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Asymmetric reduction of methoxy substituted β-tetralones using transfer hydrogenation

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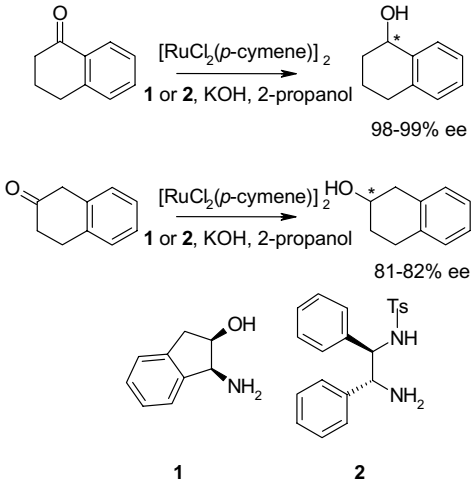
Abstract—Asymmetric reductions of methoxy substituted 2-tetralones were studied. The asymmetric transfer hydrogenation reaction developed by Noyori using chiral η^6-arene–ruthenium complexes (arene = *p*-cymene or benzene) was found to efficiently reduce various methoxy substituted 2-tetralones with >80% ee. Their enantiomeric excesses were found to depend on the position of the methoxy group and the types of the arene complexes. The conditions were identified for the asymmetric reduction of 8-methoxy-2-tetralone to the corresponding 2-tetralol in 98% ee, which was notably higher in enantioselectivity than the other methoxy substituted 2-tetralones.

1. Introduction

Enantiomerically pure 2-tetralols substituted by methoxy or hydroxy groups serve as important synthetic intermediates for a number of pharmaceutically active 2-aminotetralin derivatives, such as dopaminergic[1] and serotonergic[2] agonists. Although several asymmetric syntheses of an unsubstituted 2-tetralol via reduction of the corresponding prochiral 2-tetralone have been reported,[3] examples with methoxy substituted 2-tetralols are limited to enzymatic reduction that resulted in high enantioselectivity specifically for the reduction of 5-methoxytetralone.[4] Furthermore, a chemoenzymatic synthesis of a chiral 8-methoxy-2-tetralol has been reported, however, the preparation involves multiple steps.[5]

Asymmetric transfer hydrogenation[6] developed by Noyori using chiral η^6-arene–ruthenium complexes is a safe, due to its use of 2-propanol as the hydrogen source and thus the reaction does not require hydrogenation apparatus, and highly practical system for the preparation of various types of chiral alcohols. Noyori et al. and Wills et al. have reported the asymmetric transfer hydrogenation of 1-tetralone with excellent enantiomeric excess by using $[RuCl_2(p\text{-cymene})]_2$ catalyst with their (1*S*,2*R*)-(+)-*cis*-1-amino-2-indanol **1**[3d] or (*R*,*R*)-*N*-(2-amino-1,2-diphenylethyl)-*p*-toluenesulfonamide **2**[3c,7] ligand, which resulted in 98% ee and 99% ee, respectively. However in the case of 2-tetralone, the asymmetric reduction resulted in reduced enantiomeric excess with only 81% ee and 82% ee, respectively.



Thus, we became interested in further optimization of the asymmetric transfer hydrogenation specifically for the reduction of methoxy substituted 2-tetralones

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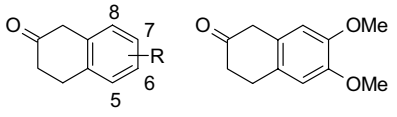
because despite their pharmaceutical usefulness, their asymmetric reduction using chemical catalysts is not known to date. Furthermore, since methoxy substituted 2-tetralones are readily available from commercial sources, this would be a convenient method to prepare various methoxy substituted chiral tetralols. We herein report an extended study of the asymmetric transfer hydrogenation for the preparation of various methoxy substituted chiral 2-tetralols from the prochiral 2-tetralones **3**–**8** (Fig. 1).



3: R = H
4: R = 5-OMe
5: R = 6-OMe
6: R = 7-OMe
7: R = 8-OMe

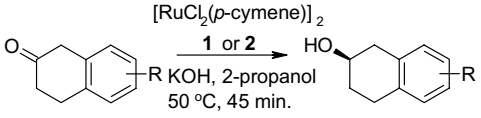
8

Figure 1. Methoxy substituted 2-tetralone substrates **3**–**8**.

2. Results and discussion

Initially, the catalyst–ligand combination reported by Wills et al. and Noyori et al., that is, Ru–*p*-cymene complex with either (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol **1** or (*R*,*R*)-*N*-(2-amino-1,2-diphenylethyl)-*p*-toluenesulfonamide **2**, in 2-propanol was applied to screen the reduction of various methoxy substituted 2-tetralones **3**–**8** (Table 1, entries 1–12).[8] Although the reduction of the unsubsitituted 2-tetralone **3** provided the product with 78% ee, remarkably higher enantiomeric excesses were obtained for 8-methoxy substituted ketone **7** with 92% ee and 96% ee using the ligands **1** and **2**, respectively.

Table 1. Results of the asymmetric transfer hydrogenation of substrates **3**–**8** using $[RuCl_2(p\text{-cymene})]_2$

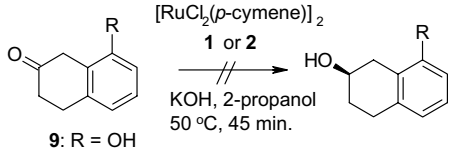


3 - 8

Entry	Ketone	Chiral ligand	Yield[a] (%)	Ee[b] (%)
1	**3**	**1**	81	78
2	**4**	**1**	80	82
3	**5**	**1**	85	83
4	**6**	**1**	81	78[c]
5	**7**	**1**	74	92
6	**8**	**1**	71	81
7	**3**	**2**	87	78
8	**4**	**2**	82	77
9	**5**	**2**	83	80
10	**6**	**2**	81	74[c]
11	**7**	**2**	80	96
12	**8**	**2**	77	73

[a] Isolated yield.
[b] Enantiomeric excess was determined by using chiral HPLC with a Chiralcel AD column unless otherwise noted.
[c] HPLC using a Chiralcel OJ column.

In order to evaluate the effect of the substituent at the 8-position using other electron donating and withdrawing groups, the asymmetric transfer hydrogenation of 8-hydroxytetralone **9** and 8-acetoxytetralone **10** was performed (Scheme 1). However, the attempts resulted in no reaction for both cases. One could speculate that the O^- anion generated in the reaction system possibly poisoned the catalyst. This indicated the limitation of the reduction of hydroxy substituted 2-tetralone using KOH and 2-propanol.

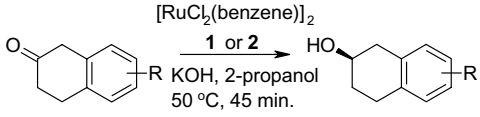


9: R = OH
10: R = OAc

Scheme 1. Attempts of the asymmetric transfer hydrogenation on 8-hydroxytetralone **9** and 8-acetoxytetralone **10**.

Next, a Ru–benzene complex was evaluated for the reduction of 2-tetralones (Table 2, entries 1–12). Although this Ru–benzene complex was previously reported to provide lower enantiomeric excesses compared to the Ru–*p*-cymene complex in the case of α-ketones such as acetophenone derivatives,[3d] the Ru–benzene complex surprisingly provided equal or better enantiomeric excesses for the reduction of the 2-tetralone derivatives. Furthermore, ligand **2** (Noyori ligand) was found to provide the chiral 2-tetralol derivatives with over 88% ee in all cases (Table 2, entries 7–12).

Table 2. Results of the asymmetric transfer hydrogenation of substrates **3**–**8** using $[RuCl_2(benzene)]_2$



3 - 8

Entry	Ketone	Chiral ligand	Yield[a] (%)	Ee[b] (%)
1	**3**	**1**	80	84
2	**4**	**1**	95	87
3	**5**	**1**	83	83
4	**6**	**1**	82	84[c]
5	**7**	**1**	77	92
6	**8**	**1**	79	86
7	**3**	**2**	72	88
8	**4**	**2**	99	88
9	**5**	**2**	97	92
10	**6**	**2**	82	88[c]
11	**7**	**2**	81	98
12	**8**	**2**	79	89

[a] Isolated yield.
[b] Enantiomeric excess was determined by using chiral HPLC with a Chiralcel AD column unless otherwise noted.
[c] PLC using a Chiralcel OJ column.

The effect of the position of the methoxy group was again noted in this catalyst system that while only a marginal difference in the enantioselectivity was ob-

served among the substrates **3**, **4**, **6**, and **8**, a notable increase in selectivity was seen for 6-methoxy-2-tetralone **5** with 92% ee (Table 2, entry 9) and 8-methoxy-2-tetralone **7** affording (2*R*)-8-methoxy-2-tetralol with 98% ee (Table 2, entry 11). This new finding of the enantioselectivity toward 8-methoxy-2-tetralone **7** is especially valuable for the study of serotonin (5-HT) and dopamine (DA) receptor agonists since substrate **7** is readily available either commercially or by the reported procedure of Nichols and co-workers[9] while the obtained enantiomerically pure 8-methoxy-2-tetralol can be easily converted to the chiral 8-methoxy-2-aminotetralin derivatives by the known method in good yields.[5]

3. Conclusion

In conclusion, an application of the asymmetric transfer hydrogenation for the preparation of various methoxy substituted chiral 2-tetralols, was evaluated. The resulting materials are interesting intermediates for the chiral synthesis of many serotonin and dopamine agonists. The reaction conditions using the $[RuCl_2(benzene)]_2$ complex with (*R*,*R*)-*N*-(2-amino-1,2-diphenylethyl)-*p*-toluenesulfonamide (Noyori ligand) were found to give the best results, with moderate to excellent enantiomeric excesses, most notably for (2*R*)-8-methoxy-2-tetralol, which was obtained in 98% ee.

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