Substrate vs. ligand control over absolute and relative stereochemistry in Pd-catalyzed intramolecular alkylation reactions

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The Tsuji-Trost reaction, i.e. the palladium-catalyzed alkylation of carbon, nitrogen and oxygen nucleophiles, takes a unique position among the various cross-coupling reactions as it uniquely allows the formation of C(sp3)-C(sp3) bonds. In addition, the mechanism of the reaction potentially allows control over the stereoselectivity of the process, which may be governed by either the substrate or the catalyst. Performing the reaction in an intramolecular fashion avoids potential regioselectivity issues.

Recently, we showed that (homo)allylic diacetates such as 1 with a single, carbohydrate-derived stereocenter undergo a highly diastereoselective and enantiospecific Tsuji-Trost cascade cyclization to give fused vinylcyclopropanes 2.[1] In this case, the absolute stereochemistry of the product is dictated by the substrate, while the relative configuration is thermodynamically controlled. In continuation of this work, we found that the intramolecular Tsuji-Trost alkylation of achiral diamides 3 (readily accessible via the Ugi reaction) using a suitable chiral ligand affords vinyl-substituted diketopiperazines 4 with very high enantioselectivity. In contrast, the related diamides 5 (bearing a 2-pyridyl or related heterocyclic substituent) undergo intramolecular alkylation to afford β-lactams 6. Interestingly, we were able to direct the reaction nearly exclusively to either the cis- or the trans-product by judicious choice of the ligand on palladium, indicating a switch in mechanism between the two cases.

Importantly, the reactions tolerate a variety of functional groups in the substituents, underlining their potential for the synthesis of chiral, highly functionalized drug-like heterocycles. Moreover, our results provide valuable new insights in the flexibility of the Tsuji-Trost reaction with regard to substrate- and ligand-based stereocontrol.


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