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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Efficient Access to Chiral Benzhydrols via Asymmetric Transfer Hydrogenation of Unsymmetrical Benzophenones with Bifunctional Oxo-Tethered Ruthenium Catalysts

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Supporting Information

ABSTRACT: A concise asymmetric transfer hydrogenation of diaryl ketones, promoted by bifunctional Ru complexes with an etherial linkage between 1,2-diphenylethylenediamine (DPEN) and η^6-arene ligands, was successfully developed. Because of the effective discrimination of substituents at the ortho position on the aryl group, unsymmetrical benzophenones were smoothly reduced in a 5:2 mixture of formic acid and triethylamine with an unprecedented level of excellent enantioselectivity. For the non-ortho-substituted benzophenones, the oxo-tethered catalyst electronically discerned biased substrates, resulting in attractive performance yielding chiral diarylmethanols with >99% ee.

Catalytic asymmetric synthesis of secondary alcohols from ketones has attracted considerable interest as a reliable method. Since a string of Ru catalysts with 1,2-diamine scaffolds was established for asymmetric hydrogenation or transfer hydrogenation of acetophenone derivatives in the mid-1990s,[1,2] the utility of metal/NH cooperation has been highlighted via advances in redox transformations of carbonyl or alcoholic compounds.[3] Because of breakthrough developments of the bifunctional catalysts, the scope of ketone substrates has been extensively broadened; however, a high level of stereocontrolling ability of the chiral catalysts is needed to access postchallenging targets.

Among aromatic ketones, unsymmetrical benzophenones have been less frequently subjected to enantioselective reduction, in which a catalyst must discern structural differences in the two aromatic rings.[4−8] The catalytic hydrogenation offers straightforward access to biologically and pharmaceutically valuable benzhydrols without producing stoichiometric amounts of metal waste, compared with the asymmetric catalytic addition of nucleophilic arylmetals to aromatic aldehydes.[9] Ohkuma and Noyori reported that the Ru/(*S*)-Xylbinap/(*S*)-daipen catalyst can effectively promote hydrogenation of substituted benzophenones in the presence of *tert*-BuOK under mild pressure (8 atm) and temperature conditions.[4a] Although ortho-substituted benzophenones were successfully converted to the corresponding diarylmethanols with a maximum of 99% ee, the enantiomeric excesses obtained from meta- and para-substituted substrates were lower (<47% ee). In other asymmetric hydrogenation,[4b−f] hydroboration,[5] hydrosilylation,[6] and transfer hydrogenation[7] systems with reasonable enantioselectivity, the substrate scope remains primarily limited to ortho-functionalized and monosubstituted benzophenones.[10]

Using a systematic approach to structural tuning of the bifunctional catalysts derived from sulfonylated 1,2-diphenylethylenediamine (DPEN), we designed a new family of oxo-tethered Ru complexes (DENEB)—(*R*,*R*)-**3** and (*R*,*R*)-**4**—that exhibit excellent catalytic performance for the asymmetric transfer hydrogenation of simple ketones (Figure 1).[11,12] The

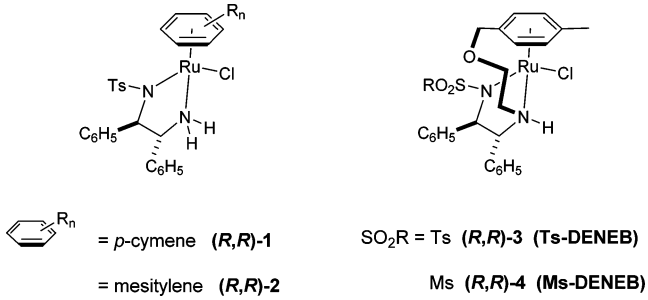


Figure 1. Structure of nontethered and tethered Ru-DPEN catalysts.

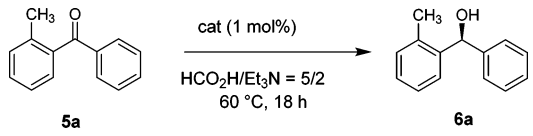
persistent three-point coordination obtained by introducing the covalently tethered unit[13] enhanced catalyst longevity and produced the highest activity of a series of the prototypic (η^6-arene)Ru/Ts-DPEN catalysts, including (*R*,*R*)-**1** and (*R*,*R*)-**2**. Regarding the imposed coordination, conformational rigidity also supported the stereodiscrimination ability of the bifunctional catalysts. Here, we report the substantial enantioselectivity of the oxo-tethered Ru complexes in the catalytic transfer hydrogenation of diaryl ketones with a variety of substituents at ortho positions and/or other positions.

We initially examined asymmetric transfer hydrogenation of 2-methylbenzophenone using 1 mol % of the DPEN-derived Ru complexes in an azeotropic mixture of formic acid and triethylamine at 60 °C. As listed in Table 1, the corresponding (*S*)-alcohol was obtained in 86−98% ees after the 18 h reaction.

Received: June 5, 2016
Published: July 27, 2016

DOI: 10.1021/jacs.6b05738
J. Am. Chem. Soc. 2016, 138, 10084−10087

Table 1. Asymmetric Transfer Hydrogenation of 2-Methylbenzophenone[a]



entry	catalyst	% yield	% ee[b]
1	(*R*,*R*)-**1**	22	86(*S*, +)
2	(*R*,*R*)-**2**	45	90(*S*, +)
3	(*R*,*R*)-**3**	98	98(*S*, +)
4	(*R*,*R*)-**4**	94	94(*S*, +)

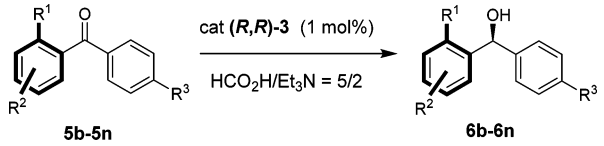
[a]Typical reaction conditions: catalyst (0.01 mmol), substrate (1.0 mmol), HCO_2H/Et_3N = 5/2 azeotropic mixture (0.5 mL). [b]Determined by HPLC analysis.

Compared to the prototype catalyst of (*R*,*R*)-**1** and (*R*,*R*)-**2** (entries 1 and 2), the oxo-tethered Ru(II) complexes (*R*,*R*)-**3**, (*R*,*R*)-**4** exhibited superior activities (entries 3 and 4), and the former Ts-derivative showed optimal catalytic performance in terms of the yield and enantioselectivity.[14] The attained optical purity is as high as those with a ketoreductase enzyme.[8b]

A variety of 2-substituted benzophenones was shown to be applicable to asymmetric transfer hydrogenation with (*R*,*R*)-**3**, which displayed enhanced enantioselectivities relative to the asymmetric hydrogenation with chiral Ru catalysts,[4a−f] as listed in Table 2. Monosubstituted benzophenones bearing chloro, bromo, and trifluoromethyl groups at the ortho position were smoothly reduced with almost complete conversions and excellent ees, exceeding 98% (entries 1−3). The results of the high-performance liquid chromatographic (HPLC) analysis with a chiral stationary phase indicated that the products were (*S*)-isomers. In contrast to the asymmetric hydrogenation with a diphosphine-diamine-Ru(II) complex,[4a] the oxo-tethered catalyst (*R*,*R*)-**4** tolerated a phenolic ketone—2-hydroxybenzophenone—and provided a satisfactory ee of 77% (entry 4). Multiply substituted aryl phenyl ketones, including 2,4-methyl-, 2,4,5-trimethyl-, 2,4-dichloro-, and 2-chloro-5-nitrobenzophenone analogues, were converted to the desired (*S*)-benzhydrols with sufficient conversions and ees (entries 5−8). Although reduction of 2,5-difluoro- and 2-fluoro-3-trifluoromethylbenzophenone produced slightly lower ees of 91% and 90% (entries 9 and 10), 2,3,4,5,6-pentafluorobenzophenone was completely hydrogenated with outstanding enantioselectivity (entry 11). Transfer hydrogenation of 2,4′-dichloro- and 2-chloro-4′-fluorobenzophenone furnished the corresponding unsymmetrical diarylmethanols in high yields and 97% ee (entries 12 and 13), indicating that (*R*,*R*)-**3** can precisely recognize the ortho-substituted phenyl group.

In a putative outer sphere mechanism involving H^+ and H^- transfer to the C=O moiety, an attractive interaction between the edge of an η^6-arene ligand and the face of an aromatic ring[15] in ketone substrates has been considered to impose their one-sided approach and enable remarkable asymmetric induction.[16] Given that the stereochemistry of all products from 2-substituted diaryl ketones has an *S*-configuration, a sterically favorable edge-to-face interaction away from the ortho-substituted phenyl groups is envisaged in the transition state, as depicted in Figure 2. The introduction of the sterically less demanding fluorine atom into the ortho position was mildly effective compared with other halogens (entries 9 and 10).

Table 2. Asymmetric Transfer Hydrogenation of 2-Substituted Benzophenones[a]



entry	R^1	R^2	R^3	temp, °C	time, h	product	% yield	% ee[b]
1	Cl	H	H	40	17	**6b**	>99	98(*S*, −)
2	Br	H	H	60	8	**6c**	>99	99(*S*, −)
3	CF_3	H	H	60	12	**6d**	99	>99(*S*, −)
4[c,d]	OH	H	H	40	13	**6e**	94	77(*S*, −)
5	CH_3	4-CH_3	H	60	17	**6f**	94	97(*S*, −)
6	CH_3	4,5-$(CH_3)_2$	H	60	23	**6g**	98	98(*S*, +)
7	Cl	4-Cl	H	30	18	**6h**	97	99(*S*, −)
8	Cl	5-NO_2	H	40	7	**6i**	>99	99(*S*, +)
9	F	5-F	H	10	40	**6j**	91	91(*S*, +)
10	F	3-CF_3	H	30	7	**6k**	>99	90(*S*, +)
11	F	perfluoro	H	60	5	**6l**	>99	99(*S*, −)
12	Cl	H	4′-Cl	30	18	**6m**	>99	97(*S*, −)
13	Cl	H	4′-F	40	17	**6n**	99	97(*S*, −)

[a]Typical reaction condition: catalyst (0.01 mmol), substrate (1.0 mmol), HCO_2H/Et_3N = 5/2 azeotropic mixture (0.5 mL). [b]Determined by HPLC analysis. [c](*R*,*R*)-**4** was employed as a catalyst. [d]Comparable yield (99%) and ee (70%) were obtained by using (*R*,*R*)-**3** under identical conditions.

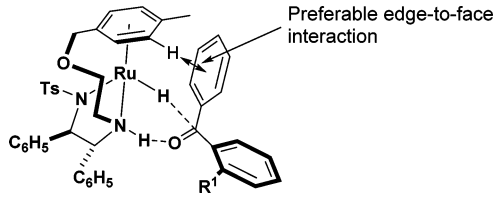
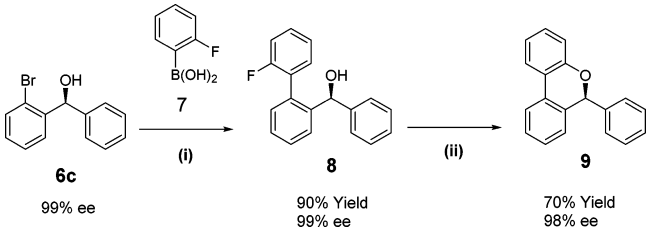


Figure 2. Proposed interaction between 2-substituted benzophenone and the oxo-tethered Ru(II) complex (*R*,*R*)-**3**.

The chiral benzohydrol product was successfully utilized in the expedient preparation of chiral benzo[*c*]chromene (**9**), for which only few synthetic methods have been reported (Scheme 1).[17] The Suzuki−Miyaura coupling reaction of (*S*)-(2-bromophenyl)(phenyl)methanol (**6c**) with 2-fluorophenylboronic acid (**7**) in the presence of $Pd(PPh_3)_4$ smoothly afforded the corresponding adduct **8** with virtually no loss of optical purity. Subsequent

Scheme 1. Synthesis of Optically Active 6-Phenyl-6*H*-benzo[*c*]chromene[a]



[a](i) 2-Fluorophenylboronic acid (**7**) (1.5 equiv), $Pd(PPh_3)_4$ (2 mol %), K_2CO_3 (1.5 equiv), toluene/THF = 1/1, 100 °C, 7 h; (ii) *tert*-BuOK (1.0 equiv), THF, 20 °C, 3 h.

DOI: 10.1021/jacs.6b05738
J. Am. Chem. Soc. 2016, 138, 10084−10087

cyclization with *tert*-BuOK in THF yielded the desired benzochromene framework **9** in 70% yield and 98% ee.

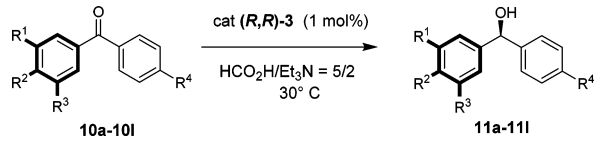
The utility of (*R*,*R*)-**3** was also demonstrated in the reaction of unsymmetrical diaryl ketones with the exception of 2-substituted benzophenones, as summarized in Table 3. From 4-chlorobenzophenone, the corresponding (*S*)-alcohol was formed with a moderate ee of 48% (**11a**, entry 1). The enantioselectivities can be substantially increased to 76% and 77% ees by doubly halogenated substrates at the meta and para position (**11b** and **11c**, entries 2 and 3). A comparable selectivity of 76% ee was attainable in the reduction of monosubstituted 4-nitrobenzophenone, implying an additional beneficial effect resulting from the incorporation of a strongly electron-withdrawing NO_2 group (**11d**, entry 4); 3-nitro-4-chlorobenzophenone produced 93% ee and complete conversion (**11e**, entry 5). When 3,4,5-trifluorobenzophenone and 3,5-dinitrobenzophenone were tested as highly biased diaryl ketones, the expected chiral alcohols (**11f** and **11g**, entries 6 and 7) were obtained with 95% and >99% ees, respectively. In these cases, the (*S*)-enantiomers were formed, possibly via a transition state by avoiding an interaction between the η^6-arene ligand and the relatively electron deficient ring, as indicated in bold in Figure 3.[18]

On the other hand, 4-methoxybenzophenone produced the (*R*)-**11h** (5% ee), as the result of a slightly better arene−arene interaction with the 4-methoxyphenyl group compared to the phenyl group (entry 8). The catalyst molecule can pointedly differentiate between two para-substituted phenyl groups with opposite electronic character, as observed in the reaction of 4-chloro-4′-methoxybenzophenone, which yields a higher ee of **11i**. A comparable ee with complete conversion was achieved in the reduction of 4-chloro-4′-hydroxybenzophenone, and the phenolic OH group remained intact (**11j**, entry 10). Additional enhancement of enantioselectivity by the nitro group was confirmed in the formation of **11k** and **11l**. The ees of the obtained methoxy-substituted alcohols—**11i** and **11k**—were consistently increased by 3−5% compared with the stereochemical outcomes of **11a** and **11d**, which were derived from the corresponding aryl phenyl ketones, possibly because the methoxyphenyl ring preferentially interacts with the η^6-arene ligand in the enantio-determining step.

The excellent enantioselectivity was also realized for other aromatic ketones with distinct electronic properties. As shown in Schemes 2 and 3, the reaction of benzoylferrocene afforded (*S*)-alcohol (**11m**) in 90% ee via a similar asymmetric induction, albeit producing only a 53% yield after 20 h at 60 °C. In addition, 3-nitrophenyl 2-thienyl ketone was converted to the corresponding (*R*)-product (**11n**) in 96% yield with almost complete enantioselectivity (Scheme 3). These results provide evidence for enantioselective reduction, i.e., the chiral oxo-tethered catalyst accurately avoids the sterically demanding and electron-poor ferrocene moiety and establishes the thiophene ring as an electron-rich fragment that can approach the η^6-arene ligand shown in Figure 3.

An extensive range of unsymmetrical benzophenone derivatives was successfully reduced with good to excellent ees and in high yields, because the oxo-tethered ligand ensuring precise recognition of ortho-substituted phenyl groups as well as differentiation between electron-rich and electron-poor arene rings. Considering the combination of desirable features, including a wide substrate scope, excellent enantioselectivity, mild reaction conditions, and high stability and availability of the catalyst precursor, we believe that this catalyst system has significant potential for application in a practical streamlined method to obtain chiral diarylmethanols.

Table 3. Asymmetric Transfer Hydrogenation of Non-ortho-Substituted Diaryl Ketones[a]



entry	R^1	R^2	R^3	R^4	time, h	product	% yield	% ee[b]
1	H	Cl	H	H	11	**11a**	>99	48(*S*, +)
2	Cl	Cl	H	H	18	**11b**	>99	76(*S*, +)
3	F	F	H	H	7	**11c**	>99	77(*S*, +)
4	H	NO_2	H	H	11	**11d**	>99	76(*S*, +)
5	NO_2	Cl	H	H	11	**11e**	>99	93(*S*, +)
6[c]	F	F	F	H	16	**11f**	>99	95(*S*, +)
7[c]	NO_2	H	NO_2	H	26	**11g**	90	>99(*S*, +)
8[d]	H	H	H	OCH_3	20	**11h**	80	5(*R*, +)
9	H	Cl	H	OCH_3	21	**11i**	59	53(*S*, +)
10	H	Cl	H	OH	6	**11j**	>99	55(*S*, +)
11	H	NO_2	H	OCH_3	30	**11k**	>99	79(*R*, +)
12	NO_2	H	NO_2	OCH_3	9	**11l**	92	99(*S*, +)

[a]Typical reaction condition: catalyst (0.01 mmol), substrate (1.0 mmol), HCO_2H/Et_3N = 5/2 azeotropic mixture (0.5 mL). [b]Determined by HPLC analysis. [c]Reaction was performed at 10 °C. [d]Reaction was performed at 60 °C.

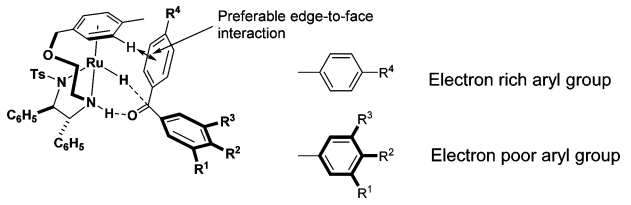
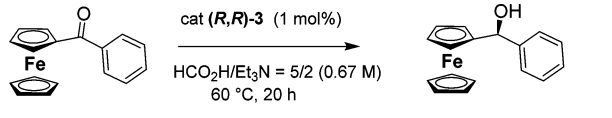


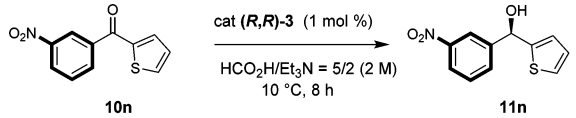
Figure 3. Plausible transition state in asymmetric transfer hydrogenation of non-ortho-substituted benzophenones with (*R*,*R*)-**3**.

Scheme 2. Asymmetric Transfer Hydrogenation of Benzoylferrocene



53% Yield, 90% ee (*S*)

Scheme 3. Asymmetric Transfer Hydrogenation of 3-Nitrophenyl 2-Thienyl Ketone



96% Yield, 98% ee (*R*)

DOI: 10.1021/jacs.6b05738
J. Am. Chem. Soc. 2016, 138, 10084−10087

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05738.

Experimental details and data (PDF)
Crystallographic data **6g** derivative (**13g**) (CIF)
Crystallographic data **6i** derivative (**13i**) (CIF)
Crystallographic data **6j** derivative (**13j**) (CIF)
Crystallographic data **6k** derivative (**13k**) (CIF)
Crystallographic data **11b** derivative (**14b**) (CIF)
Crystallographic data **11c** derivative (**14c**) (CIF)
Crystallographic data **11e** derivative (**14e**) (CIF)
Crystallographic data **11f** derivative (**14f**) (CIF)
Crystallographic data **11n** derivative (**14n**) (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was financially supported by JSPS KAKENHI grant nos. 24350079 and 26621043 and in part by Grant for Basic Science Research Projects from The Sumitomo Foundation. We are grateful to Messrs. Yoshihiro Yaguchi, Akihiro Kawaraya, Kazuhiko Sakaguchi, Jun Kurabe, Hiroaki Izumi, Masayuki Sentou and Mses. Hisae Kasuga, Kyoko Zaizen, Chikako Kawata, Seika Abe, Noriko Yamamoto of Takasago International Corporation for the measurement of NMR and mass spectra and experimental assistance. We also thank Prof. Takeshi Nakai and Prof. Masahiro Terada for helpful discussions.

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DOI: 10.1021/jacs.6b05738
J. Am. Chem. Soc. 2016, 138, 10084−10087