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Asymmetric Hydrogenation of Dibenzo[*c*,*e*]azepine Derivatives with Chiral Cationic Ruthenium Diamine Catalysts

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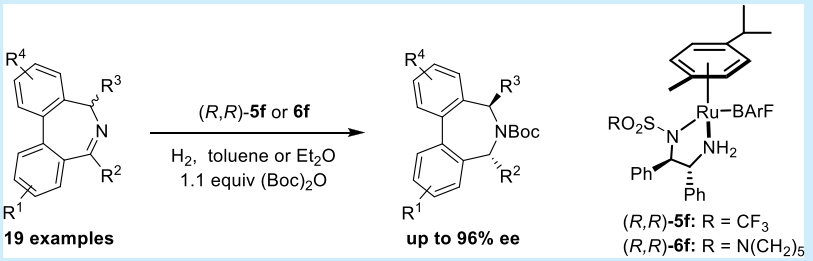
Supporting Information



ABSTRACT: An efficient Ru-catalyzed asymmetric hydrogenation of dibenzo[*c*,*e*]azepines is reported. A series of seven-membered cyclic amines were obtained with moderate to excellent enantioselectivity. The catalyst counteranion played an important role in achieving high-level chiral induction. Moreover, a one-pot synthesis of chiral 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines via two-step reductive amination was also developed.

Chiral N-heterocycles are ubiquitous structural units found in various biologically active substances like natural products and pharmaceutical and agrochemical compounds.[1] Transition metal-catalyzed asymmetric hydrogenation (AH) of cyclic imines and enamines represents a versatile method for synthesizing these chiral heterocycles.[2] To date, hydrogenation of various five- and six-membered cyclic imines has been realized with high enantiomeric excesses.[2d] However, there have been few successful reports of AH of seven-membered cyclic imines (azepines).[3−5] In 1994, Buchwald first reported the Ti-catalyzed AH of 7-phenyl-3,4,5,6-tetrahydro-2*H*-azepine with 98% ee.[3a] Since then, several iridium and ruthenium complexes have been employed in the AH of similar seven-membered cyclic imines.[3b−e] Recently, some successful examples have been reported in the AH of some benzo-fused seven-membered cyclic imines for the preparation of chiral benzazepines and benzodiazepines (Figure 1a,b).[4,5] For example, Zhou and co-workers reported that some benzo-fused seven-membered cyclic imines like dibenzo[*b*,*f*][1,4]-oxazepines,[4a] benzodiazepines,[4b] and dibenzo[*b*,*f*][1,4]-thiazepines[4c] were efficiently hydrogenated by using iridium diphosphine catalysts (Figure 1a). Following these leading works, a few Ir, Pd, and Rh complexes of chiral phosphines have been applied to the AH of such seven-membered cyclic imines (Figure 1a).[4d−h]

Recently, the ruthenium/diamine complexes[6] and iridium/P,N ligand complexes have been demonstrated to be effective for the AH of seven-membered cyclic imines (Figure 1b) by our group.[5a−e] In particular, the chiral ruthenium catalysts proved to be very effective in the AH of not only cyclic and acyclic imines but also a broad range of N-heteroaromatics.[3e,5a,b,7] It was found that a series of benzodiazepines were hydrogenated smoothly with excellent enantioselectivity and diastereoselectivity.[5a,b] Intrigued by these results and on the basis of our continuing interest in synthesizing chiral cyclic amines via enantioselective hydrogenation, we hope to expand

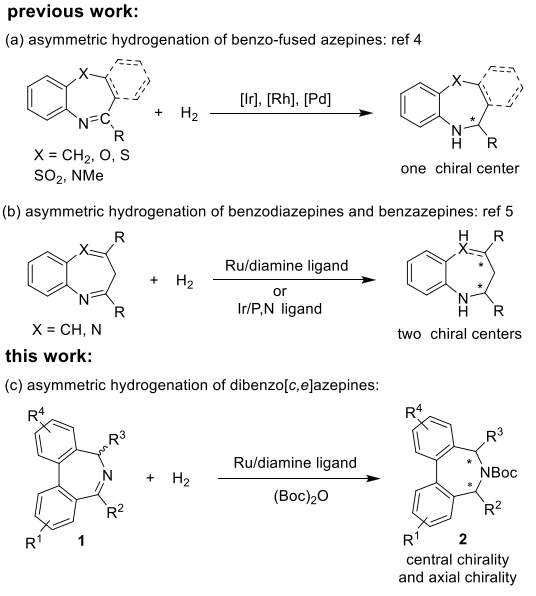


Figure 1. Representative examples of AH of benzo-fused azepines.

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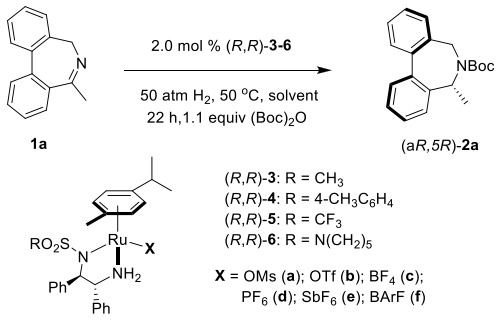
the substrate scope to dibenzo[*c*,*e*]azepines (Figure 1c). The resulting chiral products, 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines, are one kind of seven-membered cyclic amines, which contain a biaryl motif and possess both central chirality and switchable axial chirality.[8] Moreover, these chiral heterocycles have been attracting a great deal of attention because of the potential biological activities[9] and promising applications in organocatalysis.[10] Great efforts have been made to construct this kind of framework by using chiral-pool starting materials or an auxiliary strategy.[8,11] However, only a few catalytic asymmetric strategies have been reported.[12,13] Very recently, Turner and co-workers reported the synthesis of chiral 6,7-dihydrodibenz[*c*,*e*]azepines through the reductase-catalyzed asymmetric reduction of the corresponding imines.[12a] Herein, we disclose the details of the AH of dibenzo[*c*,*e*]azepines with Ru/diamine catalysts (Figure 1c), including one-pot preparation of these chiral amines via direct asymmetric reductive amination (DARA).[13]

In our initial study, 7-methyl dibenzo[*c*,*e*]azepine **1a** was subjected to hydrogenation as a model substrate with $(Boc)_2O$ in dichloromethane (DCM) under 50 atm of H_2 and 50 °C. We first examined the counteranion effect of the catalyst (Table 1, entries 1−6). (*R*,*R*)-**3f** bearing a noncoordinating BArF anion led to the highest selectivity (entry 6). Notably, a lower activity and a lower enantioselectivity were observed without $(Boc)_2O$ (entry 7), possibly due to the catalyst poisoning effect of the resulting amine.[3e,7a] Subsequently, the screening of organic solvents (entries 6 and 8−10) showed toluene was optimal (entry 8). Then, various Ru catalysts were tested (entries 11−13), and (*R*,*R*)-**6f** gave the best results (entry 13). Finally, the effect of hydrogen pressure and reaction temperature was also studied (see the Supporting Information and Table S1), and the highest enantioselectivity was obtained under 30 atm of H_2 at 25 °C (entry 14).

The substrate scope was then studied under the optimized reaction conditions described above (Table 1, entry 14). Generally, various 7-alkyl-substituted dibenzo[*c*,*e*]azepines were hydrogenated smoothly, providing the chiral cyclic amines with high ee values (Table 2, 81−96% ee). The enantioselectivity was observed to be more sensitive to the electronic properties than position of the substituents on the phenyl rings. For example, substrates bearing a methyl substituent at the 2, 3, 4, or 9 position (**1b**, **1c**, **1d**, or **1h**, respectively) exhibited similar enantioselectivity. However, an electron-withdrawing substituent F at position 3 of the phenyl ring (**1f**) decreased the enantioselectivity obviously. Notably, replacement of the methyl group with an ethyl group (**1k**) resulted in a quite low reactivity and a quite low enantioselectivity. Interestingly, hydrogenation of 5,7-dimethyl-substituted dibenzo[*c*,*e*]azepine (**1l**) proceeded smoothly with 5.0 mol % (*R*,*R*)-**6f**, giving the *trans* isomer with 76% ee and a ratio of *trans*-**2l** to *cis*-**2l** of approximately 1.3:1.

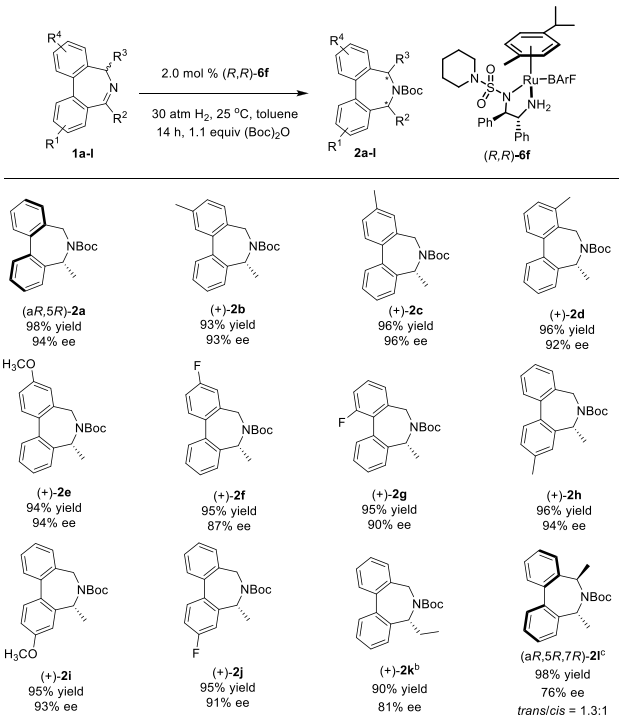
Table 1. Optimizing the Conditions for Asymmetric Hydrogenation[a]



entry	catalyst	anion $[X]^-$	solvent	conversion (%)[b]	ee (%)[c]
1	(*R*,*R*)-**3a**	OMs	DCM	>99	3
2	(*R*,*R*)-**3b**	OTf	DCM	>99	12
3	(*R*,*R*)-**3c**	BF_4	DCM	>99	26
4	(*R*,*R*)-**3d**	PF_6	DCM	>99	50
5	(*R*,*R*)-**3e**	SbF_6	DCM	>99	59
6	(*R*,*R*)-**3f**	BArF	DCM	>99	79
7[d]	(*R*,*R*)-**3f**	BArF	DCM	68	58
8	(*R*,*R*)-**3f**	BArF	toluene	>99	83
9	(*R*,*R*)-**3f**	BArF	Et_2O	>99	47
10	(*R*,*R*)-**3f**	BArF	*i*PrOH	>99	34
11	(*R*,*R*)-**4f**	BArF	toluene	>99	82
12	(*R*,*R*)-**5f**	BArF	toluene	>99	73
13	(*R*,*R*)-**6f**	BArF	toluene	>99	91
14[e]	(*R*,*R*)-**6f**	BArF	toluene	>99	94

[a]Reaction conditions: **1a** (0.1 mmol) in solvent (1.0 mL), (*R*,*R*)-Ru catalyst (2.0 mol %), $(Boc)_2O$ (1.1 equiv), H_2 (50 atm), stirred at 50 °C for 22 h. [b]The conversions were determined by ^1H NMR spectroscopy of the crude reaction mixture. [c]The enantiomeric excesses were determined by HPLC with a chiral IC column, and the absolute configuration of **2a** was determined by comparison of its optical rotation with literature data.[8] [d]Without $(Boc)_2O$, and free amine **9** was obtained. [e]H_2 (30 atm), stirred at 25 °C.

Table 2. Asymmetric Hydrogenation of 7-Alkyl-Substituted Dibenzo[*c*,*e*]azepines[a]



[a]Reaction conditions: **1a**−**j** (0.1 mmol) in toluene (1 mL), (*R*,*R*)-**6f** (2.0 mol %), $(Boc)_2O$ (1.1 equiv), H_2 (30 atm), stirred at 25 °C for 14 h. Isolated yields. The enantiomeric excesses were determined by HPLC, and the absolute configuration of **2l** was determined by comparison of its optical rotation with literature data.[8] [b](*R*,*R*)-**6f** (10.0 mol %). [c](*R*,*R*)-**6f** (5.0 mol %).

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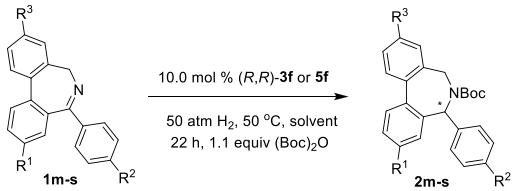
For the more difficult 7-phenyl-substituted substrate (**1m**), hydrogenation could not occur under the optimized reaction conditions described above. To further improve the reactivity and enantioselectivity, we rescreened the reaction conditions (Table 3, entries 1−4, and Table S2). Better enantioselectivity

Table 3. Asymmetric Hydrogenation of 7-Aryl-Substituted Dibenzo[*c*,*e*]azepines[a]



entry	catalyst	solvent	$R^1/R^2/R^3$	yield (%)[b]	ee (%)[c]
1	(*R*,*R*)-**3f**	toluene	H/H/H (**1m**)	17	10 (+)
2	(*R*,*R*)-**3f**	Et_2O	H/H/H (**1m**)	38	40 (+)
3	(*R*,*R*)-**3f**	Et_2O	H/H/H (**1m**)	>99	40 (+)
4	(*R*,*R*)-**6f**	Et_2O	H/H/H (**1m**)	>99	4 (−)
5	(*R*,*R*)-**5f**	Et_2O	H/H/H (**1m**)	97[d]	80 (+)
6	(*R*,*R*)-**5f**	Et_2O	H/Me/H (**1n**)	91[d]	68 (+)
7	(*R*,*R*)-**5f**	Et_2O	H/Cl/H (**1o**)	98[d]	77 (+)
8	(*R*,*R*)-**5f**	Et_2O	H/H/Me (**1p**)	94[d]	81 (+)
9	(*R*,*R*)-**5f**	Et_2O	H/H/OMe (**1q**)	87[d]	60 (+)
10	(*R*,*R*)-**5f**	Et_2O	H/H/F (**1r**)	97[d]	77 (+)
11	(*R*,*R*)-**5f**	Et_2O	OMe/H/H (**1s**)	87[d]	70 (+)

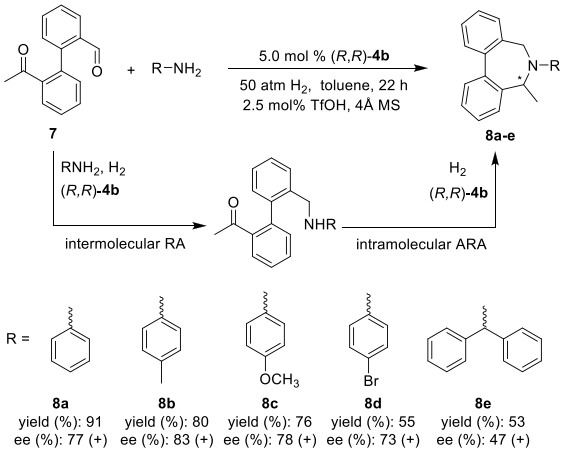
[a]Reaction conditions: substrates **1m**−**s** (0.1 mmol) in solvent (1.0 mL), (*R*,*R*)-Ru catalyst (10.0 mol %), $(Boc)_2O$ (1.1 equiv), H_2 (50 atm), stirred at 50 °C for 22 h, except for entries 1 and 2, for which a Ru catalyst (5.0 mol %) was used. [b]The yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. [c]The enantiomeric excesses were determined by HPLC. [d]Isolated yields.

was achieved in Et_2O instead of toluene, and full conversion could not be obtained until 10.0 mol % catalyst was used (entry 3). Notably, an obvious electronic effect of the *N*-sulfonate substituent on the catalyst was observed (entries 3−5). (*R*,*R*)-**5f** bearing a strong electron-withdrawing CF_3 substituent led to a significant increase in enantioselectivity (entry 5). Then, several 5-aryl-substituted dibenzo[*c*,*e*]azepines were studied, affording the chiral cyclic amines in good yields with moderate enantioselectivities (entries 5−11).

DARA has been considered to be one of the most efficient and economical approaches for directly synthesizing chiral acyclic and cyclic amines.[14] To date, only a few transition metal-catalyzed intramolecular DARAs have been reported for the construction of chiral N-heterocycles,[15] including seven-membered N-heterocycles.[13,15a−c] DARA in which a secondary amine participates is still a formidable challenge.[16,17] Most recently, an efficient cascade AH of quinolines/intramolecular reductive amination for preparing benzo-fused quinolizidines and indolizidines was developed by our group.[17] Thus, we envisioned that one-pot preparation of chiral 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines via two-step intermolecular and intramolecular cascade reductive amination (RA) could be realized (Scheme 1).

We then chose 2′-acetyl[1,1′-biphenyl]-2-carbaldehyde **7** as the model substrate with aniline for our DARA study. After a survey of reaction conditions (Table S3), chiral tertiary amine **8a** was obtained in 91% yield and 77% ee via two-step DARA by using catalyst (*R*,*R*)-**4b** (5.0 mol %). This transformation was also performed smoothly under otherwise identical

Scheme 1. One-Pot Synthesis of Chiral 6,7-Dihydro-5*H*-dibenz[*c*,*e*]azepines via Two-Step Reductive Amination[a]

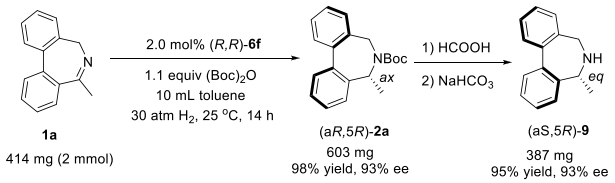


[a]Reaction conditions: **7** (0.1 mmol) in toluene (1 mL), RNH_2 (0.1 mmol), (*R*,*R*)-**4b** (5.0 mol %), 4 Å molecular sieves (100 mg), TfOH (2.5 mol %), H_2 (50 atm), stirred at 50 °C for 22 h. Isolated yields are given. The enantiomeric excesses were determined by HPLC.

conditions for other aromatic amines. A higher ee value was observed when *p*-toluidine was used (83% ee). The use of dibenzylamine resulted in a much lower reactivity and a much lower enantioselectivity (47% ee).

Finally, a scale-up preparation of 5-methyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine was developed (Scheme 2). Reaction of **1a**

Scheme 2. Scale-Up Preparation of (*R*)-5-Methyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine



was carried out on a scale of 414 mg, affording chiral amine (a*R*,5*R*)-**2a** in 98% yield and 93% ee. After a deprotection/neutralization sequence with formic acid and $NaHCO_3$, free amine (a*S*,5*R*)-**9** with an identical enantioselectivity could be obtained. Notably, after N-deprotection, a resulting switch in axial conformation occurs by the center-axis relay effect.[8]

In summary, we described the Ru-catalyzed enantioselective hydrogenation of dibenzo[*c*,*e*]azepines for the first time. It was found that the counteranion of the catalyst was critically important for high-level chiral induction, and good to excellent enantioselectivities (≤96% ee) were achieved. Moreover, a one-pot methodology for syntheses of chiral 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines via a two-step reductive amination was developed. These new protocols thus provide easy ways leading to chiral 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepines, which are attractive substructures in biological and synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, synthesis of the starting materials, and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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