Tethered Rh(III)-N-(p-Tolylsulfonyl)-1,2-Diphenylethylene-1,2-Diamine Complexes: Efficient Catalysts for Asymmetric Transfer Hydrogenation

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Abstract

Transition-metal-catalyzed asymmetric transfer hydrogenation (ATH) of prochiral ketones is an efficient method to access enantiomerically pure secondary alcohols that are key intermediates in the pharmaceutical industry and for the manufacture of advanced materials. For this reaction, Noyori developed a Ru(II) complex having a N-(p-toluene-sulfonyl)-1,2-diphenylethylendiamine (TsDPEN) ligand that was used with either isopropanol or formate salts as the hydrogen donor. Related Rh(III)-TsDPEN and Ir(III)-TsDPEN catalysts as well as modified Ru(II) and Rh(III) complexes have also been reported. In particular, Wills disclosed the Rh-tethered complex (R,R)-A containing a tethering group between the diamino group and the cyclopentadienyl unit providing extra stereochemical stability and hence higher selectivities (Scheme 1). To investigate the influence of the R substituent of the 2-benzyl tether, our group developed a series of tethered rhodium complexes (R,R)-B-(R,R)-E having electron-donating (methoxy and methyl) as well as electron-withdrawing (fluorine and trifluoromethyl) substituents, respectively, on the 2-benzyl tether. The N-pentafluorophenylsulfonyl-DPEN-based tethered Rh(III) complex (R,R)-F was also synthesized.

Complexes (R,R)-B-(R,R)-F were prepared according to the route disclosed for the parent complex (R,R)-A₁⁶ (Scheme 1). After acetal protection of the required 5-substituted 2-bromo-benzaldehyde derivatives 1 to provide compounds 2, treatment of the latter with n-BuLi followed by addition of 2,3,4,5-tetramethylcyclopent-2-ene afforded...
the corresponding alcohols that under acidic treatment underwent concomitant deprotection of the aldehyde and dehydration of the tertiary alcohol to give the cyclopentadiene derivatives. Subsequent reductive amination of the latter using \((R,R)\)-TsDPEN or \((R,R)\)-FsDPEN followed by treatment with \(\text{RhCl}_3\) led to \((R,R)\)-B\(--(R,R)\)-F as single diastereomers.

Complexes \((R,R)\)-B\(--(R,R)\)-E exhibited excellent activities for the ATH of a wide range of functionalized ketones using the formic acid/triethylamine (5:2) system as the hydrogen source, giving the corresponding alcohols with selectivities comparable to those obtained with Wills’ complex \((R,R)\)-A or slightly higher in some instances, and with a better catalytic activity observed in several cases (Table 1, A).

### Table 1: Applications of Complexes \((R,R)\)-A\(--(R,R)\)-F

<table>
<thead>
<tr>
<th>System</th>
<th>Conditions</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Functionlized Ketones</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>B</td>
<td>Aromatic α-Amino β-Keto Ester Hydrochlorides</td>
<td>63–98%</td>
<td>up to &gt;99% ee</td>
</tr>
<tr>
<td>C</td>
<td>α-Benzoylamiado β-Keto Esters</td>
<td>67–98%</td>
<td>up to &gt;99% ee</td>
</tr>
<tr>
<td>D</td>
<td>α-Methoxy-β-keto Esters</td>
<td>72–92%</td>
<td>up to &gt;98.2% ee</td>
</tr>
<tr>
<td>E</td>
<td>3-Substituted Chromones</td>
<td>76–87%</td>
<td>up to &gt;99% ee</td>
</tr>
</tbody>
</table>
In particular, complex \((R,R)-B\) having the electron-donating methoxy substituent on the 2-benzyl tether exhibited the highest catalytic performance and was used afterwards for further ATH studies. Aromatic \(\alpha\)-amino \(\beta\)-keto ester hydrochlorides 6 underwent ATH-induced by Rh complex \((R,R)-B\) with good yields, fair diastereoselection, and excellent enantioselectivities through a dynamic kinetic resolution (DKR) process. The corresponding \(\alpha\)-amino aminoalcohols 7 were obtained after N-benzylation; whereas the syn compounds 8 were formed starting from heteroaromatic ketones 6 (Table 1, B).7 On the other hand, an access to \(\alpha\)-benzoylamido-\(\beta\)-hydroxy esters 10 was developed through ATH/DKR of \(\alpha\)-benzoylamido \(\beta\)-keto esters 9 with high yields (up to 98%) and diastereomeric ratios (up to >99:1 dr) as well as excellent enantioselectivities (up to >99% ee, Table 1, C).8 The asymmetric reduction of \(\alpha\)-methoxy \(\beta\)-keto esters 11 through transfer hydrogenation using rhodium(III) complexes \((R,R)-B\) and \((R,R)-F\), respectively, was performed in 2-MeTHF with formic acid/triethylamine or in water with sodium formate in the presence of cetyltrimethylammonium bromide (CTAB) as a surfactant. The corresponding syn-\(\alpha\)-methoxy-\(\beta\)-hydroxy esters 12 were obtained with high diastereoselectivities and excellent levels of enantioselectivity via a DKR process under environmentally sustainable conditions (Table 1, D).9 Enantioenriched cis-3-hydroxymethyl chroman-4-ol derivatives 14 were conveniently prepared by ATH/DKR of 3-formyl chromones 13 using complex \((R,R)-B\) and HCO\(_2\)H/Et\(_3\)N (5:2) as the hydrogen source, delivering the reduced compounds in diastereomeric ratios up to 98:2 and enantioselectivities up to >99% ee through a new catalytic ATH cascade sequence that provided multiple reductions of C=O and C=C bonds with one catalyst (Table 1, E).10 The ATH of \(\beta\)-keto-\(\gamma\)-acetamides 15 has been studied with complex \((R,R)-B\) and the HCO\(_2\)H/Et\(_3\)N (5:2) azeotropic mixture delivering a wide range of enantioenriched \(\beta\)-hydroxy-\(\gamma\)-acetamides 16 with a high chemoselectivity observed toward the reduction of the carbonyl group over the C=C bond, yields up to quantitative and enantioselectivities up to 99% (Table 1, F).11 The same catalytic system was used to access 1,2,3,4-tetrahydroquinolin-4-ols 18 conveniently through ATH of 4-quinolone derivatives 17 with excellent enantioselectivi-
ties under mild conditions (Table 1, G). A straightforward access to enantiomerically enriched cis-3-benzylchalcones 20 was developed through ATH of (E)-3-benzylidenechromanones 19 using complex (R,R)-B. This one-pot ATH cascade protocol allowed the reduction of the C=C and C=O bonds and the formation of two stereocenters in high yields with diastereo- and enantioselectivities up to >99:1 dr and >99% ee through a DKR process using a low catalyst loading and HCO₂H/DABCO as the hydrogen source (Table 1, H).

The kinetic resolution (KR) of 2-aryl tetrahydro-4-quinolone derivatives 21 was efficiently achieved through ATH using the previous catalytic system. The reaction afforded the enantiomerically enriched 2-aryl-2,3-dihydroquinolines 22 in high isolated yields and up to >99% enantioselectivity (Table 1, I). The ATH of α-aminooethyl α′-choloromethyl ketones 24 using (R,R)-B or (S,S)-B afforded a series of chiral 3-amino-1-chloro-2-hydroxy-4-phenylbutanes 25 or 26 in excellent yields and diastereoselectivities, with both diastereomers of the reduced products available (up to 99% yield, up to 99:1 dr, Table 1, J).

Rh-tethered complexes (R,R)-B-(R,R)-E have been developed and used in the ATH of a wide range of functionalized ketones exhibiting excellent activities and selectivities. Among them, complex (R,R)-B was particularly efficient to produce a series of enantiomerically enriched alcohols including oxygen- and nitrogen-containing heterocycles such as cis-3-hydroxymethyl chroman-4-ols, cis-3-benzylchromanols, 1,2,3,4-tetrahydroquinolin-4-ols, and 2-aryl tetrahydro-4-quinolol derivatives as well as carbocycles such as α-substituted β-hydroxy carbonylketones. Additional examples of catalytic applications involved the preparation of syn-α-benzoylamido and α-methoxy β-hydroxy esters, 3-amino-1-chloro-2-hydroxy-4-phenylbutanes, and β-hydroxy-γ-ace
tal enamides. The selective transformations promoted by the Rh(III) catalysts, developed in our group, proceeded under mild conditions at low catalyst loading, and can occur in a one-pot fashion through ATH cascade reactions that demonstrated the practical applicability of these promising complexes for future applications.

**Conflict of Interest**

The authors declare no conflict of interest.

References


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