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Asymmetric ring-opening reactions of azabenzonorbornadienes through transfer hydrogenation using secondary amines as hydrogen sources: tuning of absolute configuration by acids†

Dongdong Pu,[a] Yongyun Zhou,*[a] Fan Yang,[a] Guoli Shen,[a] Yang Gao,[a] Weiqing Sun,[a] Ruhima Khan[a] and Baomin Fan *[a,b]

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Reductive transfer hydrogenation of bicyclic alkenes has been developed under the co-catalytic system of palladium and silver by using secondary amines as reductants. The reaction results in the asymmetric ring-opening product. A wide range of azabenzonorbornadienes reacted well giving 1,2-dihydronaphthalen-1-amine derivatives in high yields with good enantioselectivities. The control of the absolute configuration of the product by addition of carboxylic acids has been demonstrated.

Introduction

The hydrogenation reaction is one of the most important transformations in organic synthesis and this has been proved by its various applications from academic laboratories to industrial operations.[1] The methods used for the hydrogenation consist of direct hydrogenation using H_2 gas and transfer hydrogenation. In recent years, transfer hydrogenation (TH) has become a powerful alternative to direct hydrogenation because the reagents are cheap, readily available, easy to handle and the catalysts needed for TH are non-hazardous and easily available. TH does not involve difficult reaction steps and it does not require the usage of toxic pressurized H_2 gas.[2,3] Asymmetric variant of transfer hydrogenation has been realized to be one of the most powerful and versatile tools because of its excellent selectivity, operational simplicity and wide substrate scope.[4] The most commonly used catalysts for transfer hydrogenation are transition metal complexes involving rhodium, ruthenium and iridium and the frequently employed hydrogen sources are alcohols, acids and amines.[3c,4a,5] In recent years, asymmetric transfer hydrogenation has been studied by many groups[3a,4c,5b,6] though the application of secondary amines as a hydrogen source in reductive asymmetric transfer hydrogenation is least explored.[7] Switching of enantioselectivity in the asymmetric hydrogenation of 2,4-disubstituted 1,5-benzodiazepines has been reported.[8] Reversal in the enantioselectivity has also been observed in the asymmetric hydrogenation of cyclic imines of benzazepines and benzodiazepines by changing the achiral counteranion of the catalyst.[9] However, this phenomenon has not been observed so far in asymmetric transfer hydrogenation.

The asymmetric ring-opening (ARO) reactions of oxa/azabenzonorbornadienes provide good opportunities for the simultaneous introduction of new functionalities and new stereogenic centers into the framework of organic compounds. Because of this reason, the ARO reaction of bicyclic alkenes has become one of the most popular transformations in asymmetric synthesis and has been exploited in the preparation of a variety of organic products of biological interest featuring diverse functional groups.[10,11] Our group has been paying keen interest in the asymmetric ring-opening reactions of bicyclic alkenes. Earlier we have demonstrated the application of various transition metal complexes with chiral ligands and Lewis acids which were successfully effective in the ARO of bicyclic alkenes.[12] Even though there have been reports on the reductive ring-opening reactions using different reductants,[13] our group has succeeded in developing a co-catalytic system of palladium and zinc for the asymmetric transfer hydrogenation of azabenzonorbornadienes by alcohols.[14] So, we further envisioned the application of amines as a hydrogen source for the reductive ARO of hetero-bicycles into chiral 1,2-dihydronaphthalene derivatives. We herein report the successful

[a]YMU-HKBU Joint Laboratory of Traditional Natural Medicine, Yunnan Minzu University, Kunming 650500, China. E-mail: zhouyy@ynni.edu.cn, FanBM@ynni.edu.cn
[b]Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China

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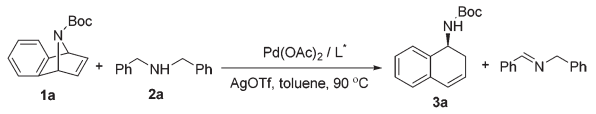
application of secondary amines as reductants in the reductive asymmetric ring-opening reactions of azabenzonorbornadienes. To our delight, during the course of our investigations, it has also been observed that the absolute configuration of the ARO product can also be altered by adding carboxylic acids as additives apart from the Lewis acids in the reaction system.

Results and discussion

We began our investigation by reacting azabenzonorbornadiene **1a** with dibenzylamine **2a** in the presence of $Pd(OAc)_2$ as a catalyst and AgOTf as a co-catalyst in toluene at 90 °C using (*R*)-BINAP as the chiral ligand. To our delight, the reaction afforded the desired product **3a** in 88% yield with 55% enantioselectivity along with the corresponding imine. Surprisingly, on the addition of 2 equivalents of benzoic acid along with (*R*)-BINAP, the absolute configuration of the product was reversed giving the *R* isomer but in a low reaction yield and 83% ee (Table 1, entries 1 and 2). In order to find out the most suitable chiral ligand for the present investigation, various ligands were screened for the same reaction. The chiral ligand (*R*)-Cl-OMe-BIPHEP also gave the *S* isomer in 80% yield but with a poor enantiomeric ratio. In this case also, when benzoic acid was added to the above reaction conditions, the absolute configuration of the product was altered from *S* to *R* with a decreased yield and increased enantioselectivity (Table 1, entries 3 and 4). Other chiral ligands such as (*R*)-OMe-BIPHEP and (*R*)-SYNPHOS could also increase the yield and enantioselectivity (Table 1, entries 5 and 6). Gratifyingly, in the presence of (*R*)-SEGPHOS, the highest yield was observed with 75% ee (Table 1, entry 7). Having known that (*R*)-SEGPHOS gives better yield, we tried the same reaction in the presence of 2 equivalents of benzoic acid and to our delight, alteration in the absolute configuration of the product was observed in this case also (Table 1, entry 8). From the above investigations, it has been confirmed that (*R*)-SEGPHOS is the most suitable chiral ligand for the present transformation. It has also been observed that the absolute configuration of the ARO reaction by transfer hydrogenation can be altered by using benzoic acid as an additive.

Next, we focused on the effect of different Lewis acids on the reaction of **1a** with dibenzylamine **2a** using (*R*)-SEGPHOS as the chiral ligand. Gratifyingly, triflates such as $Fe(OTf)_3$, $Fe(OTf)_2$, $Al(OTf)_3$ and $Zn(OTf)_2$ resulted in moderate to good yields with good enantioselectivity (Table 2, entries 3–6). The reaction took place in lesser time with excellent yield and 75% ee when AgOTf was used (Table 2, entry 7). Other Lewis acids like $AgBF_4$ and $AgSbF_6$ also gave the expected product in good yield with appreciable enantioselectivity (Table 2, entries 8 and 9). We were excited to observe that while using $AgPF_6$, the desired product was obtained with improved enantioselectivity and 85% yield (Table 2, entry 10). Surprisingly, on using weaker acids AgOAc and Ag_2CO_3, the absolute configuration of the product was altered from *S* to *R* but in reduced yield and low enantioselectivity (Table 2, entries 11 and 12). Based on the above results, we speculated whether acidity will have an effect on the absolute configuration of the product. So other weaker carboxylic acids like PhCOOH, *p*-Br-C_6H_4COOH, *p*-Me-C_6H_4COOH, *p*-MeO-C_6H_4COOH and PhCOOK were also screened. In all the cases, the *R* isomer was observed but in very poor yield with a longer reaction period (Table 2, entries 13–18). Among the Brønsted acids, benzoic acid gave the highest enantioselectivity. When the reaction was carried out in the absence of Lewis acid, both reactivity and enantio-

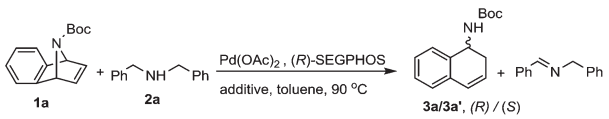
Table 1 Screening of chiral ligands for the reaction of **1a** with **2a**[a]



Entry	Ligand	Time (h)	Yield[b] (%)	ee (%)	(*R*)/(*S*)
1	(*R*)-BINAP	35	88	55	*S*
2[c]	(*R*)-BINAP	72	47	83	*R*
3	(*R*)-Cl-OMe-BIPHEP	45	80	46	*S*
4[c]	(*R*)-Cl-OMe-BIPHEP	72	36	91	*R*
5	(*R*)-OMe-BIPHEP	35	91	75	*S*
6	(*R*)-SYNPHOS	11	89	75	*S*
7	(*R*)-SEGPHOS	11	93	75	*S*
8[c]	(*R*)-SEGPHOS	12	58	88	*R*
9	(*R*)-DM-SEGPHOS	11	87	65	*S*

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), AgOTf (0.02 mmol), chiral ligand (0.012 mmol) in toluene (2 mL) at 90 °C. [b] Yield determined by ^{1}H NMR spectroscopy. [c] Added 2 equiv. of PhCOOH.

Table 2 Optimization of additives for the reaction of **1a** with **2a**[a]



Entry	Additive	Time (h)	Yield[b] (%)	ee (%)	*R*/*S*
1	$Cu(OTf)_2$	48	40	49	*S*
2	CuOTf	49	32	10	*S*
3	$Fe(OTf)_3$	20	81	78	*S*
4	$Fe(OTf)_2$	22	87	74	*S*
5	$Al(OTf)_3$	22	85	78	*S*
6	$Zn(OTf)_2$	20	60	76	*S*
7	AgOTf	11	93	75	*S*
8	$AgBF_4$	27	80	82	*S*
9	$AgSbF_6$	27	69	76	*S*
10	$AgPF_6$	48	85	82	*S*
11	AgOAc	48	4	21	*R*
12	Ag_2CO_3	48	4	7	*R*
13	CH_3COOH	72	3.3	17	*R*
14	PhCOOH	72	9	68	*R*
15	*p*-Br-C_6H_4COOH	72	3	39	*R*
16	*p*-Me-C_6H_4COOH	72	2.3	39	*R*
17	*p*-MeO-C_6H_4COOH	72	1.8	32	*R*
18	PhCOOK	72	3.5	15	*R*
19	—	72	4	12	*R*

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-SEGPHOS (0.012 mmol), additive (0.02 mmol) in toluene (2 mL) at 90 °C. [b] Yield determined by ^{1}H NMR spectroscopy.

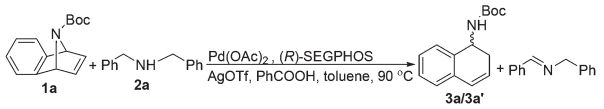
selectivity were drastically reduced (Table 2, entry 19). From the above observations, it has been observed that $AgPF_6$ is the most suitable Lewis acid. Also, the absolute configuration of the ring-opening product can be switched from *S* to *R* by using carboxylic acids.

In the above investigations, we have shown that the addition of benzoic acid as an additive results in the alteration in the absolute configuration of the ARO product. So, we further analyzed the reaction yield and enantioselectivity of the reaction by using the combination of AgOTf and different concentrations of benzoic acid as an additive (Table 3). It has been observed that 10% benzoic acid failed to give the *R* isomer and resulted in the *S* isomer in an excellent yield with high enantioselectivity (Table 3, entry 1). When 20%, 50% or 100% benzoic acid was used, the *R* isomer was obtained in an excellent yield with low to moderate enantioselectivities (Table 3, entries 2–4). Gratifyingly, the *R* isomer with improved enantioselectivity and appreciable yield was observed when 200% benzoic acid was used (Table 3, entry 5). On further increasing the concentration of benzoic acid, a drastic decrease in the reaction yield was observed but still with very high enantioselectivity (Table 3, entries 6–8). From these observations, it has been concluded that the *R* isomer can be obtained in the highest yield with good enantioselectivity when 200% benzoic acid was used as an additive along with AgOTf. It has also been proved that the carboxylic acids can alter the absolute configuration of the product when used as additives but they themselves cannot result into the product in good yield and high enantioselectivity in the absence of Lewis acids (Table 3, entries 9–13).

Next, the reaction of **1a** with **2a** was carried out under the optimized reaction conditions at different temperatures and it has been found that the reaction gave the highest yield and enantioselectivity at 90 °C. Later, we focused on to check whether the yield and enantioselectivity could be improved by using different solvents (Table 4). To our delight, the highest yield and excellent enantioselectivity were observed when 1,4-dioxane was used as a solvent (Table 4, entry 5).

Having obtained the optimized reaction conditions for the asymmetric ring-opening of **1a** through reductive transfer hydrogenation, we intended to analyze the reactivity of different secondary amines as a hydrogen source (Scheme 1). Dibenzyl amine **2a** resulted in **3a** in 91% yield with 93% ee. *N*-benzylethanamine **2b** and *N*-benzylpropan-2-amine **2c** performed well as reductants giving excellent yields and good enantioselectivities. *N*-benzyl-2-methylpropan-2-amine **2d** and cyclic secondary amines **2e** and **2f** also gave the expected product **3a** in moderate to very good yields with good enantioselectivities. Next, we carried out the transfer hydrogenation reaction using various aliphatic secondary amines as reductants and they also gave the expected product in moderate to good yields with appreciable enantioselectivities. Furthermore, the reaction was carried out using substituted dibenzylamines as reductants. Substituents like CH_3, F and Cl at the *para* position of dibenzylamine (**2j**, **2k**, and **2l**) performed well giving the product **3a** in very high yields and good enantioselectivities. A slight decrease in the enantioselectivity when methyl substituted bis (4-methylbenzyl)amine **2j** was used as a reductant may be attributed to the steric and electronic factor of the methyl group as the amine is involved in the transition state. The bromo group substituted at the *para* position **2m** could not increase the reaction yield. The fluoro group at *ortho* (**2n**) and *meta* (**2o**) positions maintained high enantioselectivity but drastically decreased the reaction yield. We tried the reaction of **1a** with phthalimide **2p** as the hydrogen source under the developed reaction conditions, but the desired product **3a** was obtained in a very low yield with 37% ee. Our attempt to carry

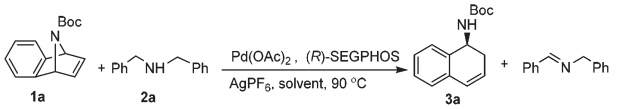
Table 3 Effect of different concentrations of PhCOOH on the reductive ARO of **1a** with **2a**[a]



Entry	AgOTf + PhCOOH	Time (h)	Yield[b] (%)	ee (%)	(*R*)/(*S*)
1	AgOTf + 10% PhCOOH	18	88	78	*S*
2	AgOTf	11	93	75	*S*
3	AgOTf + 20% PhCOOH	22	94	2	*R*
4	AgOTf + 50% PhCOOH	47	91	53	*R*
5	AgOTf + 100% PhCOOH	72	94	77	*R*
6	AgOTf + 200% PhCOOH	72	58	88	*R*
7	AgOTf + 300% PhCOOH	78	28	89	*R*
8	AgOTf + 400% PhCOOH	78	20	87	*R*
9[c]	10% PhCOOH	72	9	68	*R*
10[c]	20% PhCOOH	75	3	54	*R*
11[c]	50% PhCOOH	75	1.6	74	*R*
12[c]	100% PhCOOH	80	1.4	84	*R*
13[c]	200% PhCOOH	80	0.9	1	*R*

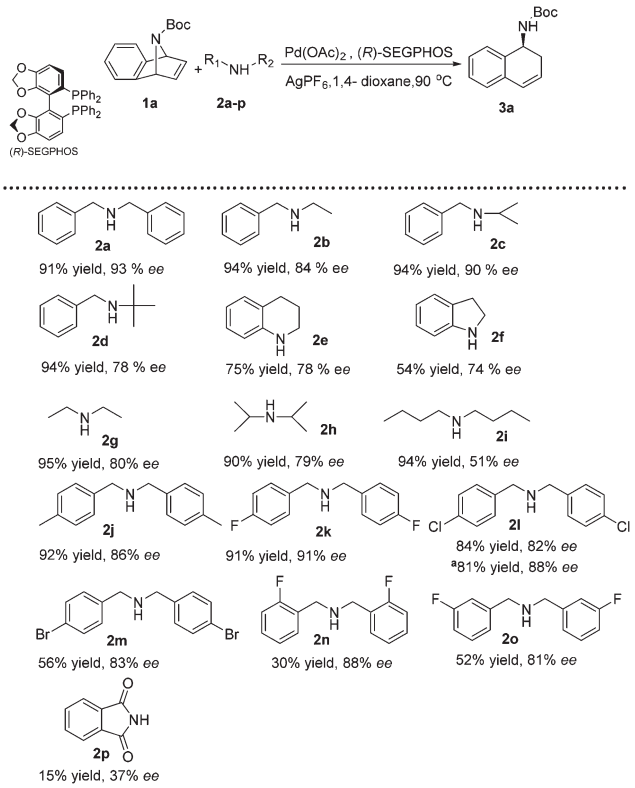
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-SEGPHOS (0.012 mmol), AgOTf (0.02 mmol), PhCOOH (as indicated in the table) in toluene (2 mL) at 90 °C. [b] Yield determined by ^1H NMR spectroscopy. [c] The reaction was carried out in the absence of AgOTf.

Table 4 Screening of different solvents and temperature[a]



Entry	Solvent	Time (h)	Yield[b] (%)	ee (%)	(*R*)/(*S*)
1	Toluene	48	85	82	*S*
2	THF	21	89	92	*S*
3	DME	21	91	91	*S*
4	DCE	38	75	83	*S*
5	1,4-Dioxane	14	91	93	*S*
6[c]	1,4-Dioxane	40	88	92	*S*
7[d]	1,4-Dioxane	6	87	90	*S*

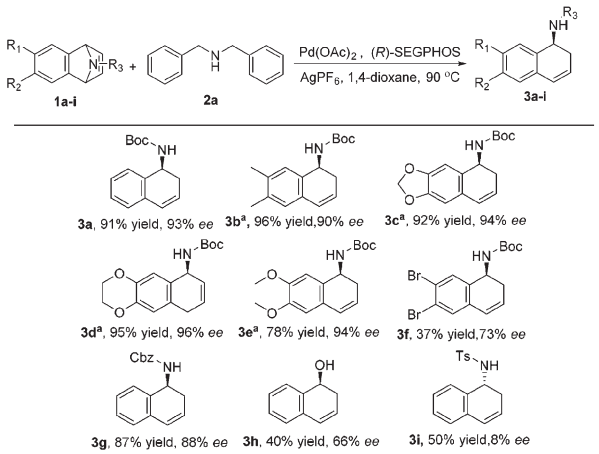
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-SEGPHOS (0.012 mmol), $AgPF_6$ (0.02 mmol) in solvent (2 mL) at 90 °C. [b] Yield determined by ^1H NMR spectroscopy. [c] Reaction temperature was 80 °C. [d] Reaction temperature was 100 °C.



Scheme 1 Asymmetric TH of **1a** by selected secondary amines. Reaction conditions: **1a** (0.2 mmol), **2a–p** (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-SEGPHOS (0.012 mmol), $AgPF_6$ (0.02 mmol) in 1,4-dioxane (2 mL) at 90 °C. Yield determined by ^{1}H NMR spectroscopy. [a]Reaction carried out at 60 °C.

out the transfer hydrogenation using primary amines as the hydrogen source was a disappointment as they resulted in a diminished yield with very low enantioselectivity.

From the above studies, it has been observed that the asymmetric ring-opening of azabenzonorbornadiene **1a** through reductive transfer hydrogenation can be successfully achieved by using different secondary amines as reductants. We next examined the reaction scope of the newly developed protocol with respect to aza/oxabicyclic alkenes (Scheme 2). Gratifyingly, electron donating groups on the azabenzonorbornadiene enhanced the reaction resulting in excellent yield and very high enantioselectivity (Scheme 2, **3b–d**). Dimethoxy substituted azabenzonorbornadiene performed well but the reaction yield was reduced to 78% with 94% ee (Scheme 2, **3e**). Cbz-protected azabenzonorbornadiene also reacted well and delivered the expected ARO product in a good yield with 88% ee (Scheme 2, **3g**). Our attempt to carry out the reaction using oxabenzonorbornadiene resulted in the product in a poor yield with 66% ee (Scheme 2, **3h**). Surprisingly, tosyl-azabenzonorbornadiene also participated in the reaction giving the product with reversed enantioselectivity but in a low yield with negligible enantioselectivity (Scheme 2, **3i**). The absolute configuration of the products were determined by comparing the

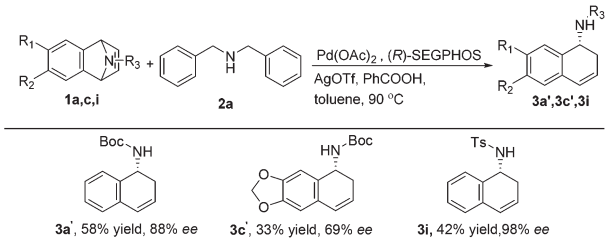


Scheme 2 Substrate scope of various aza/oxabenzonorbornadienes. Reaction conditions: Azabenzonorbornadiene (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-SEGPHOS (0.012 mmol), $AgPF_6$ (0.02 mmol) in 1,4-dioxane at 90 °C. Yield determined by ^{1}H NMR spectroscopy. [a]Reaction temperature was 80 °C.

characterization data such as ^{1}H NMR and HPLC spectra of the products with the one reported earlier.[14a]

We next carried out the ARO reaction using few azabenzonorbornadienes in the presence of benzoic acid as an additive (Scheme 3). Unsubstituted azabenzonorbornadiene resulted in the *R* isomer **3a′** in an average yield with 88% ee. The presence of electron donating groups yielded the *R* isomer **3c′** but in a reduced yield and moderate enantioselectivity. Tosyl-azabenzonorbornadiene performed well in the reaction resulting in **3i′** in 42% yield with excellent enantioselectivity.

In an attempt to investigate the reaction pathway of the newly developed protocol, we carried out the reaction of **1a** with a chiral secondary amine **2q** as the hydrogen source under the co-catalytic system of $Pd(OAc)_2$ and $AgPF_6$ using racemic (±)-BINAP as the ligand. Although the product **3a** could not be obtained in an isolable yield, we could get the *R*-isomer with 17% ee (Fig. 1a). This indicates that secondary amines also contribute in determining the absolute configuration of the transfer hydrogenation product.



Scheme 3 Substrate scope of azabenzonorbornadienes in the presence of benzoic acid. Reaction conditions: **1a,c,h** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-SEGPHOS (0.012 mmol), AgOTf (0.02 mmol), PhCOOH (0.4 mmol) in toluene (2 mL) at 90 °C. Yield determined by ^{1}H NMR spectroscopy.

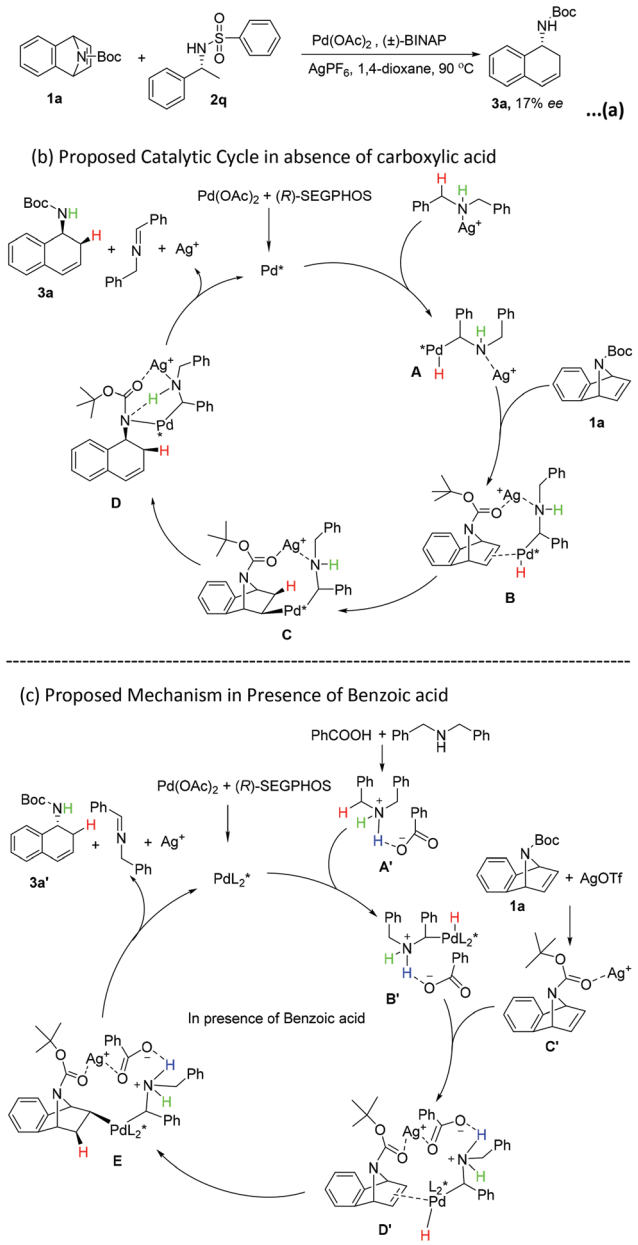


Fig. 1 Proposed reaction mechanism for the transfer hydrogenation of azabenzonorbornadiene **3a** with secondary amine **2a**.

A plausible mechanism has been reported for similar transfer hydrogenation using alcohol as the hydrogen source.[14a] However, the catalytic system and the hydrogen source being different and also based on the above studies using the chiral secondary amine, we have hypothesized another reaction pathway for the present transformation. The catalytic cycle commenced with the coordination of palladium acetate and (*R*)-SEGPHOS resulting in the chiral complex which in turn combines with the silver-amine complex to give intermediate **A**. Then it combines with **1a** to form the complex **B** that undergoes the addition of one hydrogen atom to the carbon–carbon double bond to form the complex **C**. Furthermore, **C** gets transformed into complex **D** which finally gives the product **3a** along with the corresponding imine (Fig. 1b). In the case of the transfer hydrogenation in the presence of benzoic acid, we have proposed the involvement of a transition state **D′** obtained by the insertion of a benzoate anion into the complex (Fig. 1c). This results in hydrogenation at the C3 position and binding of the Pd complex at the C2 position. This may bring about the changes in the orientation in which hydrogen approaches the nitrogen at the bridgehead position and hence results in the reversal of the absolute configuration.

Conclusions

In conclusion, we have demonstrated the asymmetric ring-opening of azabenzonorbornadienes through reductive transfer hydrogenation using the co-catalytic system of palladium and silver. Secondary amines were successfully used as the hydrogen source. The ring-opening products were obtained in high yields with good enantioselectivities. We have proved for the first time that the absolute configuration of the ARO product can be altered by using benzoic acid as an additive.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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