Letter

Chirality-Economy Catalysis: Asymmetric Transfer Hydrogenation of Ketones by Ru-Catalysts of Minimal Stereogenicity

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Chirality-Economy Catalysis: Asymmetric Transfer Hydrogenation of Ketones by Ru-Catalysts of Minimal Stereogenicity

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ABSTRACT: This manuscript describes the design and synthesis of Ru-catalysts that feature only single stereogenic element, yet this minimal chirality resource is demonstrated to be well competent for effecting high levels of stereoinduction in the asymmetric transfer hydrogenation over a broad range of ketone substrates, including those that are not accommodated by known catalyst systems. The single stereogenic center of the (1-pyridine-2-yl)methanamine) is the only point-chirality in the catalysts, which simplifies this catalyst system relative to existing literature protocols.

KEYWORDS: asymmetric transfer hydrogenation, minimal stereogenicity, ruthenium, asymmetric catalysis, diaryl ketones

The Noyori asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH) of carbonyl compounds into their optically enriched alcohol products serve as cornerstones of modern catalysis technologies, and have found widespread applications in both academic and industrial settings.[1] Catalyst systems with representative structures being (*S*)-Tol-BINAP/(*S*,*S*)-DPEN-Ru and its various structural analogs are effective in asymmetric hydrogenation of ketones, and the high level of enantioface differentiation is the synergistic effect of three stereogenic identities (all red stars denoted in Figure 1A).[2,3] Asymmetric transfer hydrogenation offers an attractive alternative to asymmetric hydrogenation, because it does not require hazardous hydrogen gas or a pressure vessel, and the hydrogen donors are environmentally friendly, inexpensive and easy to handle.[4] In Noyori's pioneering asymmetric transfer hydrogenation of aryl alkyl ketones by η^6-arene/chiral TsDPEN-Ru (Figure 1B), the remarkable enantiocontrol primarily originates from the CH/π interaction between η^6-arene and the aromatic substituent in ketone substrates.[5] A matched combination of the two stereogenic centers in the chiral diamine moiety (denoted in red stars in Figure 1B) is necessary to obtain high enantioselectivities; mismatching of the two point-chirality centers or only one stereogenic center results in a markedly decrease in the enantioselectivities.[6] Although there is a mechanistic network between asymmetric hydrogenation and asymmetric transfer hydrogenation,[7] only a few chiral (or achiral but *tropos*) diphosphine/chiral diamine (with two matching point-chirality centers) derived catalyst systems have been developed in asymmetric transfer hydrogenation of ketones in good enantioselectivities.[7a,8] Compared to simple aryl alkyl ketones that have been reduced successfully by asymmetric transfer hydrogenation, diaryl ketones especially aryl *N*-heteroaryl ketones that structurally confer significant pharmaceutical relevance have been a long-term challenge in this field, and only a few successful examples by either ATH or AH have been reported.[9a,10]

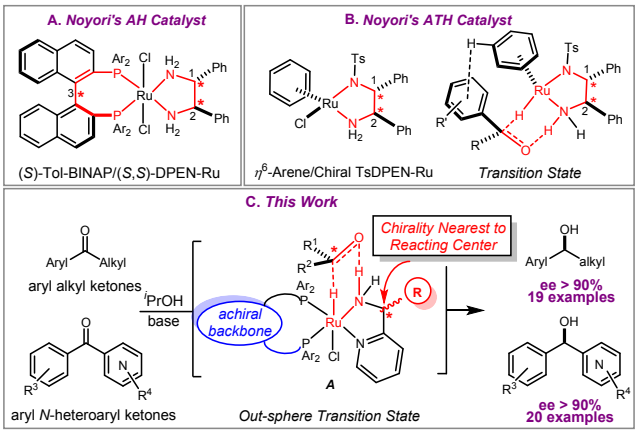
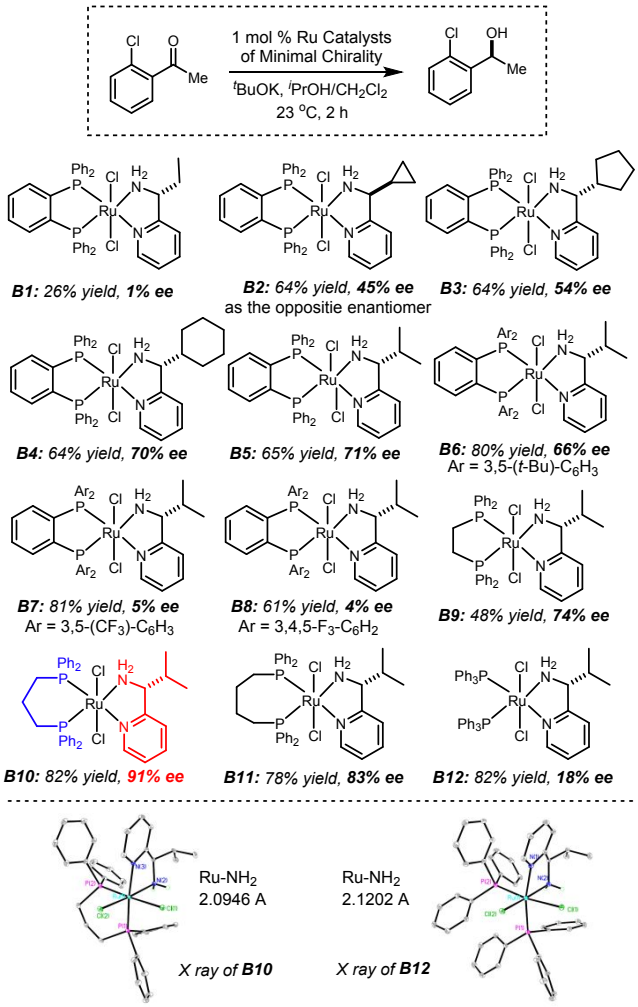


Figure 1. Ru-Catalysts of Minimal Stereogenicity and Simplified Structure in Asymmetric Transfer Hydrogenation.

A close inspection of the relevant asymmetric transfer hydrogenation transition state,[7c,e] as illustrated in Figure 1B, suggests that it is the C-2 chirality (stereogenic center bound to the active NH_2 function) of the TsDPEN diamine ligand that positions closest to reacting center as well as the corresponding pericyclic six-membered ring, and thus has the strongest influence on the chirality transfer. We therefore hypothesized that a simple amino-pyridine ligand bearing merely *a single chiral center* might be sufficient to induce desired high enantioselectivities. The design is summarized in catalyst structure ***A*** (Figure 1C), in which the combination of simple, readily available (1-(pyridine-2-yl)methanamines) with an achiral diphosphine is envisioned to replicate the stereoinduction of the canonical Noyori catalysts framework.

It was anticipated that this concept would considerably reduce the costs of the catalysts and enable modular tuning of the catalyst system through evaluation of different combination of achiral phosphine/amine ligands, leading to a practical asymmetric transfer hydrogenation of broad scope. Herein, we report the design and synthesis of Ru-catalysts with minimal stereogenicity and simplified structure that allow for practical asymmetric transfer hydrogenation of a wide range of ketones (including both aryl alkyl and aryl *N*-heteroaryl ketones) using ^{i}PrOH as the operationally convenient hydrogen source (Figure 1C).

Scheme 1. Identification of the Optimal Catalyst Structure

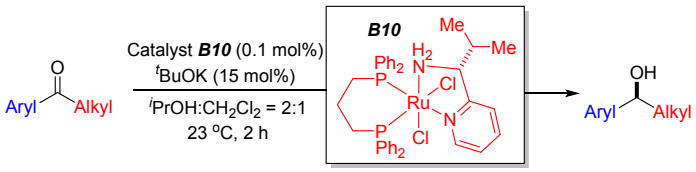


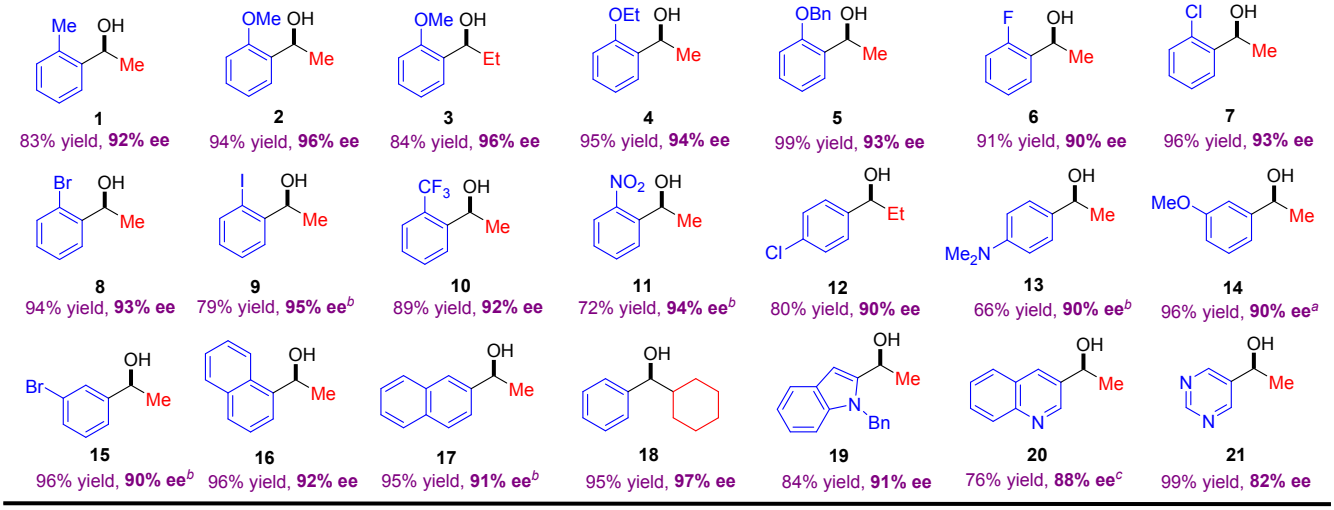
Since the two structurally simplest and readily available achiral diphosphines are 1,2-bis(diphenylphosphanyl)benzenes and bis(diphenylphosphino)alkanes, a brief catalyst screening was conducted with 1 mol % loading of Ru-complexes (***B1-B12***) formed by combining these diphosphines and (1-(pyridine-2-yl)methanmine derivatives,[10b,11] and with 2'-chloroacetophenone as the model substrate under very mild transfer hydrogenation conditions (Scheme 1). The performances of the catalysts ***B1-B5*** reveal that the enantioselectivity is improved when the branched alkyl substituents were incorporated into optically pure (1-(pyridine-2-yl)methanmines: ethyl (1% ee), cyclopropyl (45% ee), cyclopentyl (54% ee), cyclohexyl (70% ee) and isopropyl (71% ee). Use of a sterically bulkier aryl substituent in the 1,2-bis(diarylphosphanyl)benzene ligand in ***B6,*** failed to improve enantioselectivity as compared to that of ***B5***; however, tuning the electronic properties of the aryl group with electron-withdrawing CF_3 and F substituents markedly diminished the chiral induction ability of the resultant catalysts ***B7*** and ***B8*** (merely 5% and 4% ees, respectively). The linker length of bis(diphenylphosphino)alkanes in ***B9-B11*** exerted an influence on the product ees with the propane moiety of ***B10*** giving rise to the highest enantioselectivity (91% ee). Use of triphenylphosphine (2 equiv) gave an active catalyst (***B12***), but the product was formed in poor ee. Examination of the *X*-ray crystal structures of ***B10*** and ***B12*** revealed that the key Ru–NH_2 bond length was shortened from 2.1202 Å in acyclic ***B12*** to 2.0946 Å in cyclic ***B10***, hinting on more effective chirality transfer in the latter that results from closer proximity of the ligand chirality in the pericyclic transition state (Figure 1C). These results collectively established the catalyst ***B10*** to be optimal and its potential was therefore further thoroughly examined.

As compiled in Table 1, the catalyst ***B10***, even at 0.1 mol % catalyst loading, was shown to be capable of effecting asymmetric transfer hydrogenation of various aryl alkyl ketones with generally good isolated yields and enantiomeric excesses. *Ortho*-substitution on the aryl ring by electron donating substituents (Me, OMe, OEt, OBn) or electron-withdrawing substituents (F, Cl, Br, I, CF_3, NO_2) are all well tolerated leading to 90-96% ees in alcohol products **1-11**. Aryl ketones bearing *para*- or *meta*-substitution, including the strongly electron-donating dimethylamino (NMe_2) in **13**, were also reduced to their corresponding alcohols with 90% ees (**12-15**). Ketones with larger aromatic rings, such as 1- and 2-acetonaphthone, were both smoothly hydrogenated to give **16** and **17** in 92% ee and 91% ee, respectively. Phenyl cyclohexyl ketone produced **18** with an impressive 97% ee, which is remarkable as only very few known asymmetric transfer hydrogenation systems provided high enantioselectivity with this nearly iso-steric substrate.[12] Transfer hydrogenations of indole/quinolone/pyrimidine methyl ketones were also investigated, and good enantioselectivities were obtained in these cases (**19**, 91% ee; **20**, 88% ee; **21**, 82% ee).

Compared to simple aryl alkyl ketones, asymmetric transfer hydrogenations of aryl *N*-heteroaryl ketones have been rarely reported.[9a,10b] Particularly for non-*ortho*-substituted aryl *N*-heteroaryl ketones, introduction of the *N*-oxide was required to obtain high enantioselectivities.[9] A variety of this heteroaryl substrates were examined and excellent enantioselectivities were obtained (Table 2). The simplest phenyl pyridinyl ketone was reduced to alcohol **22** in 92% yield and 91% ee. These results represent a significant improvement relative to the 82% yield and merely 7% ee documented on the same substrate with the well-known η^6-arene/TsDPEN-Ir transfer hydrogenation catalyst system.[9b] Substrates bearing various pyridine ring substitution were well tolerated, with formation of alcohols **23-27** in good yields and enantioselectivities. Substrates bearing phenyl ring substitution, including at the *ortho* (**28-32**), *para* (**33-38**), and *meta* (**39-40**) positions, were all reduced in 90-97% ees. The structure of **31** was verified by *X*-ray crystallography, confirming unambiguously its absolute stereochemistry assignment. In the cases of **23**, **34**, **38**, **39**, dramatic improvements in enantioselections (90-94% ees) were once again accomplished as compared to literature results (4-15% ees).[9b] Finally, substrate with extended conjugation, i.e. naphthalene pyridinyl ketone was hydrogenation to the alcohol **41** in 91% ee.

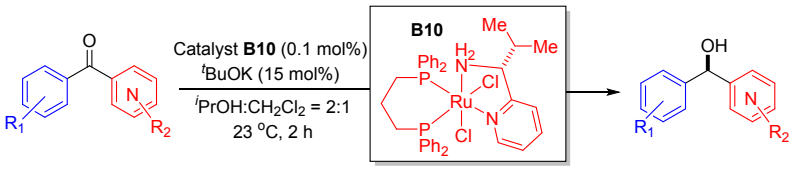
Table 1. Asymmetric Transfer Hydrogenation of Aryl Alkyl Ketones by Catalyst B10 [a]

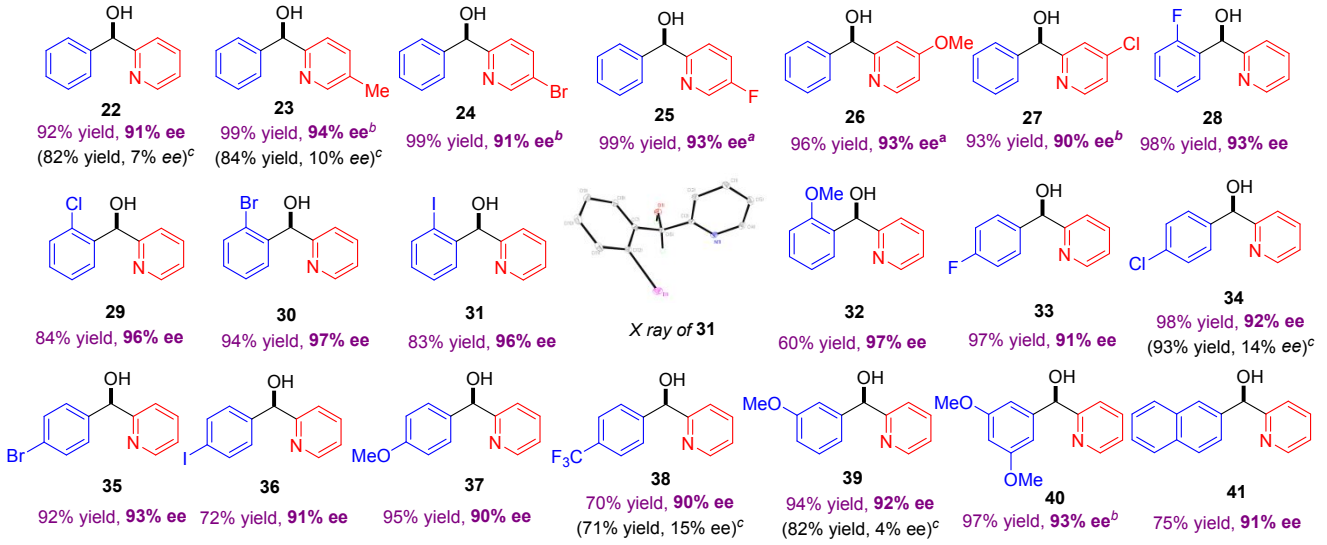




[a] General condition: ketone (0.2 mmol), catalyst ***B10*** (0.1 mol%), ^{t}BuOK (15 mol%), ^{i}PrOH/CH_2Cl_2 (2:1), 23 °C, 2 h. Yields of isolated products are given. [b] 1 mol% catalyst ***B10*** was used in order to get good conversion in 2 h. [c] 0.01 m% catalyst ***B10*** was used.

Table 2. Asymmetric Transfer Hydrogenation of Aryl *N*-heteroaryl Ketones by Catalyst B10 [a]

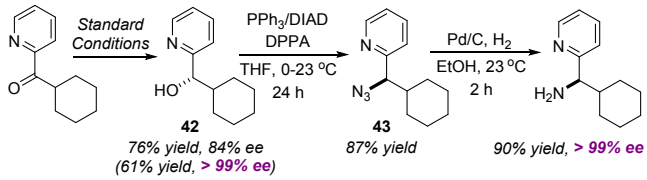




[a] General condition: ketone (0.2 mmol), catalyst ***B10*** (0.1 mol%), ^{t}BuOK (15 mol%), ^{i}PrOH/CH_2Cl_2 (2:1), 23 °C, 2 h. Yields of isolated products are given. [b] 1 mol% catalyst ***B10*** was used in order to get good conversion in 2 h. [c] Reported asymmetric transfer hydrogenation for the opposite enantiomers by η^6-arene/TsDPEN Ir catalysts.[9]

Thanks to the ligand/substrate structural similarity, the synthetic utility of this new catalysis protocol was further explored to establish a three-step preparation of a chiral (1-(pyridine-2-yl)methanmine ligand in its enantio-pure form (> 99% ee). As shown in Scheme 2, asymmetric transfer hydrogenation of cyclohexyl 2-pyridyl ketone under the above defined standard conditions provided (*S*)-configured alcohol **42** in 76% yield and 84% ee. A single recrystallization furnished this intermediate in enantiomerically pure form (> 99% ee). The subsequent stereochemical inversion was achieved under Mitsunobu conditions (PPh_3, DIAD, diphenylphosphoroazidate (DPPA), and DBU) leading to the azide **43** in 87% yield.[13] Catalytic reduction of **43** produced the desired cyclohexyl (1-(pyridine-2-yl)methanmine in 90% yield and > 99% ee. The method is more efficient and economic than the conventional chiral auxiliary-based strategy.[14]

Scheme 2. A Concise Synthesis of Chiral Amine Ligand



In summary, we have described the design and discovery of new Ru-catalysts in which a single element of chirality induces high enantioselectivity in the asymmetric transfer hydrogenation for a broad range of carbonyl substrates (39 examples, > 90% ee), including substrates that are not possible with literature-known protocols. This work would suggest a strategy for catalyst design and help stimulate structural tailoring of some catalysts towards high levels of simplicity, efficiency and practicality. Ongoing research that includes modification of the catalysts and exploration of their extended application in asymmetric catalysis is in progress.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and characterization data (^1H and ^{13}C NMR, HRMS) for all new compounds (PDF)
Crystallographic information for **B10** (CIF)
Crystallographic information for **B12** (CIF)
Crystallographic information for **31** (CIF)

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