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Enantioselective Hydrogenation of Racemic α-Arylamino Lactones to Chiral Amino Diols with Site-Specifically Modified Chiral Spiro Iridium Catalysts

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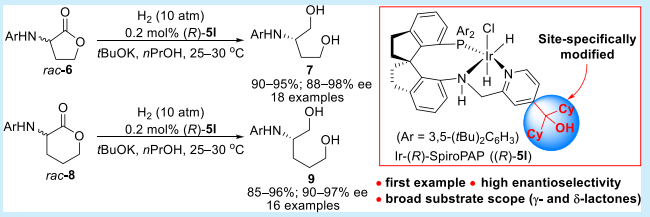
Supporting Information

ABSTRACT: A protocol for highly enantioselective hydrogenation of racemic α-arylamino lactones with catalysis by site-specifically modified chiral spiro iridium complexes has been developed. With the optimized catalyst, racemic α-arylamino-γ-lactones and α-arylamino-δ-lactones could be hydrogenated to the corresponding chiral 2-amino diols with good to excellent enantioselectivities.



Catalytic asymmetric hydrogenation of racemic carbonyl compounds via dynamic kinetic resolution (DKR) is an efficient, atom-economical way to access optically active chiral alcohols,[1] which are important building blocks in fine chemical synthesis. For example, asymmetric hydrogenation reactions of racemic α-substituted ketones and β-ketoesters afford chiral secondary alcohols with two or more stereogenic centers with high enantio- and diastereoselectivities and have been successfully used for the synthesis of chiral drugs.[1a] In addition, significant progress has recently been made in the asymmetric hydrogenation of racemic α-substituted lactones via DKR to afford chiral primary alcohols, although considerable challenges remain. In 2011, Ikariya et al.[2] reported the use of a ruthenium complex bearing a chiral 1,2-diamine ligand to catalyze the hydrogenation of a racemic α-phenyl γ-lactone, albeit with low enantioselectivity (up to 32% ee). Later, we found that chiral spiro iridium complexes (Ir-SpiroPAP) efficiently catalyze asymmetric hydrogenation of racemic α-aryl- and alkyl-substituted δ-lactones to afford chiral diols with up to 95% ee.[3] Very recently, Zhang et al. reported that the *O*-SPINOL-derived chiral spiro iridium complex Ir-*O*-SpiroPAP is a highly efficient catalyst for the asymmetric hydrogenation of racemic bridged-biaryl lactones to afford primary alcohols with biaryl-axial chirality with excellent enantioselectivities (up to >99% ee).[4] However, all the successful examples of asymmetric hydrogenation of racemic α-substituted lactones via DKR reported to date have involved δ-lactones with α-aryl or α-alkyl substituents.[5]

Like chiral alcohols, chiral amino alcohols are of great importance in organic synthesis and medicinal chemistry,[6] and chiral 2-aminobutane-1,4-diols, particularly those with *N*-aryl groups, are potentially useful synthons for chiral pharmaceuticals. A number of pharmaceuticals containing *N*-aryl-2-aminobutane-1,4-diol moieties are shown in Figure 1. For example, ABT-263 (navitoclax, **1**), an orally bioavailable inhibitor of Bcl-2 family of proteins, is currently in clinical trials for treatment of small-cell lung cancer and hematological

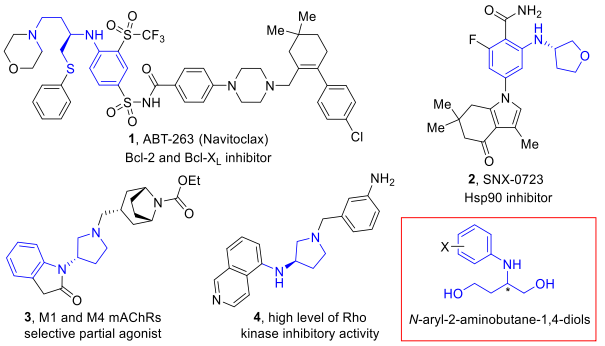


Figure 1. Typical chiral pharmaceuticals containing *N*-aryl-2-amino-1,4-butyl units.

malignancies.[7] SNX-0723 (**2**) is a brain-permeable, orally active selective inhibitor of Hsp 90 that prevents α-synuclein oligomerization (EC50 = 48 nM).[8] Molecule **3**[9] is a structurally novel selective partial agonist of both the M1 and the M4 subtypes of the muscarinic acetylcholine receptor, and molecule **4**[10] is a potent Rho kinase inhibitor. Because of the significance of chiral *N*-aryl-2-aminobutane-1,4-diols, the development of new, efficient, reliable methods for their stereoselective synthesis has attracted considerable research attention.[11] In this paper, we report the first example of highly enantioselective hydrogenation of racemic α-arylamino lactones via DKR, providing a novel approach to chiral *N*-aryl-2-aminobutane-1,4-diols and *N*-aryl-2-aminopentane-1,5-diols. We found that site-specifically modified chiral spiro iridium complexes (Ir-SpiroPAPs) efficiently catalyze asymmetric hydrogenation of both α-arylamino γ-lactones and α-arylamino δ-lactones (Scheme 1).

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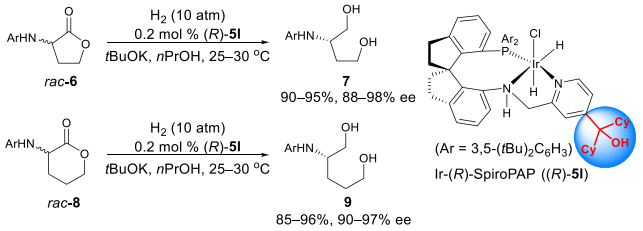
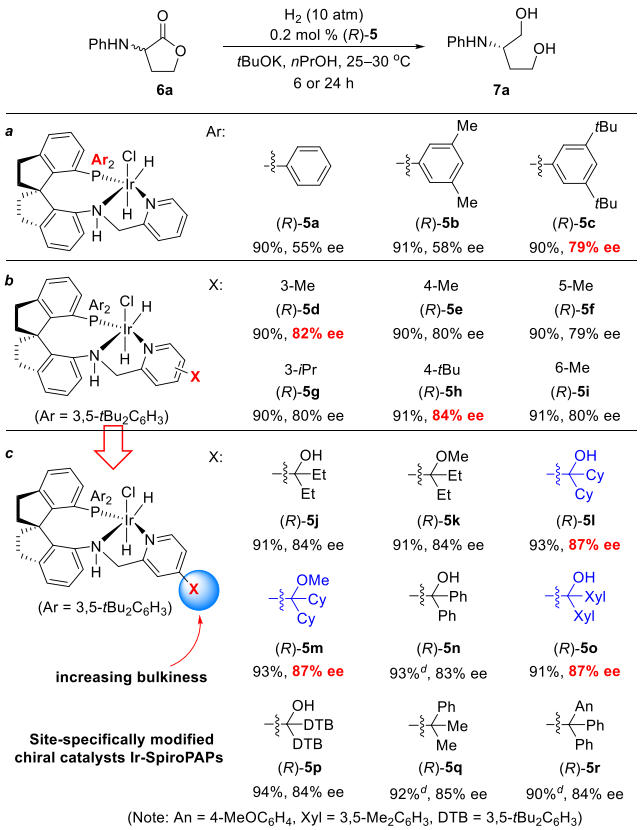
Scheme 1. Asymmetric Hydrogenation of Racemic α-Arylamino Lactones to Chiral Arylamino Diols



To evaluate various chiral catalysts, we chose racemic α-phenylamino γ-butyrolactone (**6a**) as a model substrate. Ir-SpiroPAP catalysts **5**,[12] which were developed by our group, were found to efficiently catalyze the desired hydrogenation reaction to afford chiral *N*-phenyl-2-aminobutane-1,4-diol (**7a**, Scheme 2). Catalyst (*R*)-**5c** (79% ee), which has a 3,5-di-*tert*-butylphenyl moiety on the P atom, gave higher enantioselectivity than analogues (*R*)-**5a** (55% ee) and (*R*)-**5b** (58% ee), which have a phenyl group and a 3,5-dimethylphenyl group, respectively (Scheme 2, a). That is, a bulky aryl group on the P atom enhanced the enantioselectivity of the reaction. Experiments with catalysts bearing an alkyl group at various positions on the pyridine ring revealed that a bulky *tert*-butyl group at the 4-position (**5h**) increased the enantioselectivity to 84% ee (Scheme 2, b). Therefore, we conducted additional experiments using catalysts that were site-specifically modified at the 4-position of the pyridine ring with the hope of improving the enantioselectivity even further.

Scheme 2. Evaluation of Spiro Iridium Catalysts (*R*)-5 for Asymmetric Hydrogenation of 6a[a,b,c]



[a]Reaction conditions: 1.0 mmol scale, (*R*)-**5**/*t*BuOK/**6a** = 1:500:500, *n*PrOH (4.0 mL), room temperature (25−30 °C), 10 atm H_2, 6 h, 100% conversion. [b]Isolated yield. [c]Determined by HPLC using chiral column. [d]24 h.

For this purpose, we prepared a series of Ir-SpiroPAP catalysts, (*R*)-**5j−r**, bearing a dialkyl(hydroxy)methyl, diaryl(hydroxy)methyl, dialkylarylmethyl, or triarylmethyl group at the pyridine 4-position. All the tested catalysts showed high yields and good enantioselectivities in the hydrogenation of **6a** (Scheme 2, c), with (*R*)-**5l**, (*R*)-**5m**, and (*R*)-**5o** giving the highest enantioselectivity (87% ee). These results demonstrate that site-specific modification is a useful strategy for generating efficient catalysts. In view of the ready availability of (*R*)-**5l**, we used it for further optimization of the reaction conditions.

Using substrate **6a** and catalyst (*R*)-**5l**, we varied the reaction parameters (base, solvent, hydrogen pressure, and reaction time) and evaluated their effects on the reaction outcome (Table 1). The bases *t*BuOK, *t*BuONa, and K_2CO_3 gave comparable enantioselectivities, although K_2CO_3 required a longer reaction time and gave a slightly lower yield (entries 1−3). In contrast, no reaction occurred when KOH was the base (entry 4). We attributed this to the fact that KOH could readily convert the lactone substrate into the corresponding carboxylate, which is difficult to hydrogenate with most catalysts. The solvent that gave the best enantioselectivity was *n*PrOH (compare entries 1 and 5−7). Reducing the amount of *t*BuOK from 1 equiv to 5 mol % (**6a**/*t*BuOK [S/B] = 20) resulted in a slight increase in enantioselectivity (from 87% ee to 90% ee) without any obvious effect on the reaction rate (compare entries 1 and 8−10). Increasing the H_2 pressure to 50 atm shortened the reaction time to 2 h (entries 11 and 12). Changing the reaction temperature from room temperature to 0 or 50 °C had a negligible effect on the enantioselectivity, although the reaction at 0 °C took longer and showed a lower yield (entries 13 and 14). Comparable

Table 1. Asymmetric Hydrogenation of 6a Catalyzed by (*R*)-5l[a,b]

entry	base	S/B	solvent	PH_2 (atm)	time (h)	yield (%)[c]	ee (%)[d]
1	*t*BuOK	1	*n*PrOH	10	6	92	87
2	*t*BuONa	1	*n*PrOH	10	6	90	86
3	K_2CO_3	1	*n*PrOH	10	24	83	88
4	KOH	1	*n*PrOH	10	24	NR	–
5	*t*BuOK	1	MeOH	10	6	87	85
6	*t*BuOK	1	EtOH	10	6	91	86
7	*t*BuOK	1	*n*BuOH	10	6	90	83
8	*t*BuOK	5	*n*PrOH	10	6	92	89
9	*t*BuOK	10	*n*PrOH	10	6	92	90
10	*t*BuOK	20	*n*PrOH	10	6	92	90
11	*t*BuOK	10	*n*PrOH	30	2	92	89
12	*t*BuOK	10	*n*PrOH	50	2	93	89
13[e]	*t*BuOK	10	*n*PrOH	10	24	57	90
14[f]	*t*BuOK	10	*n*PrOH	10	4	93	87
15[g]	*t*BuOK	10	*n*PrOH	10	6	93	89

[a]Optimizing the reaction conditions. [b]Reaction conditions: 1.0 mmol scale, (*R*)-**5l**/*t*BuOK/**6a** = 1:500:500, *n*PrOH (5.0 mL), 10 atm H_2, room temperature (25−30 °C). [c]Isolated yield. [d]Determined by HPLC using a chiral column. The configuration of product **7a** is *S* determined by single-crystal X-ray diffraction analysis (see SI). [e]At 0 °C. [f]At 50 °C. [g]0.1 mol % catalyst.

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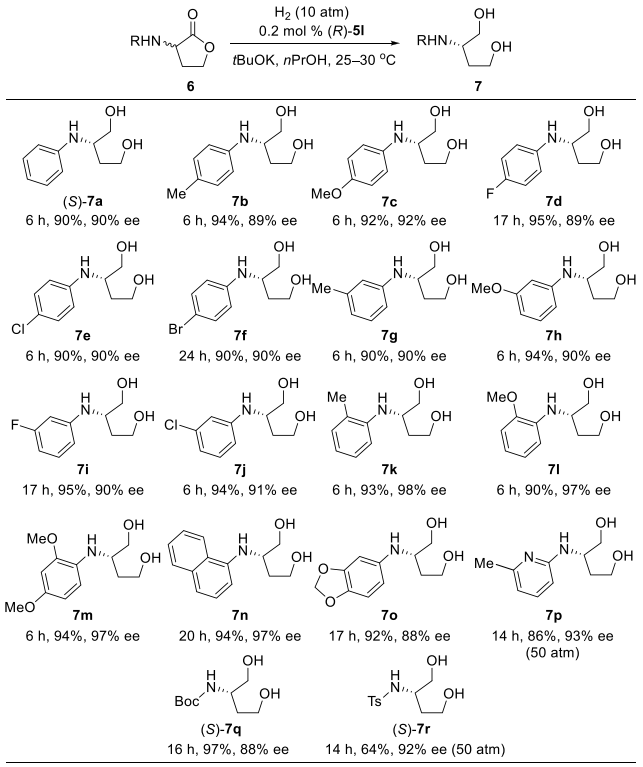
results were obtained even when the catalyst loading was lowered to 0.1 mol % (entry 15).

Under the optimized conditions (Table 1, entry 9), we hydrogenated a variety of racemic α-arylamino γ-butyrolactones **6** to obtain corresponding 2-*N*-arylaminobutane-1,4-diols **7** (Scheme 3). The electronic properties of the

Scheme 3. Asymmetric Hydrogenation of Racemic α-Arylamino γ-Butyrolactones 6[a,b,c]

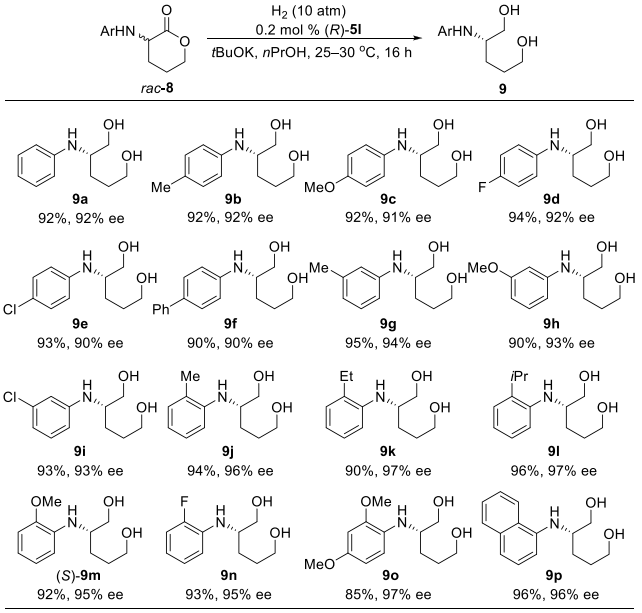


[a]Reaction conditions: The same as those listed in Table 1, entry 9. [b]Isolated yield. [c]Determined by HPLC using chiral column. Boc = *tert*-butoxycarbonyl; TS = *p*-toluenesulfonyl.

substituent on the aryl group of the substrate had no obvious effect on the enantioselectivity, but substrates with a fluoro- or bromo-substituted aryl group had lower reaction rates (**6d**, **6f**, and **6i**). Substrates with an *ortho*-substituted aryl group (**6k**, **6l**, **6m**, and **6n**) showed the highest enantioselectivity (97−98% ee). The substrate **6p** with a (6-methylpyridin-2-yl)amino group provided the product **7p** in 86% yield and 93% ee, but a relatively higher pressure was required. When the aryl amino group was changed to the Boc (**6q**) or Ts group (**6r**), the hydrogenations performed well and provided the corresponding products (*S*)-**7q** and (*S*)-**7r** in moderate to high yields with comparable enantioselectivities.

Chiral *N*-aryl-2-aminopentane-1,5-diols are important building blocks for the synthesis of chiral 3-amino piperidines and tetrahydropyrans,[11d,e] which are common structural units in pharmaceuticals (e.g., linagliptin[13] and ibrutinib[14]). Therefore, we also investigated the asymmetric hydrogenation of racemic α-arylamino δ-valerolactones **8** with catalyst (*R*)-**5l** under the standard conditions, and the results are summarized in Scheme 4. Generally, α-arylamino δ-valerolactones showed slightly lower reaction rates than the α-arylamino γ-butyrolactones, but all the reactions were complete within 16 h. The electronic properties of the substituent on the aryl group had no influence

Scheme 4. Asymmetric Hydrogenation of Racemic α-Arylamino δ-Valerolactones 8[a,b,c]

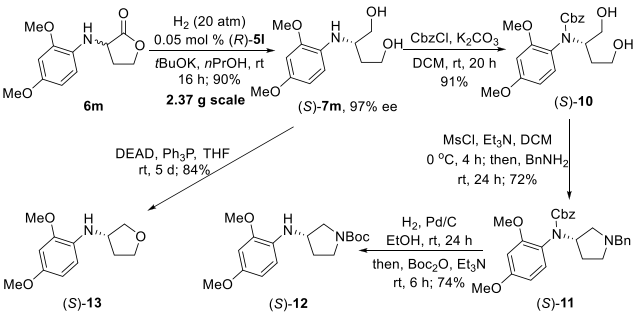


[a]Reaction conditions: the same as those listed in Table 1, entry 9. [b]Isolated yield. [c]Determined by HPLC using chiral column. The configuration of product **9m** is *S* determined by single-crystal X-ray diffraction analysis (see SI).

on either the yield or the enantioselectivity of the reaction, but as was the case for the α-arylamino γ-butyrolactones, substrates with an ortho-substituted aryl group showed higher enantioselectivities than substrates with an aryl group in the meta or para position.

This asymmetric hydrogenation reaction could be performed on a gram scale, and the catalyst loading could be reduced. For example, hydrogenation of 2.37 g of racemic α-arylamino γ-butyrolactone **6m** in the presence of 0.05 mol % (S/C = 2000) of (*R*)-**5l** produced *N*-arylaminobutane-1,4-diol (*S*)-**7m** in 90% yield with 97% ee (Scheme 5). Diol (*S*)-**7m** is an ideal starting

Scheme 5. Gram-Scale Hydrogenation of 6m to (*S*)-7m and Its Applications



(CbzCl = benzyl chloroformate; MsCl = methanesulfonyl chloride; DEAD = diethyl azodicarboxylate)

material for constructing chiral 3-arylamino 1-aza/oxocycloalkanes, which are present in many chiral pharmaceuticals.[15] Specifically, selective protection of the arylamino group of (*S*)-**7m** with benzyl chloroformate generated 1,4-diol (*S*)-**10** in 91% yield. Activation of the hydroxyl groups of (*S*)-**10** with methanesulfonyl chloride (MsCl) and subsequent treatment with benzyl amine ($BnNH_2$) gave 3-arylamino-1-pyrrolidine

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(*S*)-**11** in 72% yield. The *N*-Cbz and *N*-Bn protecting groups could be removed by catalytic hydrogenation of in (*S*)-**11** over charcoal-supported palladium, and the resulting aliphatic amine was selectively protected with Boc_2O, yielding 3-arylamino-1-pyrrolidine (*S*)-**12** in 74% yield. Furthermore, direct reaction of (*S*)-**7m** with diethyl azodicarboxylate in the presence of PPh_3 produced 3-amino-tetrahydrofuran (*S*)-**13** in 84% yield.

In order to understand why the site-specifically modified chiral spiro iridium complexes gave higher enantioselectivity and the stereochemistry of the hydrogenation, we proposed a preliminary mechanism involving a metal−ligand bifunctional interaction between the catalyst and substrate (a precyclic six-membered transition state)[1a] according to the crystal structure of Ir-SpiroPAP[12b] (Figure 2). For avoiding the steric

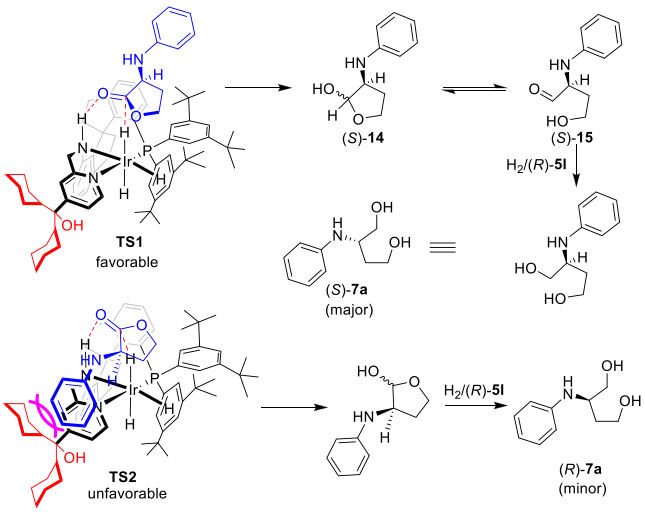

Figure 2. Stereochemistry of the hydrogenation of **6a**.

interaction between the *N*-phenyl group of the substrate **6a** and the bulky substituent at the 4-position of the pyridine ring of the catalyst (*R*)-**5l**, **TS1** is a more favorable transition state than **TS2**, yielding the hemiacetal **14**[16] with a 2*S* configuration. Then, the hemiacetal **14** was converted to aldehyde (*S*)-**15** and followed by a hydrogenation to afford (*S*)-**7a**.

In conclusion, we have achieved the first asymmetric hydrogenation of racemic α-arylamino lactones via DKR for the synthesis of optically active chiral 2-arylamino diols. With catalysis by site-specifically modified chiral spiro iridium complex (*R*)-**5l**, a series of α-arylamino γ-butyrolactones and α-arylamino δ-valerolactones were hydrogenated under mild conditions to afford the corresponding chiral 2-arylamino diols in high yields with good to excellent enantioselectivities. This reaction, which could be performed on a gram scale at low H_2 pressure, provides a practical method for the enantioselective synthesis of chiral drugs and natural products containing 3-arylamino-1-aza/oxo-cycloalkane moieties.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01290.

Synthesis and characterization of detailed experimental procedures (PDF)

Accession Codes

CCDC 1910496 and 1910508 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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