

Chiral β -substituted acids via catalytic direct conjugate additions of organometallics to simple α,β -unsaturated carboxylic acids

Xingchen Yan, Syuzanna R. Harutyunyan

*Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen
xingchen.yan@rug.nl*

Conjugate addition (CA) reactions of hard carbon nucleophiles to α,β -unsaturated carbonyl derivatives that forge carbon-carbon bonds, rank among the most fundamental reactions in chemical synthesis. Catalytic enantioselective versions of these reactions have become powerful synthetic tools for the asymmetric formation of C-C bonds but are only applicable to derivatives of carboxylic acids. Carboxylic acids themselves are the most ubiquitous and variegated building blocks in chemistry, however, despite almost 80 years of intensive research in the field of copper catalyzed CA reactions, catalytic asymmetric conjugate additions to simple α,β -unsaturated carboxylic acids have not been found.

The fundamental problem of the direct use of carboxylic acids in conjugate additions results from the formation of unreactive carboxylates upon addition of an organometallics thus preventing their further transformations. Recently, our group developed several protocols that employs Lewis acids to activate poorly reactive alkenyl-heteroarenes and α,β -unsaturated carboxamides towards nucleophilic addition of Grignard reagents.¹⁻³

Here we report that readily available LAs in combination with chiral copper catalysts are able to tackle the problematic issues associated with carboxylic acids towards alkylation with organomagnesium reagents. The method is distinguished by unprecedented reaction scope, allowing even the most challenging and synthetically important methylations to be accomplished with good yields and excellent enantioselectivities. The products can be further transformed into several valuable molecules through catalytic decarboxylative cross-coupling reactions. The relatively high reaction temperature ($-20\text{ }^{\circ}\text{C}$), scalability, recyclability of the catalyst, and the simplicity to separate the products, make this methodology very attractive for future applications. Through mechanistic studies, the active intermediates were observed and isolated.

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3. R. P. Jumde, F. Lanza, M. J. Veenstra, S. R. Harutyunyan, *Science*, **352**, 433, **2016**