Published in final edited form as:

Angew Chem Int Ed Engl. 2017 June 19; 56(26): 7354–7356. doi:10.1002/anie.201703311.

Catalytic Desymmetrization by C–H Functionalization as a Solution to the Chiral Methyl Problem

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Breaking the mirror (plane)

A palladiumcatalyzed desymmetrization strategy via β C–H activation provides an alternate approach for solving the age-old challenge of introducing an α -methyl stereocenter to a molecule.

Keywords

asymmetric catalysis; β C–H functionalization; C–H activation; desymmetrization; α -methyl groups

Three years ago, medicinal chemists from industry and academia jointly issued a challenge to the synthetic community: Solve the long-standing problem of selective methylation.^[1] Apparently, this smallest alkyl group remains a disproportionately large hurdle to the synthesis of new molecules with improved medicinal properties. Despite the so-called “magic methyl effect,” wherein up to 100-fold greater potency can be imparted on a medicinal agent by installation of a simple $-\text{CH}_3$ group, only limited methylation tools remain at the synthetic chemist’s disposal. These imperfect methods for incorporating a motif found in two-thirds of top-selling medicines frequently rely on heteroatom (O, N, S) methylation with strongly electrophilic Me-X reagents (for example, $\text{X}=\text{I}$, OTf , $^+\text{OMe}_2$). However, methylation of drug candidates, or other chemical targets, by C–C coupling continues to pose an outsized challenge. In recent years, the synthetic community has responded by developing a range of new tools for radical-mediated C–C methylation using alcohols,^[2] peroxides,^[3] and zinc sulfinates^[4] as methyl radical precursors. Nevertheless, the catalytic asymmetric methylation problem remains unsolved.

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Conflict of interest

The author declares no conflict of interest.

A tempting idea for solving this challenge is the carbonyl α -methyl stereocenter found in the amino acid alanine. It might be expected that asymmetric α -methylation of glycine could be an efficient enzymatic approach to alanine. However, the biosynthetic route to alanine actually involves asymmetric, reductive amination of pyruvate, which already contains a methyl C–C bond (Figure 1). Similarly, the circuitous enzymatic synthesis of vitamin E by formal desymmetrization of an isopropyl ester does not entail direct β C–H oxidation. Instead, the enantiodetermining step is the conjugate addition of water to a methacrylate, which similarly already contains a methyl C–C bond.

In the de novo synthetic realm, development of powerful methods for catalytic asymmetric alkylation via Lewis acid, phase transfer, photoredox, and organocatalysis have enabled certain types of α -carbonyl alkylation, including allylation, benzylation, and β -EWG-alkylation (for example, CF_3 , β - CO_2R , β -CN).^[5] Nonetheless, direct incorporation of a methyl C–C bond via catalytic asymmetric methylation, remains unknown. Perhaps the closest solution is a recent, formal α -methylation via a two-step strategy, involving asymmetric sulfonyl alkylation ($-\text{CH}_2\text{SO}_2\text{R}$) and subsequent desulfonylation.^[6]

With this background in mind, Jin-Quan Yu and co-workers recently developed a palladium-catalyzed β C–H activation approach to solve this ongoing problem (Figure 2).^[7] Through biomimetic inspiration (see Figure 1) and rational catalyst design, catalytic desymmetrization of the prochiral α -isopropyl group of an isobutyrate was achieved. To accomplish this, a new catalyst had to be developed in order to differentiate between the enantiotopic methyl groups. In the Yu group's previous β C–H activation studies,^[8] methylene C–H bonds could be differentiated with the help of a larger, sterically biasing alkyl group on the amide. Conversely, for this problem, a new catalyst must discriminate between methyl groups, with a smaller methine C–H as the only other control element. Confirming the difficulty in achieving this type of enantiotopic discrimination, the optimal catalyst scaffolds (β -amido quinolines) for their previous β C–H activations (via methylene functionalization) led only to racemic β C–H arylation in this methyl desymmetrization.

Building on a combination of computational and rational design, as well as targeted investigation of ligand libraries, a new class of privileged ligands was discovered to enable highly enantioselective differentiation of the isobutyramide in Figure 3. These α -amido oxazoline ligands are more modular than their predecessors, as they are directly accessible by combining two amino acid precursors. This more streamlined catalyst synthesis also enabled metal-binding tunability via oxazoline substitution. This is a noteworthy improvement compared to the less variable quinolone group employed in their previous system. Furthermore, a significant advantage of the dual amino acid ligand structure is the ability for the chirality of each building block to reinforce the other. For example, when either component was exchanged for its achiral substitute, minimal desymmetrization selectivity was observed for the β C–H arylation (6–14% *ee*). However, when both chiral blocks were combined, a significant synergistic boost resulted in enantioselectivity much greater than the sum of its parts (96% *ee*). Finally, the racemic product encountered by using the mismatched enantiomer of one component further illustrates the cooperative diastereoselective binding pocket formed by these privileged α -amido oxazoline ligands.

In a tour de force of synthetic scope investigation, Yu and co-workers have thoroughly demonstrated this great leap in solving the α -methyl stereocenter problem is no mere parlor trick. Rather, this robust method includes over 40 examples of β C–H arylation and heteroarylation, leaving little doubt about its breadth of scope with respect to steric or electronic effects of the aryl iodide coupling partners that facilitate this desymmetrization (Figure 4). Interestingly, despite effective coupling of both electron-rich and -poor arenes, only electron-rich heteroarenes are employed (for example, thiophenes, indoles). More electron-deficient heteroarenes (for example, pyridines), such as those previously used as ligand structures, are potentially too coordinating and may interfere with reactivity.

Notably, the β -aryl products were subjected to subsequent methyl C–H functionalization to access diverse, chiral scaffolds. In an extravagant showcase, the authors have also presented over 20 examples of β C–H alkenylation (and alkynylation) using the same desymmetrization strategy. Apart from illustrating the synthetic utility of these versatile γ,δ -unsaturated amides, these examples showcase how tunability of the oxazoline ligand scaffolds can solve new challenges, including the incorporation of ever smaller coupling partners (alkenes, alkynes). Finally, Yu and co-workers have included a bonus solution for desymmetrization of an isobutyryl amino acid derivative (bottom right, Figure 4) that enables asymmetric access to fully α -substituted, α -methyl benzyl amino acids.

In conclusion, through a β C–H desymmetrization strategy, Yu and co-workers have introduced a novel solution to the long-standing problem of introducing an α -methyl stereocenter to a molecule. While it is certainly a robust and powerful approach, this is not quite the long-sought-after solution for direct C–C coupling of a methyl electrophile and prochiral enolate equivalent. Needless to say, nature has also not yet found this solution; and perhaps, catalytic enantioselective α -methylation may never be achieved in the lab either. If so, synthetic chemists in need of α -methyl stereocenters will have to rely on either classic chiral-auxiliary-based methods,^[9] or this new, Pd-catalyzed desymmetrization strategy via β C–H activation. In the latter case, there remains some room for improvement. For example, limitations include: 1) prerequisite conversion of isobutyric acid to its perfluoroaryl (Ar_F) amide^[10] before C–H activation, as well as 2) post-reaction deprotection of the amide auxiliary with $\text{BF}_3 \cdot \text{Et}_2\text{O}$. To this end, a new challenge will be application of a transient directing group strategy, employed in recent Pd-catalyzed C–H activations.^[11] Invention of a suitable catalytic directing group to facilitate this desymmetrization may someday enable direct conversion of free isobutyric acid into valuable α -methyl building blocks through dual-catalytic asymmetric C–H activation.

Acknowledgments

The Ohio State University, National Institutes of Health (NIH R35 GM119812), and American Chemical Society (ACS PRF 55704) are appreciated for financial support.

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Figure 1.
The catalytic asymmetric α -methylation of carbonyls, which remains an unsolved synthetic challenge. Bn=benzyl; EWG=electron-withdrawing group.

Figure 2.
The challenge of a catalytic desymmetrization approach to α -methyl stereocenters.

Figure 3.
Catalyst design, entailing a modular, cooperative scaffold.

Figure 4.
Synthetic scope of β C–H functionalization. Phth=phthalyl.