Asymmetric Hydrogenation

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Asymmetric Hydrogenation of 2,4-Disubstituted 1,5-Benzodiazepines Using Cationic Ruthenium Diamine Catalysts: An Unusual Achiral Counteranion Induced Reversal of Enantioselectivity**

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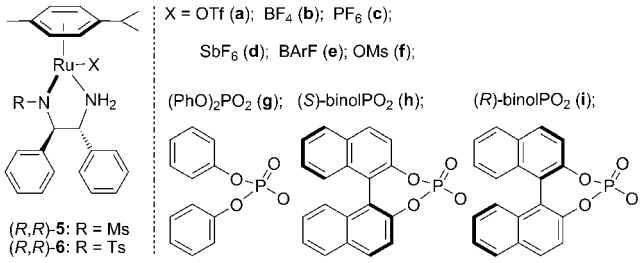
Benzodiazepines form an important class of heterocycles with pharmacological activities and are considered as "privileged"[1a] scaffolds in medicinal chemistry.[1] 1,5-Benzodiazepines and their derivatives belong to this family, and have recently attracted much attention.[2,3] Recent medical research has shown that the sense of chirality of the 1,5-benzodiazepine core of these molecules can play a very important role in determining their bioactivity.[3] However, the asymmetric synthesis of enantiomerically pure 1,5-benzodiazepine derivatives has been less investigated,[3b,4] and to the best of our knowledge, there is only one report describing the synthesis of 2,4-substituted 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines.[4a,5]

The ability to prepare both enantiomers of a chiral compound is extremely important to pharmaceutical and bioorganic chemistry.[6] In addition to the conventional method, in which chirality is introduced using a metal-catalyzed transformation wherein both enantiomers of a chiral ligand are used, a number of alternative approaches have recently been developed wherein only a single enantiomer of the chiral ligand is required.[7,8] For example, the sense of asymmetric induction of a metal-catalyzed reaction can be reversed by using different metals in the presence of the same enantiomer of ligand,[7a–c] the use of additives,[7d,e] and by changing reaction parameters such as pressure, temperature, and solvent. [7f–h] Also, the identity of the counteranion was found to play an important role in the reactivity and stereoselectivity of cationic metal catalysts in asymmetric reactions.[9] Although the use of counteranions to control reaction enantioselectivity has attracted increased attention over the past several years,[10,11] the use of achiral counteranions for the reversal of asymmetric induction has been rather limited.[8]

Recently, we have found that cationic ruthenium complexes of chiral mono-tosylated diamines[12] are very efficient catalysts of unprecedented reactivity for the asymmetric hydrogenation (AH)[13–15] of a broad range of quinoline derivatives in a highly enantioselective manner.[14a–e] A study of the mechanism indicated that the choice of the achiral counteranion is critical for achieving high enantioselectivity.[14b] Subsequently, this catalytic system was demonstrated to be highly enantioselective in the AH of the often problematic *N*-alkyl imines and quinoxalines; the achiral counteranions influenced the reaction enantioselectivity significantly.[14f–h] Based on these results, we envisioned that the choice of counteranion may serve as a new way to control the enantioselectivity of the AH of other difficult substrates, thus extending the application of this ruthenium diamine catalyst. Herein, we report the first example of highly enantioselective and diastereoselective hydrogenation of a range of readily available 2,4-disubstituted-3*H*-1,5-benzodiazepines using chiral cationic ruthenium diamine catalysts (Scheme 1). Unexpectedly, the choice of achiral counteranions determined the sense of asymmetric induction in the hydrogenation of 2,4-diarylsubstituted-3*H*-1,5-benzodiazepines, thus providing a facile way for accessing either enantiomer of 2,4-diaryl-2,3,4,5-tetrahydro-1*H*-benzodiazepine derivatives.



Scheme 1. Chiral ruthenium diamine catalysts used in this study. In some cases the counterion is not coordinated to the ruthenium center.

In our initial study, we chose the AH of 2,4-diphenyl-3*H*-1,5-benzodiazepine (**1a**) with catalyst (*R*,*R*)-**5a** as the model reaction. The reaction proceeded smoothly under 50 atm of H_2 at 40 °C in CH_2Cl_2 (Table 1, entry 1), to afford (*S*,*S*)-2,4-diphenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**2a**) in full conversion with 75:25 d.r. and 39% *ee*. Based on our previous finding that the identity of the counteranion affects the outcome in AH reactions,[14f–h] we examined a series of more weakly coordinating anions, such as BF_4^-, PF_6^-, SbF_6^-,

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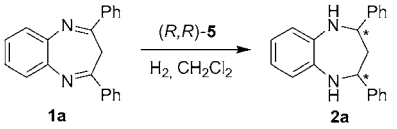
Table 1: Optimization of the reaction conditions for the AH of 2,4-diphenyl-1,5-benzodiazepine (**1a**).[a]



1a **2a**

Entry	Catalyst	Anion [X^-]	Conv. [%][b]	d.r.[b]	*ee* [%][c]
1	(*R*,*R*)-**5a**	OTf^-	>99	3:1	39 (*S*,*S*)
2	(*R*,*R*)-**5b**	BF_4^-	>99	3:1	12 (*R*,*R*)
3	(*R*,*R*)-**5c**	PF_6^-	>99	4:1	87 (*R*,*R*)
4	(*R*,*R*)-**5d**	SbF_6^-	>99	5:1	84 (*R*,*R*)
5	(*R*,*R*)-**5e**	$BArF^-$	>99	6:1	92 (*R*,*R*)
6	(*R*,*R*)-**5f**	OMs^-	>99	19:1	98 (*S*,*S*)
7	(*R*,*R*)-**5g**	$(PhO)_2PO_2^-$	>99	>20:1	99 (*S*,*S*)
8	(*R*,*R*,*S*)-**5h**	(*S*)-binolPO_2^-	>99	18:1	98 (*S*,*S*)
9	(*R*,*R*,*R*)-**5i**	(*R*)-binolPO_2^-	>99	13:1	97 (*S*,*S*)
10[d]	(*R*,*R*)-**5g**	$(PhO)_2PO_2^-$	>99	20:1	99 (*S*,*S*)
11[e]	(*R*,*R*)-**5g**	$(PhO)_2PO_2^-$	97[f]	15:1	99 (*S*,*S*)

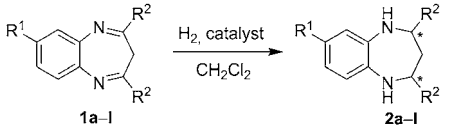
[a] Reaction conditions: **1a** (0.1 mmol) in CH_2Cl_2 (1 mL), catalyst (2.0 mol%), 50 atm of H_2, stirred at 40°C for 10 h. [b] The conversions and d.r. (*trans*/*cis*) were determined by ^1H NMR analysis of the crude reaction mixture. [c] The *ee* values were determined by HPLC with a chiral OD-H column. [d] With (*R*,*R*)-**5g** (1.0 mol%). [e] With (*R*,*R*)-**5g** (0.2 mol%), 1 mmol (296 mg) of **1a** in CH_2Cl_2 (1 mL), 24 h. [f] Yield of isolated product. Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl.

and $BArF^-$ (tetrakis(3,5-bistrifluoromethylphenyl)borate). To our great delight, a distinct increase in diastereo- and enantioselectivity was observed (Table 1, entries 2–5), and the $BArF^-$ ion gave the best result (92% *ee*, 6:1 d.r.). Notably, the use of the ruthenium catalyst in the presence of these weakly coordinating anions, gave the product of opposite configuration to that obtained when using the catalyst containing OTf^-. Intrigued by this interesting achiral anion-induced reversal in the sense of asymmetric induction, we further investigated the reaction using a series of anions capable of forming hydrogen bonds, and we found that they gave the same product enantiomer as that obtained when using OTf^- (Table 1, entries 6–9). Notably, replacing OTf^- with OMs^- led to a significant increase in diastereo- and enantioselectivity (Table 1, entry 6). The use of catalysts bearing a phosphate anion also gave a very efficient reaction, and the achiral $(PhO)_2PO_2^-$ ion was found to be optimal in terms of both diastereo- and enantioselectivity (Table 1, entry 7). Thus, both enantiomers of **2a**, (*R*,*R*)-**2a** and (*S*,*S*)-**2a**, were obtained in 92% *ee* and 99% *ee*, respectively (Table 1, entries 5 and 7). To the best of our knowledge, this is the first example of an AH reaction that displays a marked achiral counteranion-induced reversal of enantioselectivity.

The effects of solvent, hydrogen pressure, and temperature on the performance of catalysts (*R*,*R*)-**5e** and (*R*,*R*)-**5g** in the reaction were investigated (the results are summarized in the Supporting Information; Table S1 and Table S2). It was found that weakly polar solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$, and toluene were suitable for both catalytic systems, and CH_2Cl_2 turned out to be optimal in terms of diastereo- and enantioselectivity (see the Supporting Information; Table S1, entry 1, and Table S2, entry 1). In addition, the enantioselectivity of the reaction was insensitive to hydrogen pressure and temperature. Notably, when the catalyst loading of (*R*,*R*)-**5g** was decreased to 0.2 mol%, full conversion and excellent diastereo- and enantioselectivity were still observed (Table 1, entry 11). In the case of (*R*,*R*)-**5e**, a decrease in the catalyst loading (1.0 mol%) resulted in lower conversion and lower diastereo- and enantioselectivity (see the Supporting Information; Table S1, entry 10). Therefore, both enantiomers of **2a** were obtained with excellent enantioselectivity under 50 atm of H_2 at 40°C in CH_2Cl_2 (Table 1, entries 5 and 10).

With optimized reaction conditions established, the generality of the achiral counteranion induced reversal of enantioselectivity was investigated using a variety of 2,4-diaryl-1,5-benzodiazepine derivatives. As shown in Table 2, all reactions proceeded smoothly to give full conversion of substrate, regardless of the steric and electronic properties of the substrates. The use of the Ru/$(PhO)_2PO_2$ catalyst system, (*R*,*R*)-**5g**, gave the desired products (*S*,*S*)-**2a–l** in good to excellent diastereoselectivity (6:1 to >20:1 d.r.) and excellent

Table 2: Reversal in the sense of asymmetric induction of the AH reaction and scope of 2,4-diaryl-1,5-benzodiazepines **1**.[a]



1a–l **2a–l**

Entry	R^1/R^2 (Substrate)	Anion [X^-]	d.r.[b]	*ee* [%][c,d]
1	H/Ph (**1a**)	$(PhO)_2PO_2^-$ (**5g**)	20:1	99 (*S*,*S*)
2	H/Ph (**1a**)	$BArF^-$ (**5e**)	6:1	92 (*R*,*R*)
3	H/*p*-tolyl (**1b**)	$(PhO)_2PO_2^-$ (**5g**)	>20:1	>99 (*S*,*S*)
4	H/*p*-tolyl (**1b**)	$BArF^-$ (**5e**)	8:1	92 (*R*,*R*)
5	H/*p*-FC_6H_4 (**1c**)	$(PhO)_2PO_2^-$ (**5g**)	16:1	>99 (*S*,*S*)
6	H/*p*-FC_6H_4 (**1c**)	$BArF^-$ (**5e**)	5:1	88 (*R*,*R*)
7	H/*p*-ClC_6H_4 (**1d**)	$(PhO)_2PO_2^-$ (**5g**)	16:1	>99 (*S*,*S*)
8	H/*p*-ClC_6H_4 (**1d**)	$BArF^-$ (**5e**)	5:1	93 (*R*,*R*)
9	H/*p*-BrC_6H_4 (**1e**)	$(PhO)_2PO_2^-$ (**5g**)	18:1	>99 (*S*,*S*)
10	H/*p*-BrC_6H_4 (**1e**)	$BArF^-$ (**5e**)	5:1	96 (*R*,*R*)
11	H/*p*-$CF_3C_6H_4$ (**1f**)	$(PhO)_2PO_2^-$ (**5g**)	6:1	>99 (*S*,*S*)
12	H/*p*-$CF_3C_6H_4$ (**1f**)	$BArF^-$ (**5e**)	3:1	96 (*R*,*R*)
13	H/*m*-tolyl (**1g**)	$(PhO)_2PO_2^-$ (**5g**)	>20:1	>99 (*S*,*S*)
14	H/*m*-tolyl (**1g**)	$BArF^-$ (**5e**)	6:1	90 (*R*,*R*)
15	H/*m*-ClC_6H_4 (**1h**)	$(PhO)_2PO_2^-$ (**5g**)	7:1	>99 (*S*,*S*)
16	H/*m*-ClC_6H_4 (**1h**)	$BArF^-$ (**5e**)	3:1	92 (*R*,*R*)
17	H/*m*-BrC_6H_4 (**1i**)	$(PhO)_2PO_2^-$ (**5g**)	7:1	>99 (*S*,*S*)
18	H/*m*-BrC_6H_4 (**1i**)	$BArF^-$ (**5e**)	3:1	92 (*R*,*R*)
19	H/2-naphthyl (**1j**)	$(PhO)_2PO_2^-$ (**5g**)	>20:1	>99 (*S*,*S*)
20	H/2-naphthyl (**1j**)	$BArF^-$ (**5e**)	6:1	>99 (*R*,*R*)
21	MeO/Ph (**1k**)	$(PhO)_2PO_2^-$ (**5g**)	16:1	97 (*S*,*S*)
22	MeO/Ph (**1k**)	$BArF^-$ (**5e**)	7:1	90 (*R*,*R*)
23	Cl/Ph (**1l**)	$(PhO)_2PO_2^-$ (**5g**)	18:1	99 (*S*,*S*)
24	Cl/Ph (**1l**)	$BArF^-$ (**5e**)	14:1	95 (*R*,*R*)

[a] Reaction conditions: substrate (0.2 mmol) in CH_2Cl_2 (2 mL), (*R*,*R*)-**5g** (1.0 mol%) or (*R*,*R*)-**5e** (2.0 mol%), 50 atm of H_2, stirred at 40°C for 10–24 h. [b] Complete conversions were obtained in all cases, and d.r. (*trans*/*cis*) were determined by ^1H NMR analysis of the crude reaction mixture. [c] The *ee* values were determined by HPLC using a chiral stationary phase. [d] The absolute configurations were assigned by analogy to a derivative of **2a** (Scheme S2 in the Supporting Information, **2m**),[16] which was characterized by single crystal X-ray analysis.

enantioselectivity (97% to >99% *ee*); the Ru/BArF system, (*R*,*R*)-**5e**, provided the corresponding enantiomers (*R*,*R*)-**2a–l** in good diastereoselectivity (3:1 to 14:1 d.r.) and excellent enantioselectivity (88% to >99% *ee*). With both catalytic systems, hydrogenation of substrates bearing Cl (**1h**) and Br (**1i**) substituents in the *meta* position of the phenyl ring gave relatively lower diastereoselectivity, albeit with high enantioselectivity (Table 2, entries 15–18). Notably, when using *para*-substituted substrates in reactions catalyzed by (*R*,*R*)-**5e**, the enantioselectivity of the products was found to increase gradually as follows: F (**1c**, 88% *ee*), Cl (**1d**, 93% *ee*), and Br (**1e**, 96% *ee*). The reactions of a substrate bearing a more electron-withdrawing group (**1f**) were less diastereoselective for both catalytic systems, albeit the product was obtained in higher enantioselectivity when using (*R*,*R*)-**5e** as the catalyst (Table 2, entries 11 and 12 versus entries 3 and 4). In addition, the presence of the electron-donating methoxy group on the fused phenyl ring resulted in slightly lower enantioselectivity (Table 2, entries 21 and 22). Remarkably, a complete reversal in the sense of asymmetric induction ((*S*,*S*)-**2j**, >99% *ee* to (*R*,*R*)-**2j**, >99% *ee*) was observed when using substrate **1j** (Table 2, entries 19 and 20).

Although a detailed mechanistic investigation will form part of future studies, we herein propose that the hydrogenation of the C=N bond can proceed via either of two different transition states depending on the ability of the catalyst counteranion to participate in hydrogen bonding. In the case of the Ru/$(PhO)_2PO_2$ catalyst system, (*R*,*R*)-**5g**, we propose a pericyclic transition state that is similar to the one we proposed previously for the AH of quinoline (Figure 1);[14b,17] this transition state involves a CH–π interaction

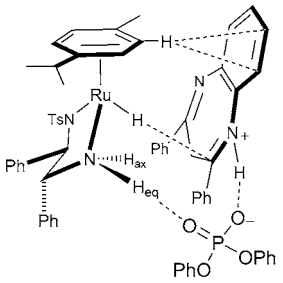


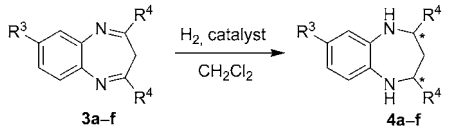
Figure 1. Proposed transition state involving (*R*,*R*)-**5g** as the catalyst.

between the η^6-arene ligand in the ruthenium complex and the fused phenyl ring of the substrate. Based on this model, we propose that a hydride is transferred from the ruthenium center to the *Re* face of the C=N moiety to give the *S*-configured product, consistent with the experimental results. In addition, this model also explains the pronounced difference in enantioselectivity between the reaction catalyzed by the complex bearing a OTf^- and that by the complex bearing a OMs^- (39% *ee* for OTf^- and 98% *ee* for OMs^-), as these counterions have very similar structures but different hydrogen bond forming ability.

On the other hand, the ruthenium hydride intermediate bearing weakly coordinating anions, such as $BArF^-$, probably forms an electrostatic ion pair with the activated substrate (see the Supporting Information, Scheme S4). To explain the reversal in the sense of asymmetric induction by switching to a more weakly coordinating anion, we propose the presence of an alternative set of CH–π interactions in the transition state, in this case, interactions between the η^6-arene ligand in the ruthenium complex and the substituted phenyl rings of the substrate (see the Supporting Information, Scheme S4). This hypothesis is supported by the observation of changes in the stereoselectivity of the reaction upon modification of the electronics of the phenyl substituents at the 2- and 4-positions of the substrate when the Ru/BArF catalyst system was used (Table 2); a similar effect was previously observed in the asymmetric transfer hydrogenation of aryl ketones using similar half-sandwich Ru^{II} complexes as the catalyst.[18] Thus, unlike the Ru/$(PhO)_2PO_2$ system, in which both hydrogen bonding and CH–π interactions guide the hydride transfer, the selectivity of the Ru/BArF system is probably only governed by CH–π interactions alone. To support this hypothesis, we carried out the hydrogenation of **1a** with (*R*,*R*)-**5g** in a mixture of MeOH/CH_2Cl_2. The diastereo- and enantioselectivities decreased gradually in the presence of increasing amounts of MeOH (see the Supporting Information, Table S5) and a reversal in the sense of asymmetric induction was observed when the ratio of MeOH/CH_2Cl_2 reached 1:2 (v/v) or higher. A similar decrease in diastereo- and enantioselectivity was observed when the same investigation was carried out with the ruthenium/BArF catalyst, (*R*,*R*)-**5e**, although the reversal in the sense of enantioselectivity did not occur. This result indicates the weakening or even the breaking of hydrogen bonds between the $(PhO)_2PO_2^-$ ion, activated substrate, and ruthenium species, in the presence of protic solvent. Notably, almost identical diastereo- and enantioselectivities were observed for both catalytic systems when only MeOH was used as the solvent (see the Supporting Information, Table S5, entries 9 and 10).

To further support this hypothesis and extend the substrate scope, we investigated the AH of 2,4-dialkyl substituted substrates, in which only one phenyl ring on the substrate is available for the formation of CH–π interactions. Initially, 2,4-dimethyl-1,5-benzodiazepine (**3a**) was used as the substrate for catalyst screening (Table 3, entries 1—4, and the Supporting Information, Table S3). Unsurprisingly, the counteranion-induced reversal in enantioselectivity was not observed despite an obvious effect on diastereoselectivity.[19] On the other hand, upon catalyst screening, we found that the hydrogenation of **3a** with 1.0 mol% of (*R*,*R*,*S*)-**6h** (see Scheme 1) gave fairly good diastereoselectivity and excellent enantioselectivity (Table 3, entry 5; 10:1 d.r. and >99% *ee*). After investigating the effects of solvent, temperature and pressure on the reaction outcome (see the Supporting Information, Table S5), several 2,4-dialkyl-1,5-benzodiazepines were hydrogenated under optimized conditions (Table 3, entry 5). It was found that all substrates were efficiently reduced to afford the corresponding products in full conversions with good diastereoselectivity and excellent enantioselectivity (Table 3, entries 6–11; 5:1 to 9:1 d.r., and >99% *ee*).

Table 3: Optimization of the reaction conditions for the AH of 2,4-dialkyl-1,5-benzodiazepine and the substrate scope.[a]



3a–f **4a–f**

Entry	R^3/R^4 (Substrate)	Catalyst	Conv. [%][b]	d.r.[b]	*ee* [%][c,d]
1	H/Me (**3a**)	(*R*,*R*)-**6e**	>99	3:1	>99 (*R*,*R*)
2	H/Me (**3a**)	(*R*,*R*)-**6g**	>99	6:1	99 (*R*,*R*)
3	H/Me (**3a**)	(*R*,*R*,*S*)-**6h**	>99	10:1	>99 (*R*,*R*)
4	H/Me (**3a**)	(*R*,*R*,*R*)-**6i**	>99	4:1	98 (*R*,*R*)
5	H/Me (**3a**)	(*R*,*R*,*S*)-**6h**	>99	10:1	>99 (*R*,*R*)
6[e]	H/Me (**3a**)	(*R*,*R*,*S*)-**6h**	98[f]	9:1	>99 (*R*,*R*)
7	H/Et (**3b**)	(*R*,*R*,*S*)-**6h**	>99	5:1	>99 (*R*,*R*)
8	H/*i*Bu (**3c**)	(*R*,*R*,*S*)-**6h**	>99	9:1	>99 (*R*,*R*)
9	H/*n*Pen (**3d**)	(*R*,*R*,*S*)-**6h**	>99	6:1	>99 (*R*,*R*)
10	MeO/Me(**3e**)	(*R*,*R*,*S*)-**6h**	>99	5:1	>99 (*R*,*R*)
11	Me/Me (**3f**)	(*R*,*R*,*S*)-**6h**	>99	5:1	>99 (*R*,*R*)

[a] Reaction conditions: substrate (0.2 mmol) in CH_2Cl_2 (2 mL), ruthenium catalyst (1.0 mol%) except for entries 1–4 (2.0 mol%) and entry 6 (0.5 mol%), 50 atm of H_2, stirred at 40°C for 10–24 h. [b] The conversions and d.r. (*trans*/*cis*) were determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The *ee* values were determined by HPLC using a chiral stationary phase. [d] The absolute configurations were assigned by analogy to a derivative of **4a** (Supporting Information, Scheme S3, **4g**),[16] which was characterized by single crystal X-ray analysis. [e] 2 mmol (344 mg) of **3a** in CH_2Cl_2 (4 mL), 24 h. [f] Yield of isolated product.

In conclusion, a highly enantioselective hydrogenation of 2,4-disubstituted-1,5-benzodiazepines using chiral cationic ruthenium diamine catalysts has been developed. Both enantiomers of 2,4-diaryl-2,3,4,5-tetrahydro-1*H*-benzodiazepine derivatives were obtained with good to excellent diastereoselectivity and excellent enantioselectivity by using the same enantiomer of the ligand but in the presence of different achiral counteranions. A detailed study of the mechanism of this reaction and further exploration of this catalytic system for the hydrogenation of more challenging substrates are in progress.

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