THE CATALYTIC, ENANTIOSELECTIVE HYDROGENATION OF HIGHLY-SUBSTITUTED, UNFUNCTIONALIZED ALKENES

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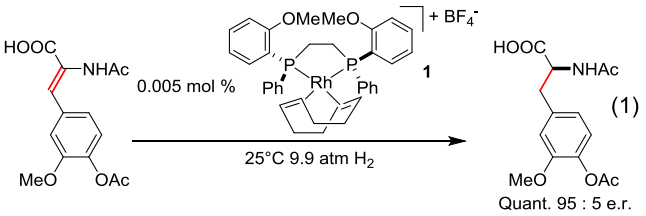
INTRODUCTION TO CATALYTIC ASYMMETRIC HOMOGENEOUS HYDROGENATION

In 1968 Knowles[1] and Horner[2] separately reported the first two catalytic asymmetric homogeneous hydrogenations (CAHHs). These examples, however, had enantiomeric ratios (e.r.) below 60:40.[1, 2] Knowles' continued ligand optimization led to his discovery of DIPAMP, the ligand in catalyst **1**, which afforded a 95:5 e.r. for the hydrogenation of a precursor to L-Dopa (Eq. 1). This process is used to produce one ton of L-Dopa annually to treat Parkinson's disease. Unfortunately, these rhodium and similar ruthenium catalysts fail to enantioselectively hydrogenate highly substituted alkenes without coordinating functional groups.[3]



EARLY PUBLICATIONS IN THIS FIELD

Broene and Buchwald reported the first CAHH of highly-substituted, unfunctionalized alkenes in 1993.[4] Unfortunately this catalyst (Figure 1) and the subsequent zirconium analogue are very sensitive to air and moisture, need additives for activation, require long reaction times, and high catalyst loadings and pressures. This methodology is limited to aryl-substituted alkenes.

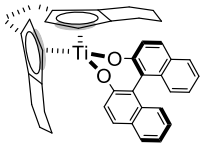
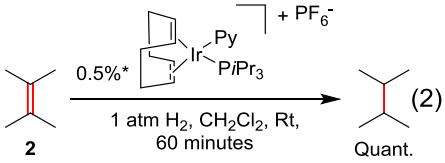


Figure 1. Titanocene hydrogenation precatalyst.

HISTORICAL INSPIRATION FOR NOVEL CATALYST DESIGNS

The first viable catalytic, homogeneous hydrogenation of unfunctionalized tetrasubstituted alkenes was reported by Crabtree in 1977 (Eq. 2).[5] Crabtree showed that the hydrogenation of **2** could be effected with low catalyst loadings at STP using a highly electrophilic iridium catalyst. Using chiral analogues, Pfaltz *et al*. reported the hydrogenation of several trisubstituted alkenes and one tetrasubstituted alkene in high yields and moderate to excellent e.r.s, but were limited to aryl-substituted alkenes (Fig. 2).[6] In 2006, Pfaltz *et al.* showed the first stereoselective hydrogenation of aliphatic trisubstituted olefins using bicyclic pyridine phosphinite ligand **4** (Eq. 3).[3] This was applied to the hydrogenation of the vitamin E sidechain (**3**) to afford exclusively the desired enantiomer in 98% yield. Vitamin E, an essential vitamin, is



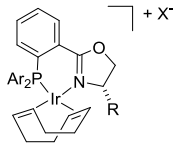
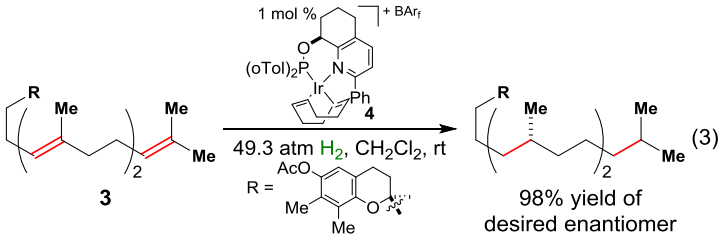
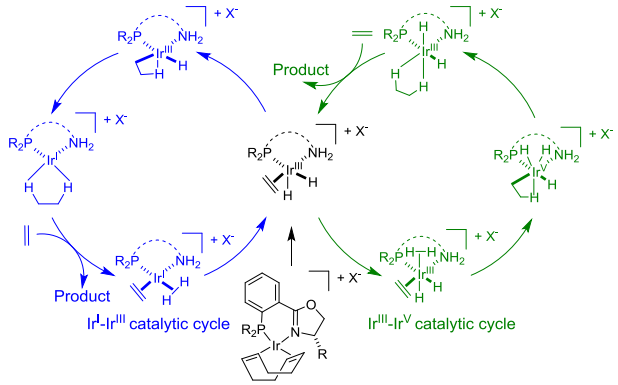


Figure 2: Skeleton of first-generation chiral Crabtree's catalyst mimics.



produced on 20 kiloton scale annually.[3] Tetrasubstituted alkenes have also been hydrogenated using chiral Crabtree's catalyst analogues, albeit with lower enantiomeric ratios and a limited substrate scope. Also, no reports of enantioselective, tetrasubstituted all-alkyl olefin hydrogenation have been reported.[5]

MECHANISTIC STUDIES



Scheme 1: The two proposed mechanisms for this reaction

The mechanism of iridium catalyzed hydrogenation has been debated. An Ir^{I}-Ir^{III} cycle, analogous to Rh and Ru systems, and a novel Ir^{III}-Ir^{V} cycle have been proposed (Scheme 1).[7] Early in-*situ* mass spectroscopy supported the Ir^{I}-Ir^{III} cycle.[8] DFT calculations on full catalyst and substrate models, as well as the explored reactivity of isolated intermediates support an Ir^{III}-Ir^{V} catalytic cycle.[7]

TOTAL SYNTHESIS OF (-) MUTISIANTHOL

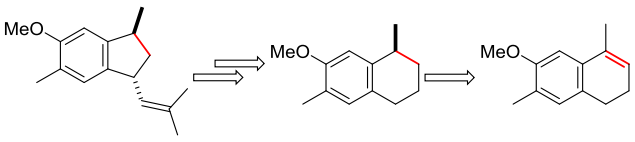


Figure 4: (-) Mutisianthol and the key disconnection using CAHH of an alkene lacking CFGs.

This method has been applied towards the synthesis of (-) mutisianthol (Figure 4), in which the anti-tumor agent is synthesized in 11 steps, setting the first stereocenter through an enantioselective hydrogenation of an unfunctionalized double bond.[9]

FUTURE DIRECTIONS

This method shows promise in terms of its capacity to produce one or two tertiary stereocenters remote to functionality using catalyst control. Unfortunately, these catalysts are sensitive to small changes in steric bulk on the substrate. Due to the high activity of these catalysts they hydrogenate all tri-substituted alkenes in the substrate, indicating low chemoselectivity. The hydrogenation of tetra-substituted alkenes also is a problem which has not yet been solved to a satisfactory level. Addressing these challenges would allow for the application of this technology in medicinal chemistry, total synthesis, and industrial chemistry.

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