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Hydrofunctionalizations

Enantioselective Hydrophosphination of Terminal Alkenyl Aza-Heteroarenes

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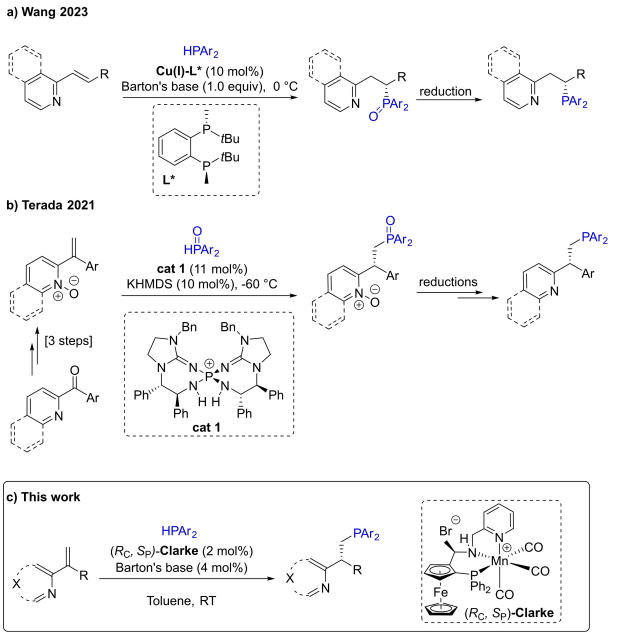
Abstract: This paper presents a Mn(I)-catalysed methodology for the enantioselective hydrophosphination of terminal alkenyl aza-heteroarenes. The catalyst operates through H–P bond activation, enabling successful hydrophosphination of a diverse range of alkenyl-heteroarenes with high enantioselectivity. The presented protocol addresses the inherently low reactivity and the commonly encountered suboptimal enantioselectivities of these challenging substrates. As an important application we show that this method facilitates the synthesis of a non-symmetric tridentate P,N,P-containing ligand like structure in just two synthetic steps using a single catalytic system.

Introduction

Chiral phosphorus containing compounds are of importance for applications in biologically active pharmaceuticals, agrochemicals and asymmetric catalysis.[1] In the latter case, phosphorus compounds are often used as standalone chiral organocatalysts or as chiral ligand components of metal complexes used in transition metal catalysis.

Stereoselective hydrophosphination is an appealing approach for direct access to chiral phosphorus containing compounds and recent years[2] have witnessed rapid development in catalytic asymmetric hydrophosphination methodologies using chiral catalysts derived from transition metals, for example Pt,[3] Pd,[4] Ni,[5] or Cu[6] complexes. However, despite these advances, enantioselective hydrophosphination is still largely limited to conventional Michael acceptors. In contrast, little progress has been made in utilizing alkenyl-aza-heteroarene acceptors, most likely due to their relatively low reactivity and difficulties to control the product stereochemistry. This is unfortunate since hydrophosphination of alkenyl aza-heteroarenes opens a direct route to chiral P,N ligand-like structures, most of which currently require multistep synthesis, often using chiral resolution to obtain enantioenriched products.[7] The recent report by Wang et al.[8a] represents an important step forward in this context. At the same time, it emphasizes the difficulties associated with reactions involving α-substituted terminal alkenes. (Scheme 1a). Their only example of hydrophosphination of terminal alkenyl quinoline shows significantly lower enantioselectivity (53 % *ee*) compared to their β-substituted counterparts (up to 92 % *ee*). The β-substituted alkenes generate a carbon stereocenter upon forming a bond with a phosphorus atom. In contrast, when using α-substituted terminal alkene, the carbon stereocenter is formed upon C–H bond formation (formal stereospecific protonation) which is known to be more challenging to control. In this context, Terada et al. reported catalytic enantioselective hydrophosphinylation of N-oxide analogues of α-substituted terminal alkenyl aza-heteroarenes. (Scheme 1b).[8b] However, this method requires multiple steps to arrive at the target chiral phosphine products. Furthermore, both reported protocols require relatively high catalysts loadings. These observations collectively under-



Scheme 1. Literature precedents on enantioselective synthesis of chiral aza-heteroaromatic phosphines with a carbon stereocenter and our work.

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