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Asymmetric Transfer Hydrogenation of Densely Functionalized Diheteroaryl and Diaryl Ketones by a Ru-Catalyst of Minimal Stereogenicity

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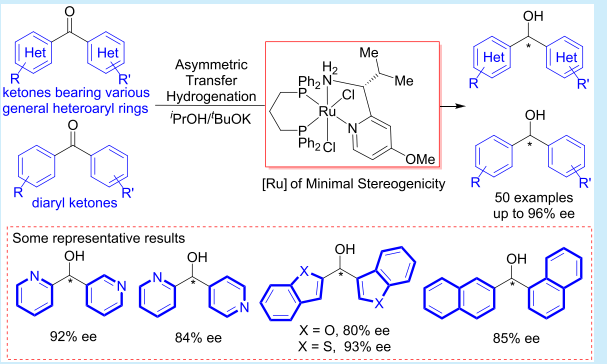
ABSTRACT: A highly enantioselective asymmetric transfer hydrogenation (ATH) of densely functionalized diheteroaryl and diaryl ketones was developed using Ru-catalysts of minimal stereogenicity. Various ketone substrates with structurally and electronically similar groups attached to the prochiral centers were reduced successfully in good to excellent enantioselectivities and yields. This protocol provides practical and efficient access to chiral diheteroarylmethanols and benzhydrols, which are key intermediates in pharmaceuticals and biologically active compounds.



Enantiopure diheteroarylmethanols are ubiquitous and valuable intermediates and structural motifs in numerous medicines, agrochemicals, and biologically active compounds (Figure 1).[1−3] It is thus of substantial importance to develop

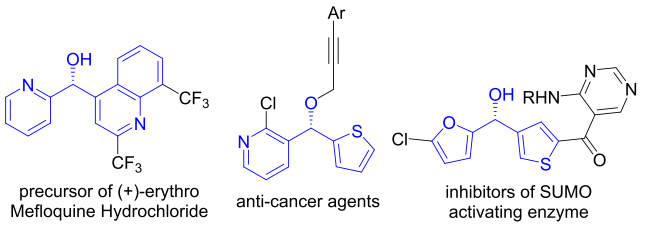


Figure 1. Substances containing chiral diheteroarylmethanols.

efficient protocols for enantioselective synthesis of these structures.[4] Among the developed synthetic strategies, the catalytic asymmetric reduction of ketones represents the most potential approach from the practical and atom-economic points of view. However, despite the great progress that has been achieved for asymmetric reduction of a wide range of ketones in the past several decades,[5,6] the enantioselective reduction of diheteroaryl ketones remains a challenging task.

In fact, due to the difficulty for chiral catalysts to differentiate two structurally and electronically similar groups in the ketones and the capability of the diheteroaryl ketones as well as the alcohol products to inhibit the catalytic activity by coordination of the heteroatoms to metal complexes,[7,8] few reports for asymmetric reduction of diheteroaryl ketones have emerged.[2a,9,10] In 2003, Chen[9a] reported asymmetric hydrogenation of aryl-heteroaryl ketones using *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen] as the catalyst, and only two diheteroaryl ketones were disclosed, both of which have bulky substituents on heteroaromatic rings (Scheme 1a). Recently, Rueping and co-workers[10] reported asymmetric hydroboration of heteroaryl ketones, and three diheteroaryl ketones without bulky substituents were found to lead to excellent yields and ee's. However, mechanistic studies in this work showed that a 2-pyridyl group was required for coordinating to the aluminum center to control the enantioselectivity (Scheme 1a).[10] It is transparent that a generally viable catalytic enantioselective protocol to deliver such diheteroarylmethanols remains elusive.

Very recently, we[11] developed a class of chiral Ru-catalysts with minimal stereogenicity (i.e., merely a single chirality element) and fairly simplified structure that has been shown to be highly versatile in the asymmetric transfer hydrogenation of aryl alkyl and aryl *N*-heteroaryl ketones. This finding encouraged us to explore the asymmetric transfer hydrogenation of the more challenging diheteroaryl ketones that bear two structurally and/or electronically similar groups attached to prochiral centers by such Ru-catalyst system. Herein, we reported an efficient asymmetric transfer hydro-

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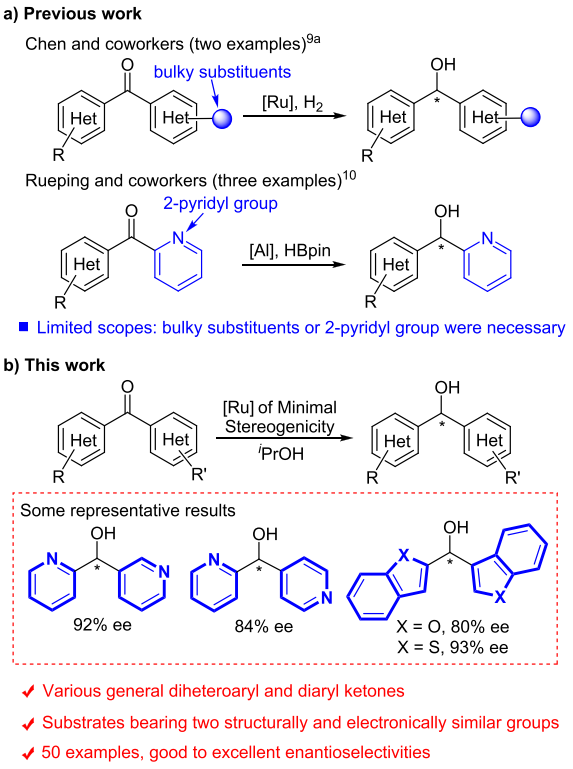
Scheme 1. Catalytic Asymmetric Reduction of Diheteroaryl Ketones



genation of a series of general diheteroaryl ketones as well as diaryl ketones, producing the corresponding chiral diheteroarylmethanols and benzhydrols in good to excellent ee's (Scheme 1b). It is worth noting that substrates bearing two groups with exactly same structures but different substitution positions, thus leading to subtle difference in both sterics and electronics, were successfully reduced in high levels of enantioselectivities (Scheme 1b). To the best of our knowledge, it is the first time that these kinds of ketones could be enantioselectively reduced.

We initially selected pyridin-2-yl(pyridin-3-yl)methanone as a model substrate, which contains two potentially coordinative pyridyl groups (Figure 2). Moreover, the substituents attached to the prochiral center, 2-pyridyl group and 3-pyridyl group, are of virtually the same size. As such, considerable difficulty may be readily anticipated for chiral transition-metal catalysts to differentiate their corresponding *Si*- and *Re*- faces of the substrate. When using our previously reported Ru-(*S*)-^{i}PrPyme-catalyst **A1**, we were delighted to find that the alcohol product **1** was obtained in 89% ee and 94% yield. The absolute configuration of (*R*)-**1** was determined via X-ray diffraction analysis. Encouraged by this preliminary result, we further attempted to modify catalyst **A1** by tuning the electronic nature of the pyridyl group in the diamine ligand. Pleasingly, an electron-donating methoxy substituent at the *para* position of the pyridyl group in catalyst **A2** helps to improve the enantioselectivity of alcohol product **1** to 92%. In contrast, catalyst **A3** with an electron-withdrawing chloro-substituent at the *para* position of the pyridyl group resulted in poor yield and moderate ee. Other catalysts, such as **A4** and **A5** with electron-rich, larger conjugated system in the diamine ligand, provided similar results with catalyst **A1**. As a result, **A2** was chosen as the optimal catalyst for the following screening

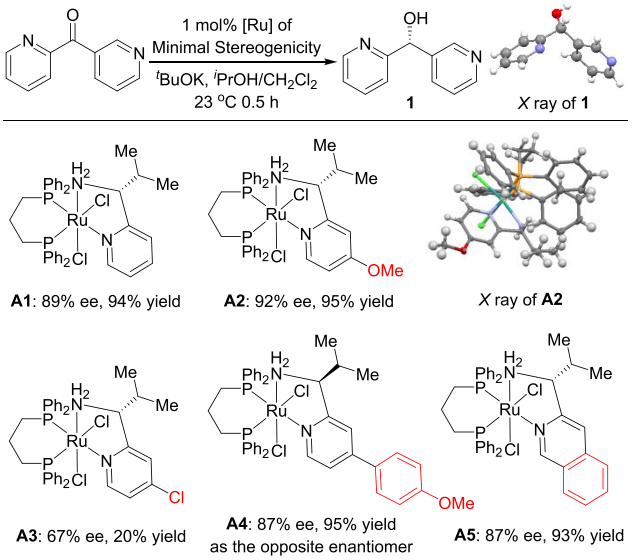


Figure 2. Catalyst screening.

of substrate scope. The structure of **A2** was also unambiguously determined by X-ray diffraction analysis.

As shown in Table 1, we initially evaluated a number of bispyridyl ketones, and good to excellent ee's and yields were obtained (**1**−**15**, 80−96% ee's and 73−98% yields). Ketone substrates with both electron-donating and electron-withdrawing groups at 2- and 5-positions of the 3-pyridyl group can be reduced to the desired alcohols **2**−**6** in excellent ee's and yields (92−96% ee's, 82−98% yields). Halogen groups on the 4-position of the 2-pyridyl group can be tolerated, furnishing reduced products (**7**−**8**) in good ee's (84−86%) and excellent yields (90−97%). Notably, the disubstituted substrates can also be smoothly reduced to corresponding products **9**−**12** in good to excellent ee's (81−94%). Besides pyridin-2-yl(pyridin-3-yl)methanones, substrates with pyridin-2-yl(pyridin-4-yl)methanone as skeleton could be transformed into chiral alcohols **13**−**15** successfully (80−93% ee's, 91−95% yields). It merits a note that pyridin-2-yl(pyridin-4-yl)-methanone, which also bears two exactly the same structures but with different substitution positions, was reduced in good enantioselectivity (**13**, 84% ee). We had unambiguously determined the absolute stereochemistry of products **9** and **15** by X-ray diffraction analysis.

Next, the diheteroaryl ketones with different heteroaryl groups were examined. Pleasingly, we found that substrates bearing varieties of heteroaryl rings could be asymmetrically reduced in good to excellent ee's and yields (**16**−**30**). Diheteroaryl ketones bearing pyridyl groups and quinolinyl or isoquinolinyl groups were demonstrated to be suitable substrates, delivering corresponding chiral diheteroarylmethanols in good results (**16**−**20**, 83−93% ee's and 85−95% yields). Transfer hydrogenations of furan/thiophene/thiazole pyridyl ketones were also investigated and good to excellent enantioselectivities and yields were obtained (**21**−**25**, 85−95% ee's and 77−99% yields). It was noteworthy that diheteroaryl ketones without 2-pyridyl groups and bulky substituents, which have not been asymmetrically reduced by those reported strategies, were smoothly reduced in our reaction systems (**22**−**25**). Encouraged by the above results, we further explored more challenging diheteroaryl ketone bearing two heteroaryl groups with very similar structural and electronic

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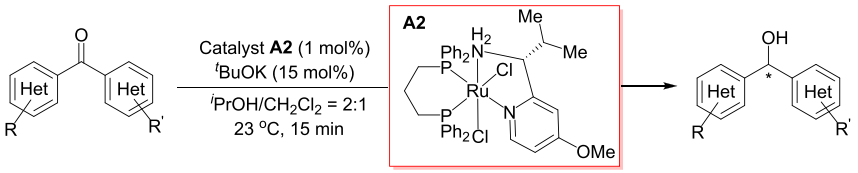
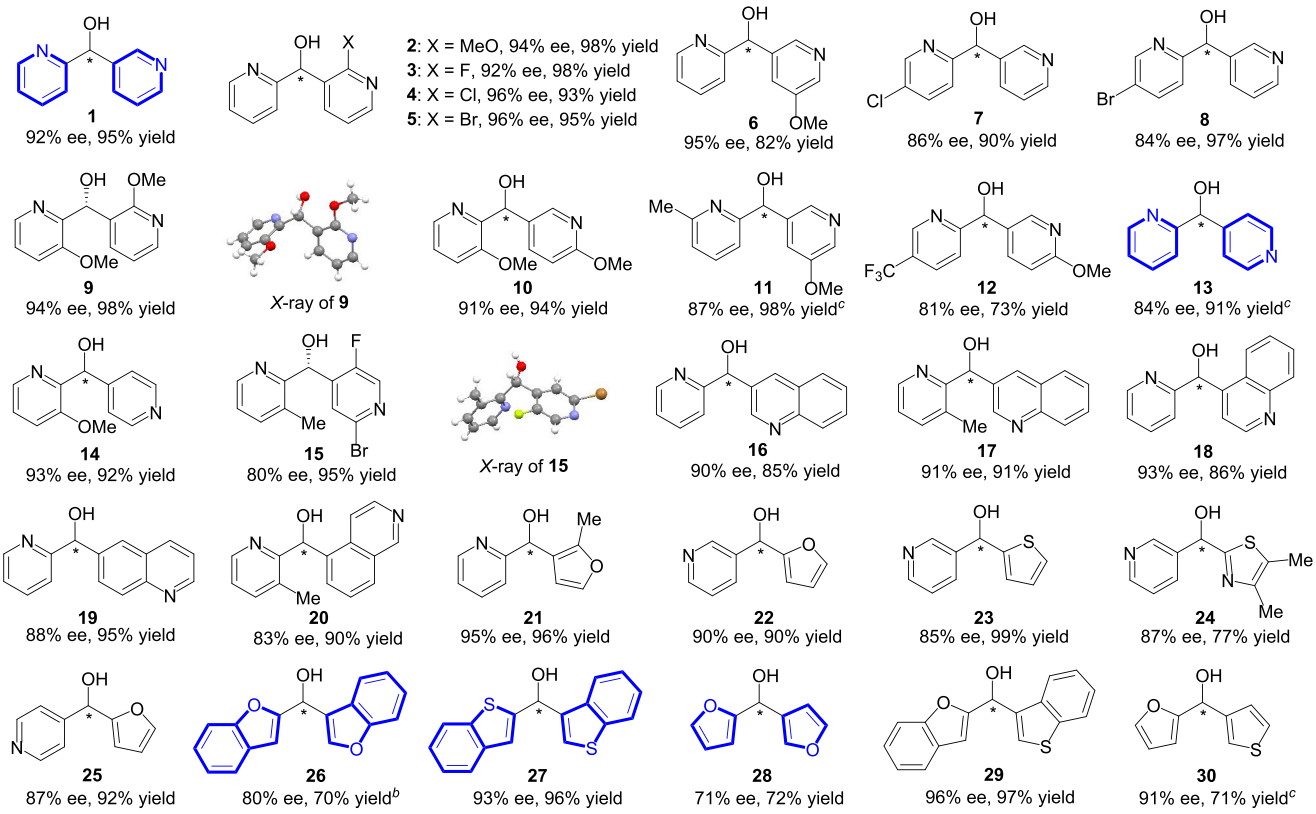
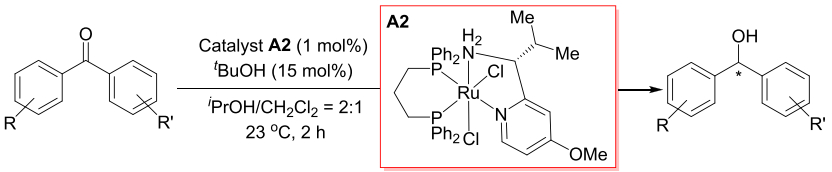
Table 1. Substrate Scope for Diheteroaryl Ketones[a]

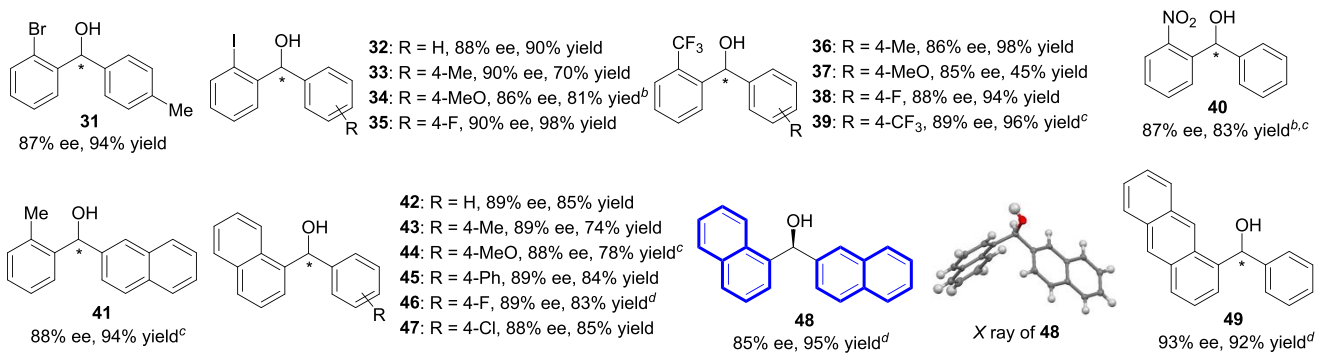




[a]General conditions: ketone (0.1 mmol), catalyst **A2** (1 mol %), ^{t}BuOK (15 mol %), ^{i}PrOH/CH_2Cl_2 (2:1), room temperature, 15 min. Yields of isolated products are given. [b]Reaction was conducted at 0 °C. [c]Reaction was conducted in 5 min.

Table 2. Substrate Scope for Diaryl Ketones[a]





[a]General conditions: ketone (0.1 mmol), catalyst **A2** (1 mol %), ^{t}BuOK (15 mol %), ^{i}PrOH/CH_2Cl_2 (2:1), 23 °C, 2 h. Yields of isolated products are given. [b]Reaction was conducted in 1 h. [c]1 mol % catalyst **A4** was used. [d]1 mol % catalyst **A5** was used.

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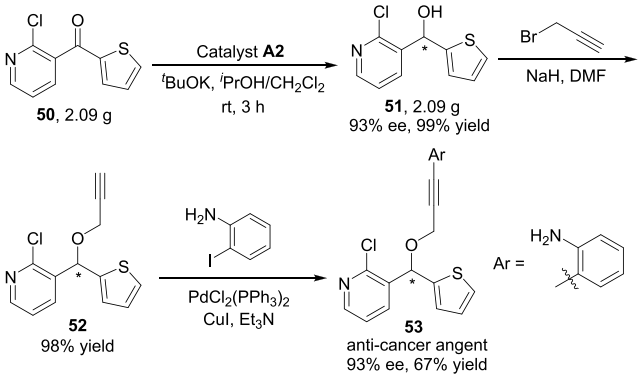
properties (**26**−**30**). Ketone substrates bearing bis-benzofuran, bis-benzo[*b*]thiophene, and bis-furan rings were efficiently transformed to chiral alcohols **26** (80% ee, 70% yield), **27** (93% ee, 96% yield) and **28** (71% ee, 72% yield) respectively. When benzo[*b*]thiophen-3-yl(benzofuran-2-yl)methanone and furan-2-yl(thiophen-3-yl)methanone were used as substrates in this developed catalytic system, excellent enantiomeric excesses (**29**, 96% ee; **30**, 91% ee) were obtained. These results again proved the powerful ability of the catalyst to differentiate similar enantiotopic faces of the substrates.

Diaryl ketones also represent a large class of challenging substrates for catalytic asymmetric reduction due to the difficulty for catalysts to discern the two structurally and electronically similar substituents.[12−15] Thus, to further exemplify the utilities of this Ru-catalyst system, we additionally surveyed asymmetric transfer hydrogenation of diaryl ketones, and the results were summarized in Table 2. Initially, various *ortho*-substituted diaryl ketones were investigated (**31**−**41**). The *ortho*-substitutents could range from electron-withdrawing groups (Br, I, CF_3, and NO_2) to electron-donating group (Me), and good enantioselectivities (84−90% ee's) were consistently obtained. Diaryl ketones bearing 1-naphthyl group could also be transfer hydrogenated to corresponding alcohol product (**42**−**48**) in good enantioselectivities (85−89% ee's). Interestingly, the ketone substrate bearing two exactly the same naphthyl groups but with different substitution positions (1-naphthyl and 2-naphthyl groups) could be reduced to **48** in 85% ee and 95% yield. The absolute configuration of **48** was verified by X-ray diffraction. Finally, a ketone substrate bearing larger aromatic ring, such as 1-anthracenyl group, was transfer hydrogenated to **49** in 93% ee and 92% yield.

To further demonstrate the synthetic utility of the present catalyst system, a potential anticancer agent **53** with IC_{50} value less than 1.0 μM (against MDA-MB 231)[2b] was prepared (Scheme 2). To our delight, diheteroaryl ketone **50** could be

Scheme 2. Synthetic Application



asymmetrically transfer hydrogenated to **51** in gram scale with excellent enantioselectivity and yield (93% ee, 99% yield). After two steps according to ref 16 chiral compound **53** was obtained successfully without loss of optical purity.

In summary, we have described a highly robust asymmetric transfer hydrogenation protocol of densely functionalized diheteroaryl ketones and diaryl ketones using Ru-catalysts of minimal stereogenicity, leading to a wide range of chiral diheteroarylmethanols and benzhydrols in good to excellent ee's and yields. The catalyst demonstrates unusual capability in differentiating structurally and electronically similar heteroaryl groups, which have long proved to be difficult by many other literature-known chiral catalysts. No currently available steric or stereoelectronic theories seem to be capable of providing a self-consistent as well as predictive rationale that could comfortably account for the observed high levels of ee's and origin of asymmetric inductions, and a detailed investigation on the topic is forthcoming.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03064.

Experimental procedures and characterization data (^{1}H and ^{13}C NMR, HRMS) for all new compounds (PDF)

Accession Codes

CCDC 2017188, 2017293, 2017295, 2017297, and 2019561 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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