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N-Benzyl-norephedrine derivatives as new, efficient ligands for ruthenium-catalyzed asymmetric transfer hydrogenation of functionalized ketones

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Abstract

Significant catalytic activities (up to 600 h^{-1} at 20°C) and enantiomeric excesses ranging from 56 to 89% for the asymmetric transfer hydrogenation of β-ketoesters, methoxyacetone and 2-acetylpyridine to the corresponding alcohols are achieved in the presence of catalytic combinations of $[RuCl_2(\eta^6\text{-arene})]_2$ and *N*-substituted derivatives of (1*S*,2*R*)-norephedrine such as *N*-benzyl-norephedrine and *N*-(4-biphenyl)methyl-norephedrine.

Much effort has been devoted in recent years to the development of asymmetric transfer hydrogenations of ketones. As a result, several excellent chiral catalytic systems, combining a ruthenium or a rhodium precursor with chiral bidentate *N,X* ligands (X=N, O), have been reported for the enantioselective reduction of simple *aryl* alkyl ketones and α,β-acetylenic ketones.[1–7] Noteworthy among these top ligands are (1*S*,2*S*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine (TsDPEN **1**, Scheme 1) and (1*S*,2*R*)-ephedrine **2**.[2] However, the few results available from the literature[8] and our studies[9] clearly demonstrate that the existing catalytic systems are unsatisfactory for the reduction of functionalized ketones bearing heteroatoms such as the important β-ketoesters (sluggish activity and/or poor enantioselectivities).[10] In this regard, we have recently reported that chemoselective transfer hydrogenation of *alkyl* β-ketoesters to the corresponding alcohols is achieved in the presence of catalytic combinations of ephedrine and a suitable $[RuCl_2(\eta^6\text{-arene})]_2$ precursor with activities up to 190 h^{-1} at 20°C but only moderate enantiomeric excesses ranging from 36 to 44%.[9] We here report that *N*-benzyl substituted derivatives of norephedrine are promising chiral ligands for the ruthenium-catalyzed transfer hydrogenation of various functionalized ketones.

(1*S*,2*R*)-Norephedrine **3** was *N*-alkylated via a one-pot two-step procedure[11] as described in Scheme 1 using a variety of aldehydes. Among the numerous derivatives thus prepared, it turned out that *N*-

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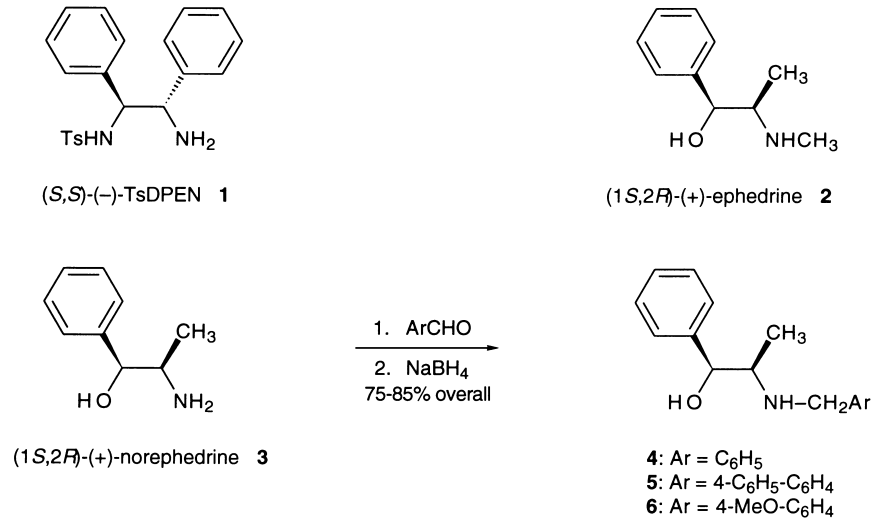
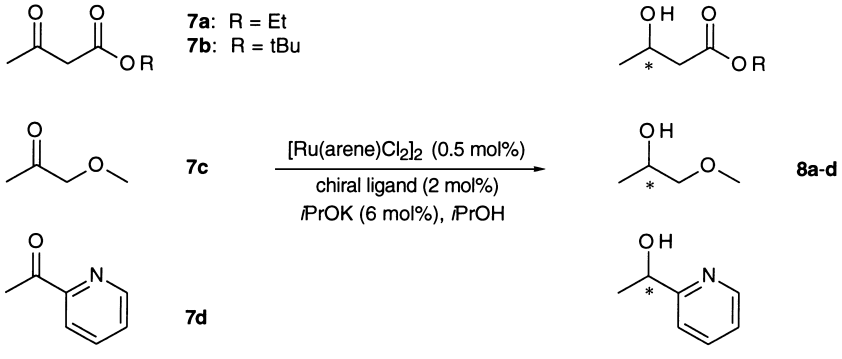


Scheme 1.

CH_2Ar-type compounds, of which **4–6** are representative examples, led to the most interesting catalytic properties. The effectiveness of these ligands was assessed in the reduction of ketones **7a–d** (Scheme 2). The chiral Ru catalyst precursors were prepared in situ by heating a mixture of $[RuCl_2(\eta^6\text{-arene})]_2$ and a chiral ligand (2 equiv. versus Ru) in 2-propanol, and transfer hydrogenation was carried out under usual reactions conditions as previously described.[9]



Scheme 2.

The results reported in Table 1 emphasize the main features of these reactions:

(i) The new *N*-benzyl-norephedrine type ligands **4–6** lead to significantly more enantioselective catalytic species than reference systems based on **1** and **2**. This trend proved to be general for the different ketones investigated. More particularly, ethyl acetoacetate **7a** (entries 1–4) and *tert*-butyl acetoacetate **7b** (entries 5–11) are reduced in up to 56 and 68% *ee*, respectively; these values, although still modest, are so far the best reported for transfer hydrogenation of simple alkyl β-ketoesters. The level of enantioselectivity is comparable for the reduction of methoxyacetone **7c** (entries 12–14) and reaches nearly 90% *ee* in the case of 2-acetylpyridine **7d** (entries 15–21).

(ii) For a given ruthenium precursor, the activity of the catalytic systems, as judged from the half-reaction time, follows the order **2**>**5**≈**6**>**4**≫**1**. As aforementioned, TsDPEN **1** systems proved to always be extremely sluggish in the case of functionalized ketones, and are thus almost inoperative. A neat illustration of this limitation is the reduction of methoxyacetone **7c** for which only 39% conversion is achieved with **1** in 16 h, while both ligands **2** and **4** allow complete conversion within

Table 1
Asymmetric transfer hydrogenation of functionalized ketones **7a–d**[a]

Entry	Subst.	Catalytic system arene / chiral ligand		*T* (°C)	Time[b] (h)	Conv. (mol %)	$t_{1/2}$ [c] (min)	*ee* (%)	Conf.[d]
1	**7a**	benzene	**1**	50	3	100	70	15	*R*-(–)
2	**7a**	benzene	**2**	50	0.5	100	10	36	*S*-(+)
3	**7a**	benzene	**4**	50	1	100	10	56	*S*-(+)
4	**7a**	benzene	**5**	50	0.5	100	10	58	*S*-(+)
5	**7b**	benzene	**1**	20	17	21	nd	<5	nd
6	**7b**	benzene	**2**	20	1	98	16	44	*S*-(+)
7	**7b**	benzene	**4**	20	5	100	135	68	*S*-(+)
8	**7b**	benzene	**5**	20	2.5	100	65	67	*S*-(+)
9	**7b**	benzene	**6**	20	4	100	60	66	*S*-(+)
10	**7b**	1,2,4-TMB[e]	**2**	20	14	100	150	17	*S*-(+)
11	**7b**	1,2,4-TMB[e]	**4**	20	16	100	300	46	*S*-(+)
12	**7c**	benzene	**1**	20	16	39	–	nd[f]	nd[f]
13	**7c**	benzene	**2**	20	0.33	100	5	54	*S*-(+)
14	**7c**	benzene	**4**	20	0.33	100	5	66	*S*-(+)
15	**7d**	*p*-cymene	**1**	20	17	43	–	84	*R*-(–)
16	**7d**	*p*-cymene	**2**	20	0.5	100	8	83	*R*-(–)
17	**7d**	*p*-cymene	**4**	20	16	100	420	89	*R*-(–)
18	**7d**	*p*-cymene	**5**	20	6	100	120	88	*R*-(–)
19	**7d**	benzene	**4**	20	2	100	15	79	*R*-(–)
20	**7d**	*t*-butylbenzene	**4**	20	15	100	180	83	*R*-(–)
21	**7d**	anisole	**4**	20	1	98	10	78	*R*-(–)

[a] [**7**] / [*i*PrOK] / [chiral ligand] / [Ru] = 100 : 6 : 2 : 1, [**7**] = 0.1 mol.l^{-1}, *i*PrOH = 20 mL. Conversion of **7a-d** into **8a-d** (the sole product observed) and *ee*s of **8a-d** were determined by quantitative GLC analysis (BPX5 and chiral permethylated-β-Cyclodex columns). [b] Reaction time was not necessarily optimized. [c] Half-reaction time determined by GLC monitoring. [d] Determined by polarimetry comparisons and/or GLC comparisons with authentic samples. [e] 1,2,4-trimethylbenzene. [f] The *ee* could not be determined because of overlapping between the GLC signals of **7c** and one enantiomer of **8c**.

20 min (TOF_{50}=600 h^{-1}) (entries 12–14). Derivatives **4–6** lead to somewhat less active species than their ephedrine (**2**) equivalents for the reduction of **7b** and **7d**. For these ketones, further substitution of the *N*-benzyl group of derivative **4**, i.e. introduction of a *para*-phenyl group (**5**) or a *para*-methoxy group (**6**), significantly enhances the catalytic activity with minimal effects on the enantioselectivity (compare entries 6–9 and 16–18).

(iii) For a given catalytic system, transfer hydrogenation of the *t*Bu ester **7b** always proceeds much faster than that of **7a**. This allows the reduction of **7b** to be completed at room temperature within a short reaction time with a substrate/catalyst ratio of 100. This dramatic increase in the reduction rate

going from ethyl to *tert*-butyl acetoacetate is assumed to be related to the bulkiness of the alkoxy group, which possibly prevents the formation of less reactive chelated species.

(iv) For a given chiral ligand, the catalytic performance is also strongly affected by the nature of the arene ligand in the Ru precursor.[9] This effect is emphasized here for the reduction of ketones **7b** and **7d**. The comparison of series of results, such as entries 6/10, 7/11, and 17/19/20/21, suggests that the bulkier the arene, the lower the catalytic activity. However, these effects are undoubtedly more complex, and the major influence of the arene ligand on enantioselectivity could not be rationalized so far. Efforts in this direction are under progress.

Acknowledgements

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10. There are two notable, although marginal, exceptions: (a) the transfer hydrogenation of $PhCOCH_2CO_2Et$ using HCO_2H as the hydrogen source and the catalytic combination $[RuCl_2(C_6H_6)]_2$/TsDPEN affords the corresponding alcohol in 93% *ee*; see Ref. 2a; (b) the transfer hydrogenation of $PhCOCO_2Me$ in *i*PrOH using Rh/C_2-diamine catalysts affords methyl mandelate in up to 99% *ee*; see: Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett*. **1993**, *34*, 6897–6898.
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