*}Pr)₃ inhibited the CuF-catalyzed allylation using allyltrimethoxysilane (yield < 5%), which clearly demonstrated the advantage of the present allylboration reaction over the previous allylsilylation.⁵

Substrate generality was investigated under the optimized conditions (Table 2). High enantioselectivity (up to 91% ee) was obtained from aromatic, heteroaromatic, cyclic, and aliphatic ketones, using 3 mol % catalyst in a short reaction time (1 h).¹⁴ Moreover, catalytic enantioselective crotylation of ketones proceeded, and the product was obtained with up to 93% ee (Table 3). No crotylation proceeded in the absence of La(O^{*i*}Pr)₃. Although the diastereoselectivity is substrate-dependent and requires further improvement,⁸ this is the first example of a catalytic enantioselective crotylation of ketones, giving the chiral tetrasubstituted carbons with high enantioselectivity.

The following preliminary investigations of the reaction mechanism provided pieces of meaningful information at the current stage. First, we propose that the active nucleophile in the CuF-catalyzed allylation reaction is an allylcopper. ¹¹B NMR studies of **2a** + CuF·3PPh₃ suggested the generation of an allylcopper.⁸ Furthermore, the same enantioselectivity (81–82% ee) was obtained from **1a** using allylboronate **2a**, allyltrimethoxysilane, or allyltributylstannane in the presence of CuF–*i*-Pr-DuPHOS (15 mol %). These results strongly suggest that the same active species is generated through transmetalation, and the highly probable common

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Table 2. Catalytic Enantioselective Allylboration of Ketones

$\text{CuF}_2 \cdot 2\text{H}_2\text{O}$ (3 mol %)
 $(R,R)\text{-}^i\text{Pr-DuPHOS}$ (6 mol %)
 $\text{La}(\text{O}^i\text{Pr})_3$ (4.5 mol %)

$\text{DMF}, -40^\circ\text{C}, 1\text{ h}$

entry	substrate	yield (%) ^a	ee (%) ^b
1		94	82 ^c
2		89	84
3		83	83
4		84	85
5		88	84 ^c
6		87	90
7		99	91
8		98	84
9		96	67 ^c

^a Isolated yield. ^b Determined by chiral HPLC. ^c The absolute configuration was determined to be (*S*).

Table 3. Catalytic Enantioselective Crotylboration of Ketones

$\text{CuF}_2 \cdot 2\text{H}_2\text{O}$ (3 mol %)
 $(R,R)\text{-}^i\text{Pr-DuPHOS}$ (6 mol %)
 $\text{La}(\text{O}^i\text{Pr})_3$ (4.5 mol %)

$\text{DMF}, -40^\circ\text{C}$

entry	substrate	crotylboronate (1.2 equiv)	time (h)	yield ^a (%)	dr ^b (syn/anti)	ee ^c (%)
1	1a	2b	1	73	30/70	75/90 ^d
2	1a	2c	5	94	84/16	87/74 ^d
3	1f	2b	3	80	27/73	90/93
4	1f	2c	4	90	38/62	90/92

^a Isolated yield. ^b Determined by NMR. ^c Determined by chiral HPLC. ^d The stereochemistry was determined as shown. Configurations of the products from **1f** were temporarily assigned on the basis of ¹H NMR analysis.

species from these different allylation reagents is an allylcopper.¹⁵ Second, in contrast to our initial expectation, the additive effect of $\text{La}(\text{O}^i\text{Pr})_3$ might be due to the acceleration of the transmetalation step to generate an active allylcopper¹⁶ without affecting the transition-state structure of the allylation step of a substrate ketone. Thus, the addition of either (*R*)- or (*S*)-binaphthoxylanthanum (generated from $\text{La}(\text{O}^i\text{Pr})_3$ and (*R*)- or (*S*)-BINOL (1:1) followed by evaporation of the released ⁱPrOH), instead of $\text{La}(\text{O}^i\text{Pr})_3$ gave the same enantioselectivity with a slower reaction rate than in the presence of $\text{La}(\text{O}^i\text{Pr})_3$ (Table 1, entries 4 and 5). Further studies are required to elucidate the origin of the ligand exchange facilitation effect of $\text{La}(\text{O}^i\text{Pr})_3$.¹⁷

In conclusion, we have developed the first catalytic enantioselective allylboration and crotylboration of ketones using 3 mol

% $\text{CuF}_2\text{-}^i\text{Pr-DuPHOS}$ as a chiral catalyst and 4.5 mol % $\text{La}(\text{O}^i\text{Pr})_3$ as a cocatalyst. The success of the reaction depends on a unique facilitation effect of $\text{La}(\text{O}^i\text{Pr})_3$ in the dynamic ligand exchange between boron and copper atoms. Detailed mechanistic studies and application of the present method to other important carbon–carbon bond-forming reactions are in progress.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (7) Gulliner, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153. Generation of CuF was observed on ¹⁹F NMR via the reaction of CuCl with TBAT, and CuF is the actual catalyst in our catalytic allylation using allyltrimethoxysilane. See ref 5.
- (8) See Supporting Information (SI) for details. No reaction proceeded in the absence of catalyst.
- (9) Brief conclusions of the preliminary optimization: (a) No enantioselectivity was observed using chiral diamines or monophosphines as a ligand for Cu . (b) The addition of chiral diphosphines to CuCl -TBAT or CuF - 3PPh_3 · 2EtOH produced a less active or less enantioselective catalyst. (c) As a solvent, DMF is superior to THF in terms of enantioselectivity.
- (10) A solution of $\text{CuF}_2 \cdot 2\text{H}_2\text{O}$ and **4** in MeOH was refluxed for 2 h to generate CuF-4 complex, which was suggested by ESI-MS measurement.
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- (13) Other lanthanide isopropoxides gave less satisfactory results.
- (14) Even reliable stereoselective allylation methods using chiral allylborane or allylboronate gave only moderate results when applied to ketones: Barton's allyldiisopinocampheylborane and Roush's tartrate ester-modified allylboronate gave **3a** in 41% yield with 2% ee (0 °C for 2 h) and 16% yield with 41% ee (−40 °C for 24 h), respectively.
- (15) Allylcoppers generated via the reaction of CuX + allyllithium or allyl Grignard reagent are known to give a mixture of 1,2- and 1,4-adducts to enones. See: Lipshutz, B. H.; Ellsworth, E.; Dimock, S. H.; Smith, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 4404.
- (16) On the basis of kinetic studies, the rate-determining step is the generation of the active nucleophile through a ligand exchange between boron and copper atoms, and not the addition to a substrate ketone; the initial reaction rate dependency with regard to CuF - 3PPh_3 · 2EtOH , **2a**, and acetophenone was 1.4, 1, and 0, respectively.
- (17) One possible scenario is the activation of CuF through lanthanum alkoxyfluorocuprate formation.

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