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Organic LETTERS

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Asymmetric Transfer Hydrogenation of 1,3-Alkoxy/Aryloxy Propanones Using Tethered Arene/Ru(II)/TsDPEN Complexes

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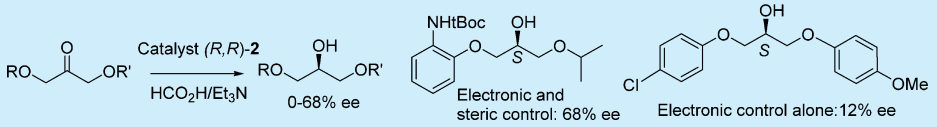
Supporting Information



ABSTRACT: A series of propanones containing combinations of aryloxy and alkoxy substituents at the 1- and 3-positions were reduced to the alcohols via asymmetric transfer hydrogenation using a tethered Ru(II)/TsDPEN catalyst. The enantioselectivities of the reductions reveal a complex pattern of electronic and steric effects which, when used in a matched combination, can lead to the formation of products of up to 68% ee (84:16 er) from this highly challenging class of substrate.

Asymmetric transfer hydrogenation (ATH) of ketones[1] has become a major area of asymmetric catalysis research, largely due to the pioneering work of Noyori et al.[2] on the arene/Ru(II)/TsDPEN class of catalysts typified by structure **1** (Figure 1).[3,4] In recent years "tethered" catalysts, for example **2** and **3**, which benefit from a high level of stability, have been developed by ourselves[5] and other groups.[6]

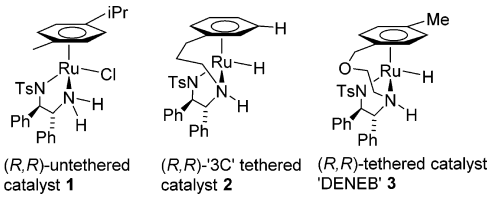


Figure 1. Arene/Ru(II)/TsDPEN complexes used in asymmetric transfer hydrogenation.

Certain classes of substrate are known to be highly compatible with the arene/Ru(II)/TsDPEN catalysts **1**−**3**, particularly acetophenone derivatives,[2,3] and propargylic ketones.[2c,4] The high level of electron density on the aromatic ring and triple bond respectively engage in a constructive electrostatic interaction in the ATH transition state (Figure 2), and this determines the absolute configuration of the products.[7] There is also evidence to support the operation of an additional element of steric control in the reaction selectivity.[7f] Very recent studies have revealed that the hydrogen-transfer process is likely to be a stepwise process, and that the selectivity is further influenced through destabilization of the alternative transition state (TS) by an interaction with the sulfonamide group.[7h,i]

We wished to determine whether it might be possible to utilize more distant electronic and steric differences within substrates to control the asymmetric selectivity of ketone reduction by catalysts **1**−**3**. We focused our studies on 1,3-dialkoxy/aryloxy ketones, where there is very little difference between the groups flanking the ketone (Figure 3).

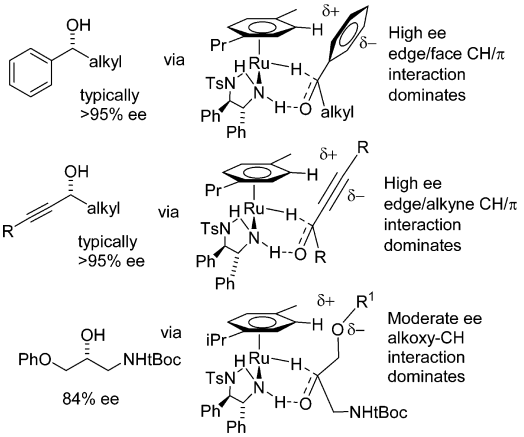


Figure 2. Classes of substrate and dominant directing effects in reductions by catalysts **1**−**3**.

A closely related precedent can be found in the catalyst-controlled diastereoselective reduction of complex ketones in

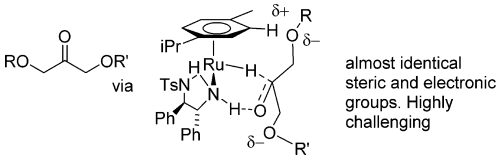


Figure 3. Class of substrate studied and speculated directing effect.

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which multiple interactions between the catalyst η^6-arene and multiple ethers in the substrate are important directing factors (Supporting Information, Figure S1).[8] The closely related asymmetric reductions of 1-alkoxy-3-amino-propanones with Ru(II)/TsDPEN complexes have previously been reported by ourselves, using nontethered catalysts (Figure 2), and these represent a relevant precedent, although on a distinct series of substrates.[9]

We prepared a series of ketone substrates (Scheme S1, Table S1) via the ring opening reactions of glycidyl ethers followed by oxidation.[10] The substrates were designed to contain contrasting substituents with respect to both electronic and steric properties in order to systematically examine the effect of each change.

In the first series of tests (Figure 4), the ATHs of alkoxy vs *para*-substituted aryloxy substrates were tested, to establish the

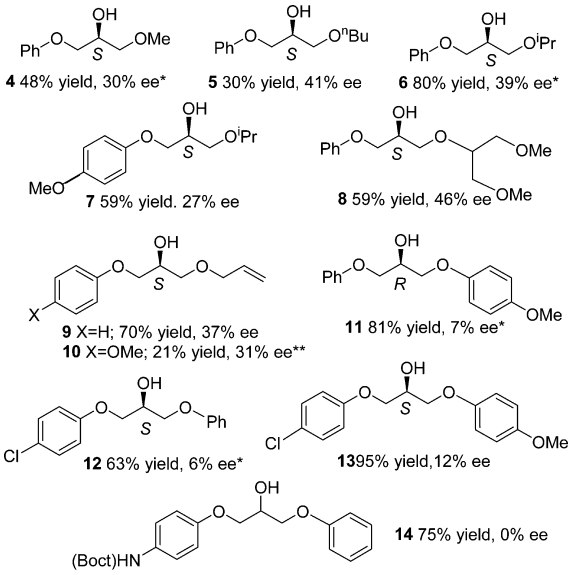
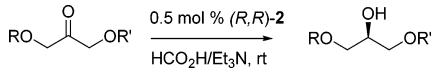


Figure 4. Reduction products of alkyoxy vs *para*-substituted aryloxy ketones by ATH using catalyst (*R,R*)-**2**. *A standard of known configuration was compared by chiral HPLC. **Comparison of the sign of optical rotation to a standard. Others assigned by analogy.

selectivity induced by purely electronic differences between substituents. Catalyst (*R,R*)-**2** was used throughout for consistency (Scheme 1). Configurations were assigned based either on a literature precedent (see below) or by analogy to a structurally related reduction product in the series.

Scheme 1. Asymmetric Transfer Hydrogenation of 1,3-Alkoxy/Aryloxy Ketones



The reduction of all the substrates containing a phenoxy vs any alkoxy group (OMe, O^{n}Bu, O^{i}Pr, Oallyl) flanking the ketone gave products with ee's fairly consistently in the 30−40% range. The absolute configurations of several products were determined by comparison with authentic samples prepared following a published synthetic method by Sharpless et al. (Scheme S2).[11] This served to confirm the nature of the transition state leading to the products; the slightly more electron-rich oxygen atom of the alkoxide occupies the position proximal to the η^6-arene group (Figure 5a). The lower ee for the slightly more electron-rich

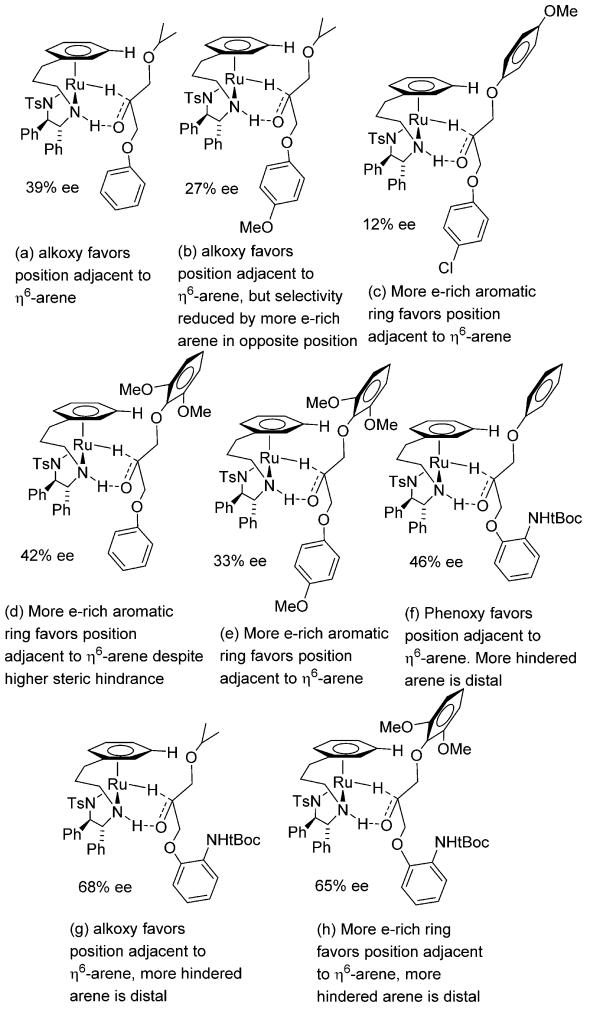


Figure 5. Modes of asymmetric reduction of ketones.

Op(MeO)C$_6$H$_4$/O^{i}Pr substrate indicates competition for the arene η^6 position by the more electron-rich (e-rich) aromatic ring (Figure 5b). On the other hand, the introduction of more methoxy groups (in the dimethoxy derivative) to the alkoxy side increased the selectivity of reduction, as would be expected by analogy with the result of Nugent et al.[8]

The 7% ee obtained for the OPh/p(MeO)C$_6$H$_4$O substrate suggests a very small electronic preference for reduction via a TS with the more electron-rich ring marginally favoring the position adjacent to the η^6-arene. The electron-poor OpCl C$_6$H$_4$/OPh gave a product of just 6% ee. It was gratifying to find that reduction of the OpClC$_6$H$_4$/p(MeO)C$_6$H$_4$O substrate gave a product of 12% ee which indicates a level of additivity in the directing effects, and reduction via the TS shown in Figure 5c. The selectivities are reflected by the Hammett[12] values for a *para*-OMe group of −0.27 (electron-donating) and for a *para*-Cl group of +0.23 (electron-withdrawing). A *para*-tBoc-amino group did not appear to influence the sense of reduction at all however.

In the next series of tests, we reduced substrates containing two aryloxy groups containing more hindered substituents (Figure 6). To our surprise, the 2,6-dimethoxyphenoxy group appeared to compete in the reduction TS with the O^{i}Pr group (the ee dropped from 39% for OPh/O^{i}Pr **6** to just 16% for **15**). To probe this further, the OPh/2,6-(MeO)$_2$C$_6$H$_3$O substrate was found to give product **16** with 42% ee while the p(MeO)Ph/2,6-(MeO)$_2$C$_6$H$_3$O ketone gave a lower ee of 33%. Since it has

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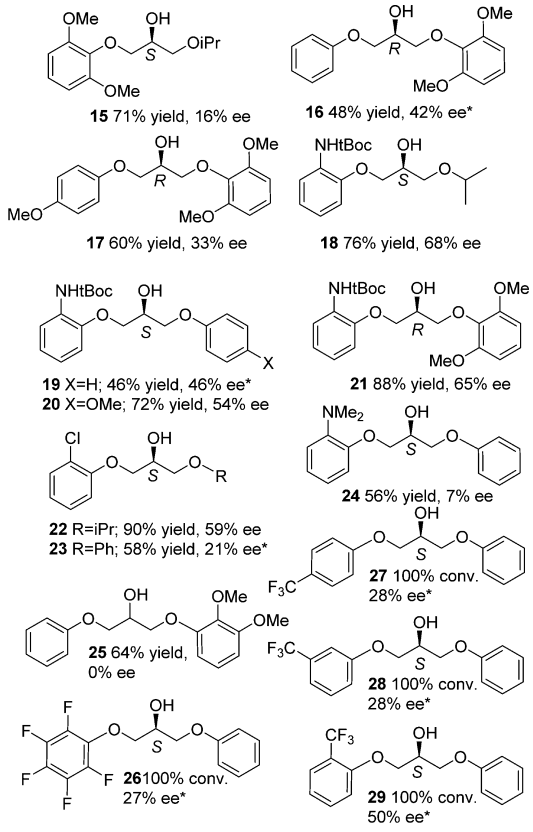

Figure 6. Reduction products of aryloxy vs aryloxy ketones by ATH using catalyst (*R*,*R*)-**2**. *A standard of known configuration was compared by chiral HPLC, others assigned by analogy.

already been shown that the more electron-rich p(MeO)C_6H_4 group favors the position adjacent to the η^6-arene, the conclusion must be that the reduction in ee results from the 2,6-dimethoxyphenoxy dominating this position over both PhO and p(MeO)C_6H_4O, but not over the ^{i}PrO. Taken together, these results suggested that, despite the steric hindrance, the 2,6-dimethoxyphenyoxy is competing for the position adjacent to the η^6-arene in the TS (Figure 5d and 5e). This may be the result of the inability of the C(alkyl)−O bond on this group to become coplanar with the aromatic ring due to steric clashes, thus reducing the ability of the lone pair to delocalize into the aromatic ring (Figure S2).

Improving the ee by purely electronic effects in such a challenging system is quite difficult, however we reasoned that a very sterically hindered group on the "electron-poor" side in the TS could increase the reduction selectivity further. In the event, using a ketone containing *ortho*-NtBocC_6H_4O vs OPh, O^{i}Pr or 2,6-$(MeO)_2C_6H_3O$ gave products of 46%, 68%, and 65% ee, respectively, in favor of the predicted enantiomers based on combined steric and electronic effects (Figures 5f−6h). These represent the highest recorded enantioselectivities for such a challenging system for ATH. The contrast with the *para*-tBocNH substrate, which gave essentially no enantioselectivity (Figure 4), underlines the feeble electronic directing effect contrasting with the strong steric effect of the NHtBoc group. The reductions of *ortho*-chloroaryloxy substrates also proceeded to give products of predictable configuration based on the combined directing effects. In the case of the o-ClC_6H_4)/O^{i}Pr combination. A good ee of 59% was generated in the product. PhO vs 2,3-dimethoxyphenoxy or 2-dimethylaminophenoxy substrates gave little or no enantioselectivity, possibly reflecting a balance of electronic and steric effects in the dimethoxy-substituted ring. In the final investigations in this study, a series of fluorine-containing ketones were reduced to alcohols **26**−**29** and in each case the absolute configurations matched those expected from the fluorine-containing ring being in the distal position from the η^6-arene in the reduction TS. In the best case, the 2-trifluoromethyl-phenyoxy substrate was reduced in 50% ee, reflecting the possible additional contribution of a steric effect.

We were interested in establishing whether a correlation existed between the difference in ^{1}H NMR chemical shift ($\delta\Delta$) between the OCH_2 groups adjacent to each ketone (other than fluorinated examples) and the enantioselectivities of their reductions (Table S1, Figure 7). Assuming that the groups on

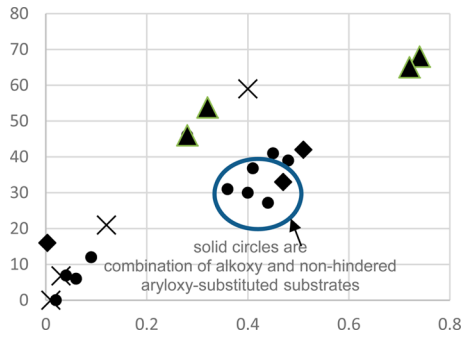

Figure 7. Enantiomeric excess of reductions vs chemical shift difference of methylene groups flanking the ketone in the substrates. Circles = combinations of alkoxy and nonhindered (unsubstituted or *p*-substituted) aryloxy. Diamonds = 2,6-dimethoxyphenoxy-containing substrates. Triangles = *o*-NHtBoc-phenoxy-containing substrates. Crosses = *o*-chloro, *o*-(dimethylamino) and 2,3-dimethoxyphenoxy-containing substrates. 65% ee point is combination of *o*-NHtBoc and 2,6-dimethoxyphenoxy dimethoxyphenyl.

the oxygen atoms can influence the electron-richness of the adjacent methylene group, its chemical shift should reflect this, and thus its ability to interact with the η^6-arene ring of the catalyst. In the event, the results appear to fall into a number of groups. First, a group at the center of Figure 7 (black circles, highlighted within an oval) are the alkoxy vs unhindered aryloxy substrates. Another group, black circles in the lower left segment (low ee), are the substrates containing unhindered aryloxy groups on either side of the ketone; the remote and weak electronic effects have only minor influence over the reduction enantioselectivity.

More interesting are the 2,6-dimethoxyphenoxy-containing substrates (diamonds) and *ortho*-NHtBocC_6H_4O- substrates (triangles; the 65% ee point is the substrate containing both these groups). Notably, the oNHtBoc-containing substrates generally give higher ee's than the chemical shift differences alone might suggest, which reflects the effect of the steric hindrance on the selectivity. In contrast, the 2,6-dimethoxyphenoxy- substrate results correlate fairly closely to the earlier set of results (circles), indicating the contribution of a primarily electronic directing effect. The final set of results, for the remaining substrates (crosses), again reflect the higher than average ee's for the more sterically congested *ortho*-chloroaryl-substrates. While not quantitative, there is broadly a relationship between the chemical shift difference of the methylene groups flanking the ketone and the induced ee's of the reductions. 2,6-Dimethoxyaryl groups also fit this trend, despite their extra steric hindrance effects.

In conclusion, we have prepared and examined in detail the ATH of a series of 1,3-dialkoxy/aryloxy propanones, which are

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regarded as highly challenging substrates for ATH using catalysts **1**−**3**. Purely electronic effects (e.g., two differently substituted aromatic rings) generally lead to product formation in low ee's, although gratifyingly the results reflect the Hammett values for the substituents. Steric factors, particularly of *ortho*-substituted aromatics, can be significant and additive to the enantioselectivity of the reductions in certain cases. Products of good ee (up to 68%) can be obtained in cases where electronic and steric effects are matched to the catalyst. To some extent, the ee's of the reductions relate to electronic differences between aromatic substituents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00756.

All experimental details, copies of NMR spectra, and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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