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

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Abstract **Key words** asymmetric catalysis, enantioselectivity, homogeneous catalysis, hydrogen transfer, rhodium, diastereoselectivity

Transition-metal-catalyzed asymmetric transfer hydrogenation (ATH)[1] 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*-toluenesulfonyl)-1,2-diphenylethylendiamine (TsDPEN) ligand that was used with either isopropanol or formate salts as the hydrogen donor.[2] 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**[3] 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.[4] The *N*-pentafluorophenylsulfonyl-DPEN-based tethered Rh(III) complex (*R*,*R*)-**F**[5] was also synthesized.

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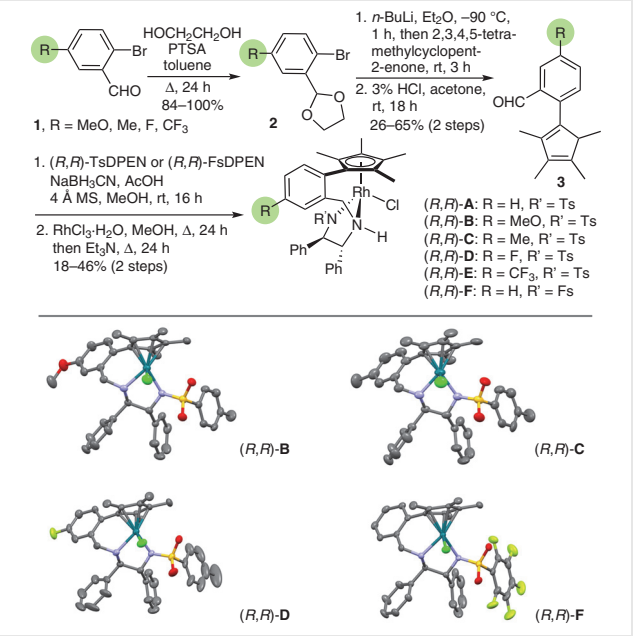
Virginie Vidal completed her PhD at Paris-Sud University under the supervision of Prof. H. P. Husson and Dr. J. Royer (Gif, France) and was a FRM postdoctoral fellow at the University of Montreal with Prof. S. Hanessian (Canada, 1989–1990), and in 1991 with Prof. P. Potier and Dr. R. H. Dodd (Gif). She was appointed as a CNRS Associate Researcher with Prof. J. P. Genêt at ENSCP. She is currently CNRS Research Director at Chimie ParisTech (Paris, France). Her research interests focus on the development of transition-metal catalysis and the design of atropisomeric ligands (Synphos and Difluorphos). The synthesis of biorelevant targets is also a focus in her research group.

Complexes (*R*,*R*)-**B**–(*R*,*R*)-**F** were prepared according to the route disclosed for the parent complex (*R*,*R*)-**A**[3,6] (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-enone afforded

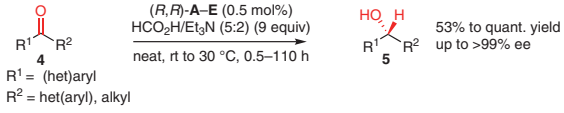
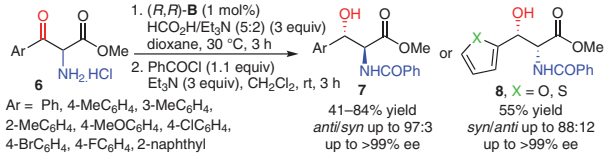
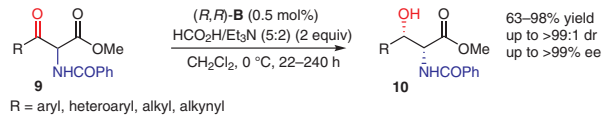
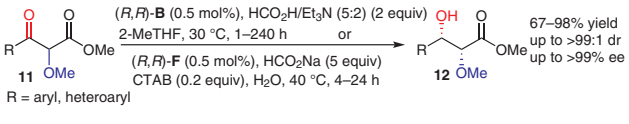
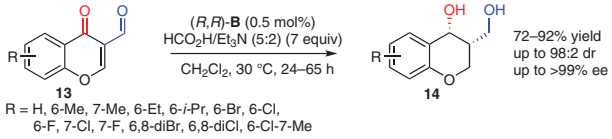


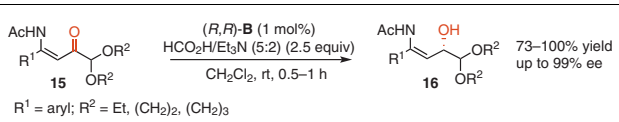
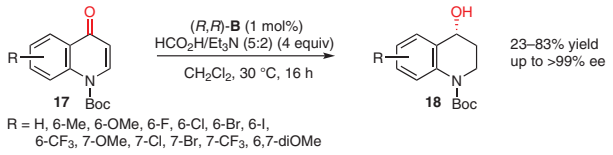
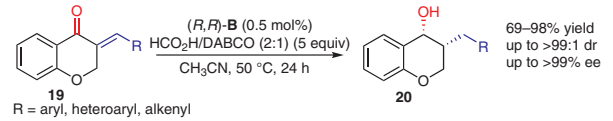
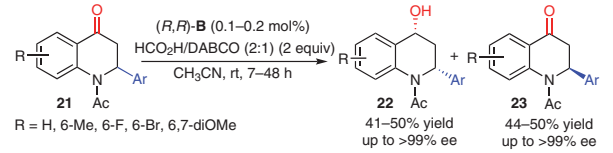
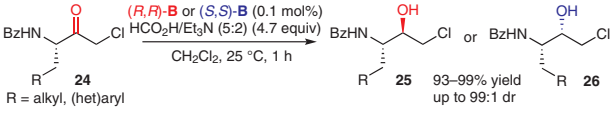
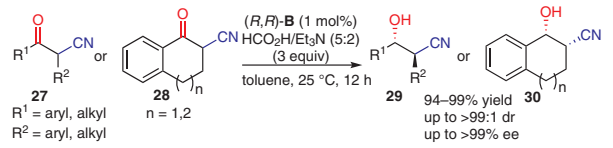
Scheme 1 Synthesis of complexes **B–F** and X-ray crystallographic structures of **B–D**, **F**

the corresponding alcohols that under acidic treatment underwent concomitant deprotection of the aldehyde and dehydration of the tertiary alcohol to give the cyclopentadiene derivatives **3**. Subsequent reductive amination of the latter using (*R*,*R*)-TsDPEN or (*R*,*R*)-FsDPEN followed by treatment with $RhCl_3$ 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 **4**[4] using the formic acid/triethylamine (5:2) system as the hydrogen source, giving the corresponding alcohols **5** with selectivities comparable to those obtained with Wills' complex (*R*,*R*)-**A**[3] 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**

(A) ATH of Functionalized Ketones[3,4] - Access to secondary alcohols under mild conditions - Low catalyst loading - High enantioselectivities - Broad substrate scope	
(B) ATH/DKR of Aromatic α-Amino β-Keto Ester Hydrochlorides[7] - Access to *anti*-α-amino-β-hydroxy ester derivatives - Fair diastereoselectivities - High to excellent enantioinductions - Access to *syn*-α-amino-β-hydroxy ester derivatives with heteroaromatic compounds	
(C) ATH/DKR of α-Benzoylamido β-Keto Esters[9] - Preparation of *syn*-α-benzoylamido-β-hydroxy esters - Low catalyst loading - 2 stereogenic centers controlled in a single step - Excellent enantioselectivities	
(D) ATH/DKR of α-Methoxy-β-keto Esters[5] - Synthesis of *anti*-α-methoxy-β-hydroxy esters - Use of environmentally sound solvents - Low catalyst loading - Control of 2 stereocenters in a single step - Excellent diastereo- and enantioselectivities	
(E) ATH/DKR of 3-Substituted Chromones[10] - Preparation of *cis*-3-hydroxymethyl chroman-4-ol derivatives - Multiple reductions of C=O and C=C bonds with one catalyst - New catalytic ATH cascade sequence - Applicability of the method for large scale reactions - 2 stereogenic centers controlled in a single step - Excellent diastereo- and enantioselectivities	

(F) ATH of β-keto-γ-acetal enamides[11] - Access to β-hydroxy-γ-acetal enamides - Mild conditions - Low catalyst loading - Excellent chemo- and enantioselectivities	
(G) ATH of Quinolone Derivatives[12] - Efficient and practical access to 1,2,3,4-tetrahydroquinolin-4-ols - Catalytic ATH cascade reaction - Mild conditions - Excellent enantiofacial discrimination	
(H) ATH/DKR of 3-Benzylidene Chromanones[13] - One-pot ATH cascade protocol to access *cis*-benzyl-chromanols - Low catalyst loading - 2 stereogenic centers controlled in a single step - Excellent diastereo- and enantioselectivities	
(I) ATH/KR of 2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones[14] - Synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones and 2-aryl tetrahydro-4-quinolols - Efficient kinetic resolution - Excellent enantioselectivities	
(J) ATH of α-Aminoalkyl α′-Chloromethyl Ketones[15] - Access to both diastereomers of 3-amino-1-chloro-2-hydroxy-4-phenylbutanes - Low catalyst loading - Excellent yields and high diastereoselectivities - Key building blocks for pharmaceutical intermediates - Broad scope	
(K) ATH/DKR of α-Substituted β-Keto Carbonitriles[16] - Efficient access to α-substituted β-hydroxy carbonitriles - Building blocks for biologically active pharmaceuticals - Excellent yields - High diastereoselectivities and excellent enantioselectivities - Rationalization of the diastereoselectivity by DFT calculations - Wide substrate scope	

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 α-amino β-keto ester hydrochlorides **6** underwent ATH-induced by Rh complex (*R*,*R*)-**B** with good yields, fair diastereoselection, and excellent enantioselectivities[7] through a dynamic kinetic resolution (DKR) process.[8] The corresponding *anti*-amino alcohols **7** were obtained after N-benzoylation; whereas the *syn* compounds **8** were formed starting from heteroaromatic ketones **6** (Table 1, B).[7] On the other hand, an access to *syn*-α-benzoylamido-β-hydroxy esters **10** was developed through ATH/DKR of α-benzoylamido β-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).[9] The asymmetric reduction of α-methoxy β-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*-α-methoxy-β-hydroxy esters **12** were obtained with high diastereoselectivities and excellent levels of enantioselectivity via a DKR process under environmentally sustainable conditions (Table 1, D).[5] 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_2H/Et_3N (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 β-keto-γ-acetal enamides **15** has been studied with complex (*R*,*R*)-**B** and the HCO_2H/Et_3N (5:2) azeotropic mixture delivering a wide range of enantioenriched β-hydroxy-γ-acetal enamides **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).[12] A straightforward access to enantiomerically enriched *cis*-3-benzylchromanols **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 HCO_2H/DABCO as the hydrogen source (Table 1, H).[13] 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-dihydroquinolin-4(1*H*)-ones **23** with excellent levels of enantioselectivity (up to >99% ee) as well as the corresponding synthetically useful enantiomerically enriched 2-aryl tetrahydro-4-quinolols **22** in high isolated yields and up to >99% enantioselectivity (Table 1, I).[14] The ATH of α-aminoalkyl α′-chloromethyl 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).[15] α-Substituted β-keto carbonitriles **27** and **28** were efficiently reduced with (*R*,*R*)-**B** and HCO_2H/Et_3N (5:2) to the corresponding α-substituted β-hydroxy carbonitriles **29** and **30** in excellent enantio- and diastereoselectivities (up to >99% ee, up to >99:1 dr) through a DKR process offering rapid access to key intermediates of biologically active pharmaceuticals (Table 1, K).[16]

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 enantioenriched alcohols including oxygen- and nitrogen-containing heterocycles such as *cis* 3-hydroxymethyl chroman-4-ols, *cis*-3-benzyl-chromanols, 1,2,3,4-tetrahydroquinolin-4-ols, and 2-aryl tetrahydro-4-quinolol derivatives as well as carbocycles such as α-substituted β-hydroxy carbonitriles. 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-acetal 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.

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