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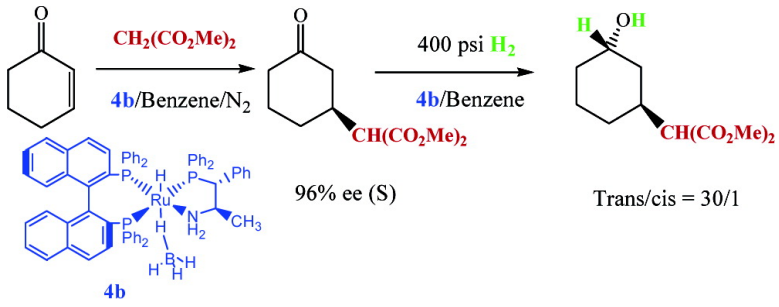

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Enantioselective Tandem Michael Addition/H_2-Hydrogenation Catalyzed by Ruthenium Hydride Borohydride Complexes Containing β-aminophosphine Ligands[1]

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An important reaction for creating carbon−carbon bonds with enantioselectivity is the catalytic asymmetric Michael addition reaction.[2] This reaction can be combined with other catalytic transformations, such as *o*-nitroso aldol,[3] or domino addition[4] to build up complex organic structures. Recently, the chiral amido complexes, Ru(η^6-arene)((*R*,*R*)-Tsdpen) [arene = cymene, mesitylene, durene, hexamethyl benzene, (*R*,*R*)-Tsdpen = (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine], were used effectively in the addition of malonates to cyclic enones[5] or to nitroalkenes[6] to give Michael addition products in excellent enantiomeric excess. The reaction was proposed to involve a metal−NH bifunctional effect related to that proposed for the asymmetric transfer hydrogenation of ketones.[7]

We have shown that amido complexes RuH(amine−amido)((*R*)-binap) and RuH(amine−amido)(PPh_3)$_2$ can also be prepared for a variety of hydridoruthenium phosphine/amine systems.[8−11] These are typically prepared by the reaction of a base with precursor ruthenium hydridochloro complexes, such as RuHCl((*R*)-binap)(diamine) or RuHCl(PPh_3)$_2$(diamine). In addition, complexes of the *trans*-RuHCl(L)$_2$ and *trans*-RuHCl(L)(binap) types, where L is derived from an amino acid[12] or norephedrine (see Figure 1),[13] in the presence of base, are effective catalysts for the asymmetric hydrogenation of ketones and imines where unstable amido complexes are thought to be the active catalysts. We reasoned that the same amido catalysts should promote both a Michael addition reaction followed by a ketone hydrogenation in the same flask.

At first, we found that the use of excess base to generate the amido complexes in situ from the hydridochloro complexes results in active catalysts for Michael addition reactions, but there is no enantioselectivity because of nonselective catalysis by the excess KO^{t}Bu (e.g., entry 2, Table 1). In the absence of base, there is no reaction (entry 1). Recently, Noyori and co-workers reported that borohydride complexes of the *trans*-RuH(η^1-BH_4)(binap)(diamine) type are active catalysts for the asymmetric hydrogenation of ketones without added base.[14,15] This lead us to find that a wide range of complexes containing borohydride ligands are excellent catalysts for the desired tandem reaction.

The reaction of the precursor complexes, *trans*-RuHCl((*S*)-Ppro)$_2$ (**1a**) [(*S*)-Ppro = (*S*)-2-(diphenylphosphinomethyl)pyrrolidine],[12] *trans*-RuHCl((*R*,*R*)-Pnor)$_2$ (**2a**), *trans*-RuHCl((*R*,*R*)-Pnor)((*R*)-binap) (**3a**), *trans*-RuHCl((*R*,*R*)-Pnor)((*S*)-binap) (**4a**)[13] [(*R*,*R*)-Pnor = (1*R*,2*R*)-$PPh_2CHPhCHMeNH_2$], with $NaBH_4$ results in the formation of the new complexes, *trans*-RuH(η^1-BH_4)((*S*)-Ppro)$_2$ (**1b**), *trans*-RuH(η^1-BH_4)((*R*,*R*)-Pnor)$_2$ (**2b**), *trans*-RuH(η^1-BH_4)((*R*,*R*)-Pnor)((*R*)-binap) (**3b**), and *trans*-RuH(η^1-BH_4)((*R*,*R*)-Pnor)((*S*)-binap) (**4b**), respectively, in excellent yield (Figure 1).

The structure of the *trans*-RuH(η^1-BH_4)((*R*,*R*)-Pnor)$_2$ complex was determined by single-crystal X-ray diffraction (Figure 2). It is similar to that of *trans*-RuH(η^1-BH_4)((*R*)-tolbinap)((*R*,*R*)-dpen),[15] with the borohydride ligand coordinating trans to hydride and

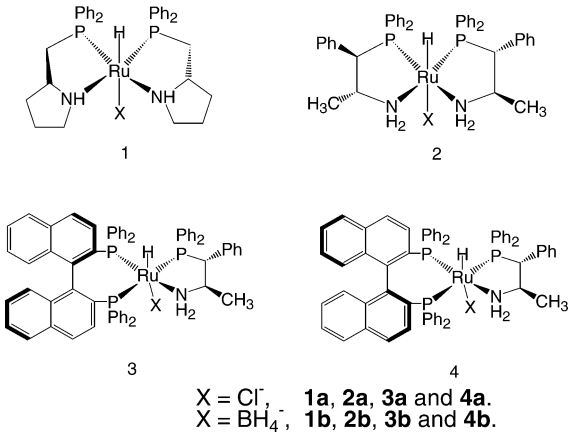

Figure 1. Complexes *trans*-RuH(X)(L)$_2$ and *trans*-RuH(X)(L)(binap).

Table 1. Catalysts for the Michael Reaction of Dimethylmalonate with 2-Cyclohexene-1-one[a]

entry	catalyst	solvent	conv. %	% ee (config)
1[b]	**4a**	2-propanol	0	
2[c]	**4a**	2-propanol	>99	racemic
3[b]	**1b**	THF	>99	33 (*R*)
4[b]	**2b**	THF	>99	56 (*S*)
5[b]	**3b**	THF	>99	82 (*R*)
6[b]	**4b**	THF	>99	96 (*S*)
7[d]	**4b**	THF	>99	97 (*S*)
8[b]	**4b**	benzene	96	95 (*S*)
9[d]	**4b**	benzene	>99	97 (*S*)
10[b]	**4b**	toluene	95	96 (*S*)
11[b]	**4b**	ether	55	96 (*S*)
12[b]	**4b**	ethanol	52	23 (*S*)
13[b]	**4b**	2-propanol	94	30 (*S*)
14[b]	**4b**	CH_3CN	47	14 (*S*)
15[e]	**5b**	THF	96	58 (*S*)

[a] In all cases, the reaction experiment was carried out at 20 °C with 0.005 mmol of the catalyst. [b] Substrate/catalyst = 100, no base, 24 h. [c] Substrate/catalyst = 100, base/catalyst = 10, 24 h. [d] Substrate/catalyst = 50, 24 h. [e] Substrate/catalyst = 100, 120 h. The enantiomeric excesses were determined by GC analysis using a CP CHIRASIL-DEX CB column (25 m × 0.25 mm), and the absolute configurations of the products were determined by optical rotation and comparison with literature values.

accepting bifurcated NH···(BH)···HN dihydrogen bonds[16,17] from the amino groups with H···H distances of 2.1 Å. A related bifurcated NH···(IrH)···HN motif has been observed in iridium hydride complexes.[18]

The borohydride complexes catalyze the addition of dimethylmalonate to 2-cyclohexene-1-one under mild conditions (Table 1). The *trans*-RuH(η^1-BH_4)((*S*)-Ppro)$_2$ complex (**1b**) shows good reactivity but low enantioselectivity (entry 3). The *trans*-RuH(η^1-BH_4)((*R*,*R*)-Pnor)$_2$ complex (**2b**) provides the (*S*) Michael adduct with an improved enantiomeric excess (entry 4). This result encouraged us to try other kinds of more rigid complexes. The

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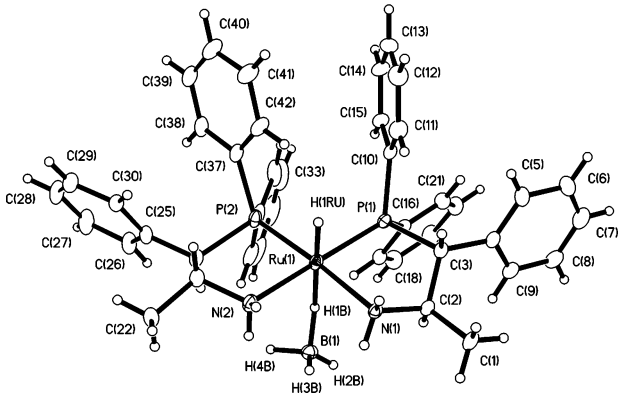
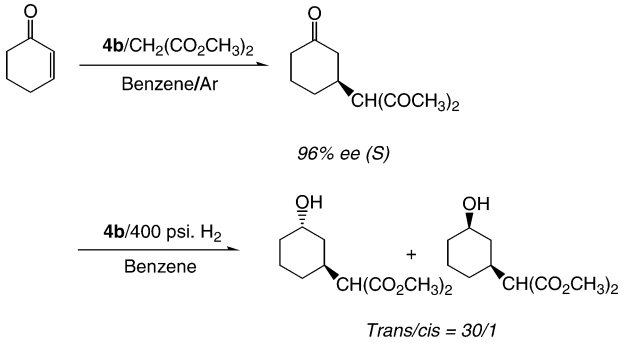


Figure 2. Structure of *trans*-RuH(η^1-BH_4)((*R*,*R*)-Pnor)$_2$, **2b**. Selected bond distances and angles: Ru(1)−H(1Ru) = 1.588(3) Å; Ru(1)−H(1B) = 1.716(4) Å; Ru(1)−N(2) = 2.183(3) Å; Ru(1)−N(1) = 2.183(2) Å; Ru(1)−P(2) = 2.2172(9) Å; Ru(1)−P(1) = 2.219(1) Å; N(2)−Ru(1)−N(1) = 92.4(1)°; P(2)−Ru(1)−P(1) = 100.96(4)°; N(1)−Ru(1)−P(1) = 83.31(8)°.

Scheme 1. Tandem Michael Addition/Hydrogenation Catalyzed by **4b**

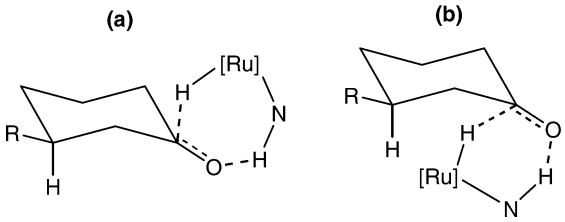


mixed-ligand ruthenium complex **3b** containing (*R*,*R*)-Pnor and (*R*)-binap catalyzed the formation of the (*R*) Michael addition product in 82% ee (entry 5). The results of these last two experiments indicate that (*R*,*R*)-Pnor favors the formation of the (*S*) product, while (*R*)-binap favors the formation of the (*R*) product (entry 5). In keeping with this idea, the combination of ligands (*R*,*R*)-Pnor and (*S*)-binap in **4b** provided the Michael adduct in the highest enantiomeric excess of 97% (*S*) (entries 7 and 9). The use of aprotic solvents, such as benzene, THF, toluene, and ether, favors the enantioselective reaction (entries 6, 8, 10, and 11), while that of protic 2-propanol and ethanol does not. The *trans*-RuH(η^1-BH_4)-((*R*)-binap)((*R*,*R*)-dpen) catalyst (**5b**)[14] gives the (*R*) configuration adduct in 58% ee (entry 15).

This system allows a one-pot, tandem asymmetric Michael addition/ketone H_2-hydrogenation protocol to synthesize a new chiral alcohol (Scheme 1). The hydrogenation of the Michael addition product of 2-cyclohexene-1-one catalyzed by **4b** occurs with excellent diastereoselectivity (trans/cis = 30/1) in benzene.

The trans isomer was characterized by NMR, MS, and optical rotation. The identity of the cis isomer was verified by independent synthesis, crystallization as the tosylate, and single-crystal X-ray structure analysis. The selectivity in the ketone hydrogenation step can be explained by the steric requirements of the transition state involving the outer sphere transfer of hydride from the ruthenium and proton from the amino group of the ligand (Scheme 2).[19] Noyori

Scheme 2. (a) Favored Transition State for H^-/H^+ Transfer to the Ketone, Resulting in the trans Product and (b) Transition State Disfavored Due to Steric Hindrance



and Ohkuma reported that the hydrogenation of a 3-substituted cyclohexanone with $RuCl_2(PPh_3)_3$/diamine/KOH resulted predominantly in the trans isomer.[20]

These reactions have been extended to pentenones, heptenones, and nitrostyrene Michael acceptors and malonitrile Michael donors. The structural variety of catalysts that can be prepared makes this a potentially very flexible tandem reaction for producing functionalized alcohols that can, for example, be converted into a lactone in a third step.

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Supporting Information Available: Preparation and characterization of the compounds. A crystallographic cif file for compound **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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