Palladium-N-Heterocyclic Carbene (NHC)-Catalyzed Asymmetric Synthesis of Indolines through Regiodivergent C(sp³)—H Activation: Scope and DFT Study

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Abstract

Two bulky, chiral, monodentate N-heterocyclic carbene ligands were applied to palladium-catalyzed asymmetric C—H arylation to incorporate C(sp3)—H bond activation. Racemic mixtures of the carbamate starting materials underwent regiodivergent reactions to afford different trans-2,3-substituted indolines. Although this CAr—Calkyl coupling requires high temperatures (140–160°C), chiral induction is high. This regiodivergent reaction, when carried out with enantiopure starting materials, can lead to single structurally different enantiopure products, depending on the catalyst chirality. The C—H activation at a tertiary center was realized only in the case of a cyclopropyl group. No C—H activation takes place alpha to a tertiary center. A detailed DFT study is included and analyses of methyl versus methylene versus methine C—H activation is used to rationalize experimentally observed regio- and enantioselectivities.

Reference


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Palladium–N-Heterocyclic Carbene (NHC)-Catalyzed Asymmetric Synthesis of Indolines through Regiodivergent C(sp³)/C₀ H Activation: Scope and DFT Study

What are the most significant results of this study?
There are two: Firstly, the development of a catalyst that is capable of reacting selectively with one of the two enantiotopic C–C₀ H bonds in an unactivated methylene group to give a single enantiomeric product. Secondly, the reaction does not leave the second enantiomer untouched (kinetic resolution), but transforms it into a regioisomeric product with, in the ideal case, equal enantiomeric purity (divergent reaction).

What future opportunities do you see?
Long regarded as inert, unactivated C–C₀ H bonds are on the way to becoming functional groups that can be engaged selectively in catalytic reactions. Finding paths conditions that enable these reactions to take place under mild conditions with high chemo-, regio-, and stereoselectivity are the targets of this rapidly growing field. With rapid progress underway, direct CH functionalization will change the way complex organic structures are assembled. The second discovery, the regiodivergent reaction of a racemic mixture (RRM) was unexpected. Efficient RRM reactions are still rare, but they receive increasing and deserved attention. This area also offers exciting prospects.

What was the inspiration for the cover design?
The image had to be simple and draw attention to the chemistry. The R enantiomer takes the right fork and the S enantiomer the left fork. When arriving at such a junction in the forest, a map or GPS data will help to figure out the destination. For the reaction shown, DFT was the tool to map the reaction course and to extend and rationalize the outcome. The choice of picture draws attention to the divergent reaction and the green color represents selective catalysis.

Invited for the cover of this issue is the group of E. Peter Kündig at the University of Geneva. The cover illustrates the regiodivergent reaction taken by two enantiomers when subjected to a chiral Pd(N-heterocyclic carbene) catalyst. The combination of a divergent reaction with an enantioselective C–H functionalization makes for fascinating chemistry. Read the full text of the article at 10.1002/chem.201403985.

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