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Efficient asymmetric transfer hydrogenation of activated olefins catalyzed by ruthenium amido complexes

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Abstract—The asymmetric transfer hydrogenation of activated olefins with chiral ruthenium amido complexes (Noyori catalyst) using formic acid–triethylamine azeotrope as hydrogen source resulted in excellent yields and high enantioselectivities (up to 88.5%).

The asymmetric reduction of β,β-disubstituted α,β-unsaturated carbonyl compounds is one of the most important reactions to construct a chiral carbon center on the β-positions.[1] Apart from asymmetric hydrogenation catalyzed by chiral diphosphine–rhodium or ruthenium complexes,[2] the conjugate reduction with other reducing agents also plays a very important role in this area. Although a number of metal catalysts have been employed for the conjugate reduction,[3] there are limited catalysts that can reduce C=C bonds to generate a stereocenter with high enantioselectivity β to a carbonyl. Pfaltz's chiral semicorrin cobalt system is a highly efficient catalyst for the asymmetric conjugate reduction of α,β-unsaturated esters, amides and other compounds[4] using sodium borohydride as the stoichiometric reducing agent, but generally the reactions proceed rather slowly. Yamada's chiral aldiminato cobalt complex is another example of asymmetric reduction catalysts for α,β-unsaturated amides with premodified $NaBH_4$.[5] Recently, Buchwald reported that the chiral phosphine–copper catalysts could catalyze the asymmetric conjugate reduction of α,β-unsaturated ester and cyclic ketones with excellent enantioselectivity, employing PMHS (polymethylhydro-siloxane) as the reductant.[6] Moreover, Noyori has recently disclosed that ruthenium amido complexes are highly efficient catalysts for the 1,2-reduction of C=O and C=N bonds,[7,8] using the formic acid–triethylamine azeotrope as hydrogen source, and *the transfer hydrogenation reaction is highly chemoselective for C=O function and tolerant of alkenes*.[7b,9] In our continuous study on these coordinately saturated monosulfonylated diamine–Ru(II) complexes catalyzed transfer hydrogenation reactions,[10] we found for the first time that the asymmetric reduction of the highly activated α,α-dicyano alkenes[11] proceeded with quantitative yields and high enantioselectivities under mild transfer hydrogenation conditions.[12]

In our initial studies, only moderate enantioselectivity (49% ee, 94% yield) was obtained in the reduction of 1-phenylethylidenemalononitrile **2g** (Fig. 2) with ruthenium amido catalyst, $[RuCl_2(cymeme)]_2$-(*R*,*R*)-TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) (**1a**).[13,14] By using the cyclic 1,2,3,4-tetrahydro-1-naphthylidene malononitrile **2a** gave higher enantioselectivity (60.6% ee, Table 1, entry 1), thus, we use **2a** as the model substrate to optimize the conditions. Solvents were found to have mild effects on the enantioselectivity, while the best results were obtained in THF (entries 1–4). In order to improve the enantioselectivity, we decided to fine tune the substitution pattern of the η-arene ligand and the structure of the TsDPEN ligand (Fig. 1). Since the bulky complex TsDPEN–$[RuCl_2(HMB)]_2$ (HMB = hexamethylbenzene)[7b,d] failed to catalyze the reaction probably due to the steric reason, we turned to modify the structure of the TsDPEN ligand. However, monoalkylation of the $-NH_2$ group of TsDPEN resulted in reducing both catalytic activity and enantioselectivity (entries 5 and 6). Fortunately, when *N*-2,4,6-mesitylenesulfonyl-DPEN[7c] (**1d**) was used (entry

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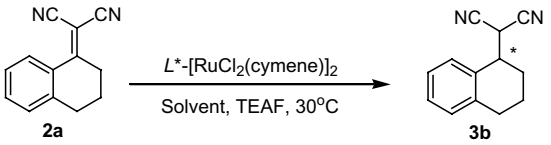
Table 1. Optimization of the catalytic conditions for asymmetric transfer hydrogenation of activated olefin **2a**[a]



Entry	Ligand	Solvent	T (h)	Yield (%)[b]	Ee (%)[c]
1	**1a**	THF	2	98	60.6
2	**1a**	CH_3CN	2	98	52.3
3	**1a**	CH_2Cl_2	2	98	53.7
4	**1a**	Toluene	2.5	97	59.2
5	**1b**	THF	3.5	97	52.1
6	**1c**	THF	10	96	46.8
7	**1d**	THF	3.5	98	84.1
8	**1e**	THF	4	98	84.3
9	**1f**	THF	4	99	85.1
10	**1g**	THF	20	95	57.9
11[d]	**1g**	THF	4	97	81.3
12[d]	**1h**	THF	6	96	81.1
13[e]	**1f**	THF	15	97	64.8
14[f]	**1f**	THF	4	99	85.9
15[g]	**1f**	THF	1.5	95	62.5

[a] The ligand and Ru precursor were initially heated in THF at 65 °C for 2 h, S/C = 100.
[b] Isolated yield.
[c] Ee was determined by HPLC on chiral OD column.
[d] **1g**, **1h** and Ru precursor were previously heated in 2-propanol at 85 °C for 2 h.
[e] S/C = 500.
[f] S/C = 50.
[g] For the reaction at 40 °C.

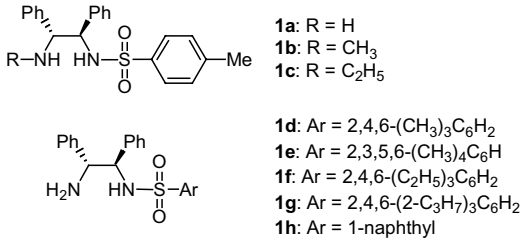


Figure 1. Chiral monosulfonylated DPEN ligands.

7), the enantioselectivity was dramatically increased to 84.1% ee without much effect on the reactivity. Moreover, through fine tuning the substituents on the benzene ring, the enantioselectivity could be marginally improved and the highest enantioselectivity (85.1%) was achieved with the complex of *N*-2,4,6-triethylbenzenesulfonyl-DPEN (**1f**) and $[RuCl_2(cymene)]_2$ (entry 9). It should be noted that further increase of the steric effect on arene ring will decrease both the reactivity and enantioselectivity (entry 10), and pre-activation in higher temperature (refluxing in 2-propanol) was very crucial to obtain high catalytic efficiency for the steric hindered ligand **1g** (entries 10 vs 11). 1-Naphthylsulfonyl-DPEN (**1h**) also gave high enantioselectivity (81.1% ee, entry 12). An increase in the S/C ratio to 500 caused a significant decrease in the enantioselectivity (64.8% ee vs 85.1% ee) but high yield (entry 13). However, a slight increase of the enantioselectivity (85.9% ee) was observed with 50 of S/C ratio (entry 14). An increase the reaction temperature to 40 °C resulted in shorter reaction time with low enantioselectivity (62.5% ee) and high yield (95%) (entry 15). At 0 °C, the reaction proceeded very slowly. These results indicated that the reaction activity depends on the temperature.

Having established the optimal catalytic system and conditions,[13] reaction scopes were assessed with the various substrates **2a**–**i** described in Figure 2. As noted in Table 2, all substrates were rapidly reduced within 5 h, and in general, high isolated yields were obtained. Activated olefins **2c**–**e** condensed from chromanones and malononitrile were reduced with high enantioselectivity (entries 3–6). Unlike the transfer hydrogenation of aromatic ketones,[7b,10c] the substituents on the

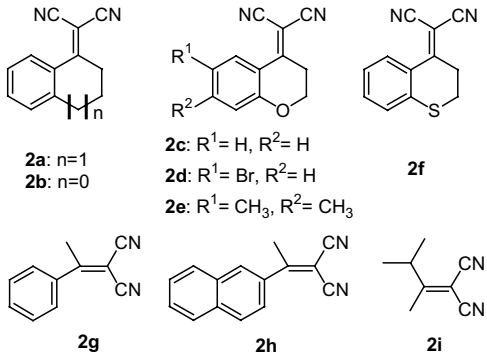


Figure 2. Activated olefins for asymmetric transfer hydrogenation.

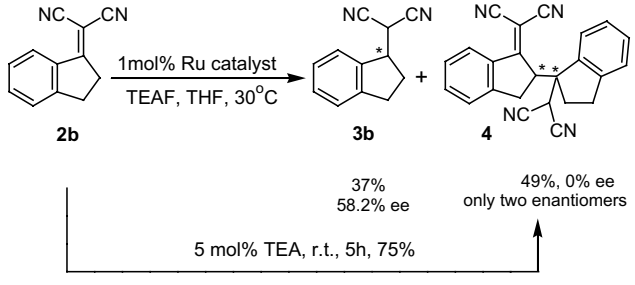
Table 2. Asymmetric transfer hydrogenation of activated olefins catalyzed by **1f**–$[RuCl_2(cymene)]_2$ complex[a]

Entry	Substrate	*T* (h)	Yield (%)[b]	Ee (%)[c] (Rotation sign)
1	**2a**	4	98	84.9 (−)
2	**2b**	3	37	58.2 (−)
3	**2c**	3	96	87.5 (−)
4	**2d**	3	93	82.5 (−)
5	**2e**	3	95 (82)[d]	88.5 (99)[d] (−)
6[e]	**2e**	3	94	88.4 (−)
7	**2f**	4	99	82.4 (+)
8	**2g**	2.5	74	72.7 (−, *S*)[f]
9	**2h**	3	85	59.2 (−)
10	**2i**	5	95	27.2 (−)

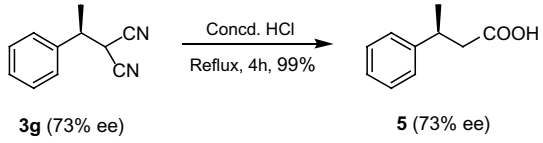
[a] **1f** and Ru precursor was initially heated in 2-propanol at 85 °C for 2 h, S/C = 100.
[b] Isolated yield.
[c] Ee was determined by HPLC on chiral OD column.
[d] After a single recrystallization from EtOAc–petroleum ether (v/v, 1:8).
[e] **1g** as the chiral ligand.
[f] The absolute configuration was determined by the rotation comparison to that of the literature, see Ref. 17.

arene ring had little effects on the reactivity and a slightly higher enantioselectivity was obtained for **2e** with electron-donating substituents. The similar result was received in the reduction of **2e**, while the steric hindered ligand **1g**-$[RuCl_2(cymeme)]_2$ complex was used as catalyst (entry 6). It is noticeable that optical pure product **3e** could be obtained through a single recrystallization from EtOAc/petroleum ether with 82% overall yield (entry 5). A thiochromanone derivative **2f** was quantitatively reduced with good enantioselectivity (entry 7). On the other hand, moderate enantioselectivities were obtained for **2g** and **2h** derived from acyclic aromatic ketones and malononitrile (entries 8 and 9). Great improvement in enantioselectivity of **2g** was also observed if using **1f** as ligand in comparison to **1a** (73% ee vs 49% ee). Substrate **2i** derived from acyclic aliphatic ketone gave lower enantioselectivity (27.2% ee) but high yield (entry 10).

Quite different from the six-member analogue **2a**, much lower yield and enantioselectivity were observed in the reduction of 1-indanylidenemalononitrile (**2b**) (Table 2, entry 2) and a byproduct **4** was isolated in higher yield, but no enantioselectivity determined by chiral HPLC analysis (Scheme 1). This showed that the γ-allylic C–H demonstrated unusually high acidity owing to the strong electron-withdrawing ability of malononitrile residue.[15] In fact, 1,4-addition product **4** readily formed in the presence of the catalytic amount of triethylamine (TEA) even at ambient temperature with 75% yield and the



Scheme 1.



Scheme 2.

same isomers were obtained (Scheme 1).[16] Moreover, 65% of γ-CH_2 of reduction product **3b** was deuterated using HCO_2D-triethylamine as hydrogen source, which proved that H–D exchange occurred at the allylic CH_2 before the reduction of the olefin.

The product **3g** was hydrolyzed in concd HCl to give the β-chiral acids **5** quantitatively without any racemization (Scheme 2). Thus, based on the rotation of known compound **5**,[17] the absolute configuration of **3g** can be assigned as (*S*)-form. This implies that other chiral β,β-disubstituted acids could be easily obtained from those chiral malononitriles **3**.

In conclusion, we demonstrated for the first time that chiral ruthenium amido complexes (Noyori catalyst) were efficient asymmetric catalysts for the transfer hydrogenation of activated olefins, using the formic acid–triethylamine azeotrope as hydrogen source.[18,19] Now, future work to extend the reaction scope and improve the enantioselectivity is in progress.

Acknowledgements

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17. **3g** was heated in concd HCl for 4 h. After a base and acid extraction procedure, the corresponding (*S*)-3-phenylbutyric acid **5** was obtained as an oil. $[\alpha]_D^{28}$ +40.9° (*c* 0.74, benzene) [lit. $[\alpha]_D^{25}$ −48.32° (*c* 2.69, benzene), 83% ee (*R*)]. See: Ref. 2b.
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