Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2017, **15**, 2359

Received 22nd January 2017,
Accepted 24th February 2017

DOI: 10.1039/c7ob00175d

rsc.li/obc

Palladium/zinc co-catalyzed asymmetric transfer hydrogenation of oxabenzonorbornadienes with alcohols as hydrogen sources†

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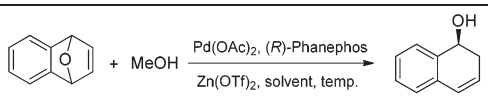
Asymmetric transfer hydrogenation of oxabenzonorbornadienes was realized by using alcohols as hydrogen sources under a co-catalytic system of palladium and zinc. Both primary and secondary alcohols could serve as reductants and afforded enantiomerically enriched 1,2-dihydronaphth-1-ol products with high optical purities.

Transition metal catalyzed transfer hydrogenation reactions have been widely applied in the synthesis of fine chemicals and pharmaceuticals because of the risk and inconvenience of using gaseous hydrogen. Rhodium, ruthenium, and iridium are frequently employed as transition metal catalysts; and alcohols and formic acid/trimethylamine mixtures are common hydrogen sources in transfer hydrogenation.[1] Among the alcohols, the use of isopropanol is the most common.[2] Although simple primary alcohols such as methanol and ethanol are more economical hydrogen sources, their application in asymmetric transfer hydrogenation is limited to the reduction of α,β-unsaturated ketones,[3] mainly because of their unfavorable oxidation potential compared with secondary alcohols. Thus, the development of asymmetric transfer hydrogenation by using simple primary alcohols is of broad interest.

Our group has a continuous interest in the asymmetric ring opening reactions of bicyclic alkenes, and the co-catalytic systems comprising chiral transition metal complexes and Lewis acids were proven to be extremely efficient.[4] Although the asymmetric reductive ring-opening reactions of bicyclic alkenes were previously studied by using DIBAL-H[5] and zinc powder[6] as reductants to give 1,2-dihydronaphth-1-ol, our group exclusively studied them by performing asymmetric transfer hydrogenation reactions. Most recently, our group has developed an unprecedented asymmetric transfer hydrogenation of azabenzonorbornadienes by using alcohols under the co-catalysis of palladium and zinc.[7] Accordingly, we envisioned that the asymmetric transfer hydrogenation of oxabenzonorbornadienes also could be realized by this kind of co-catalytic system to produce chiral 1,2-dihydronaphth-1-ol derivatives.

Our investigation commenced with the reaction of oxabenzonorbornadiene **1a** and methanol promoted by a previously established co-catalytic system that used $Pd(OAc)_2$ as a metal precursor, (*R*)-Phanephos as a chiral ligand, associated with $Zn(OTf)_2$ as the Lewis acid. To our delight, a good yield and high enantioselectivity were obtained (Table 1, entry 1). The deuterium-labeling experiment confirmed that methanol served as the hydrogen source (please see the ESI† for details). In order to improve the reaction yield by suppressing the generation of naphthalen-1-ol, several reaction solvents were screened. Although 1,4-dioxane gave a good yield of 80% with the ee unchanged (Table 1, entry 2), some other ether solvents such

Table 1 Optimization of reaction solvents and temperature[a]



1a **2a** **3aa**

Entry	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Toluene	r.t.	0.5	82	96
2	1,4-Dioxane	r.t.	0.3	80	96
3	MTBE	r.t.	0.8	66	96
4	DME	r.t.	0.3	57	96
5	DCE	r.t.	1	68	78
6	THF	r.t.	1	87	98
7	THF	0	17	55	98
8	THF	40	0.5	66	98

[a] Reaction conditions: **1a** (0.3 mmol), **1a**/**2a**/$Pd(OAc)_2$/(*R*)-Phanephos/$Zn(OTf)_2$(1 : 5 : 0.05 : 0.06 : 0.1) in solvent (2 mL) under argon for an indicated period of time. [b] Isolated yield by column chromatography. [c] Determined by HPLC with a Chiralcel OD-H column.

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†Electronic supplementary information (ESI) available: Experimental procedures, product characterization, copies of HPLC, ^1H and ^{13}C NMR spectra. CCDC 1508992 and 1526719. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob00175d

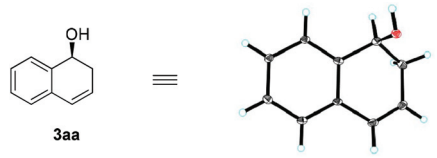


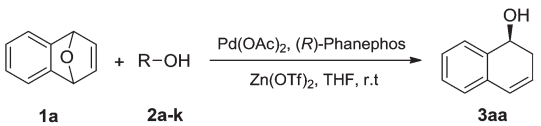
Fig. 1 The X-ray analysis of **3aa**.

as MTBE and DME both gave inferior results (Table 1, entries 3 and 4). DCE was also not suitable for the present reaction (Table 1, entry 5). The use of THF was proved to be helpful, which improved both the reaction yield and the enantioselectivity (Table 1, entry 6). Temperature reactions further confirmed that the ambient temperature was optimal (Table 1, entries 7 and 8). The reduction product **3aa** was determined to have the (*S*)-configuration by means of X-ray diffraction analysis of a single crystal (Fig. 1),[8] and its optical rotation was in agreement with that given in the literature and thus confirmed the absolute configuration.[9]

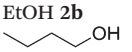
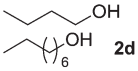
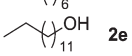
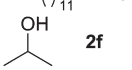
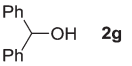
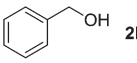
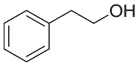
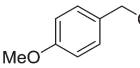
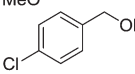
With the optimum reaction conditions in hand, various alcohols including aliphatic primary alcohols, secondary alcohols and aromatic alcohols were applied to present asymmetric transfer hydrogenation as hydrogen sources. As observed from the experimental results outlined in Table 2, all of the alcohols gave the desired products in excellent enantioselectivities, but the reaction yields were greatly affected by the types of alcohols used. For instance, all of the primary aliphatic alcohols reacted smoothly (Table 2, entries 1–5), and octanol strangely gave the best reaction yield. However, even isopropanol was frequently used as a hydrogen source in transfer hydrogenation, only 30% isolated yield was obtained in the present protocol albeit with excellent ee. By increasing the amount of isopropanol, the reaction yield was increased to 49% (Table 2, entry 6). In addition, diphenylmethanol also showed similar activity (Table 2, entry 7). In all cases of low yields of the reduction reaction, naphthalen-1-ol was generated as a by-product from oxabenzonorbornadiene directly. Primary aryl alcohols were also viable hydrogen sources for the asymmetric transfer hydrogenation and all gave satisfactory results (Table 2, entries 8–11).

To investigate the scope of oxabenzonorbornadienes, a range of oxabenzonorbornadienes were synthesized[10] and applied to the current reaction protocol (Table 3). Dibromo-substituted oxabenzonorbornadiene **1b** was compatible, and the bromo-groups that remained unreacted allowed further elaboration of the product (Table 3, entry 2). In addition, dimethyl-substituted oxabenzonorbornadiene **1c** also reacted smoothly to afford the desired products (Table 3, entry 3). Although the oxabenzonorbornadienes **1c–1f** with strong electron-donating groups reacted well, the corresponding reduction products

Table 2 Alcohol scope of asymmetric transfer hydrogenation[a]

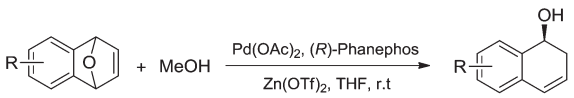


1a 2a-k 3aa

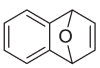
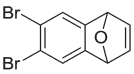
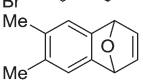
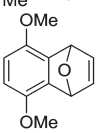
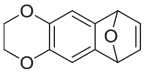
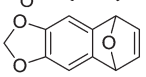
Entry	Alcohol	Time (h)	Yield[b] (%)	ee[c] (%)
1	MeOH **2a**	1	87	98
2	EtOH **2b**	0.5	66	98
3	 **2c**	0.4	79	98
4	 **2d**	0.5	91	98
5	 **2e**	0.2	89	95
6[d]	 **2f**	4	49	98
7[d]	 **2g**	2	39	98
8	 **2h**	0.5	90	98
9	 **2i**	0.2	84	98
10	 **2j**	0.5	71	98
11	 **2k**	0.2	83	98

[a] Reaction conditions: **1a** (0.3 mmol), **1a**/**2a–k**/$Pd(OAc)_2$/(*R*)-Phanephos/$Zn(OTf)_2$ (1 : 5 : 0.05 : 0.06 : 0.1) in THF (2 mL) at room temperature under argon for an indicated period of time. [b] Isolated yield by column chromatography. [c] Determined by HPLC with a Chiralcel OD-H column. [d] 20 equivalents (6.0 mmol) of alcohol were used.

Table 3 Asymmetric transfer hydrogenation of various oxabenzonorbornadienes **1a–f** with **2a**[a]

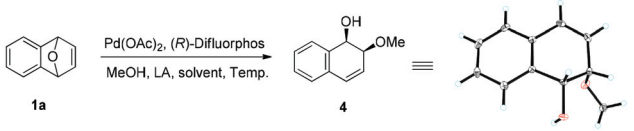


1a-f 2a 3aa-af

Entry	**1a–f**	Time (h)	Yield[b] (%)	ee[c] (%)
1	 **1a**	1	87	98
2	 **1b**	0.5	78	97
3	 **1c**	0.8	81	98
4[d]	 **1d**	2.5	70	97
5[d]	 **1e**	10	67	98
6[d]	 **1f**	6	35	98

[a] Reaction conditions: **1a–f** (0.3 mmol), **1a–f**/**2a**/$Pd(OAc)_2$/(*R*)-Phanephos/$Zn(OTf)_2$ (1 : 5 : 0.05 : 0.06 : 0.1) in THF (2 mL) at room temperature under argon for an indicated period of time. [b] Isolated yield by column chromatography. [c] Determined by HPLC with a Chiralcel OD-H or OJ-H column. [d] The reaction was performed at 0 °C.

Table 4 Asymmetric additional reaction of **1a** with methanol[a]



Entry	Lewis acid	Solvent	T (°C)	Yield[b] (%)	ee[c] (%)
1	$AgBF_4$	Toluene	60	Trace	—
2	$Zn(OTf)_2$	Toluene	40	42	7
3	$Zn(OTf)_2$	1,2-Dichloroethane	40	17	94

[a] Reaction conditions: **1a** (0.3 mmol), **1a**/**2a**/$Pd(OAc)_2$/(*R*)-Difluorphos/LA (1 : 5 : 0.05 : 0.06 : 0.1) in solvent (2 mL) under argon. [b] Isolated yield by column chromatography. [c] Determined by HPLC with a Chiralcel OD-H column.

were not stable enough and resulted in naphthalene derivatives by elimination of the hydroxyl group.

Therefore, we conducted these reactions at a lower temperature during a relatively longer reaction time to ensure the complete consumption of the starting material (Table 3, entries 4–6).

As we studied previously, the asymmetric additional reactions of oxabenzonorbornadienes with methanol were briefly investigated by switching the chiral ligand and Lewis acid, which are the main factors that affect the chemoselectivity of the reaction.[7] By using the established asymmetric additional ring opening reaction conditions of azabenzonorbornadienes employing $Pd(OAc)_2$, (*R*)-Difluorphos and $AgBF_4$,[7] only a trace of the desired product **4** was observed together with a large amount of 1-naphthol (Table 4, entry 1). We reasoned that oxabenzonorbornadiene was more reactive than the corresponding azabenzonorbornadiene,[11] and the former could generate 1-naphthol more easily in the presence of a harsh Lewis acid. By switching to $Zn(OTf)_2$, a moderate yield was obtained but the enantioselectivity was poor (Table 4, entry 2). And the reaction that was carried out in 1,2-dichloroethane gave an excellent reaction enantioselectivity, but decreased the yield (Table 4, entry 3). The absolute configuration of product **4** was determined to be 1*S*,2*R* by X-ray diffraction analysis of a single crystal.[12] Further investigations of the reaction are in progress.

Conclusions

In summary, we have established an effective co-catalytic system comprising $Pd(OAc)_2$, (*R*)-Phanephos and $Zn(OTf)_2$ that enabled a highly enantioselective transfer hydrogenation reaction of oxabenzonorbornadienes. Besides methanol and ethanol, a wide range of other alkyl alcohols and aryl alcohols are all suitable hydrogen sources, and various oxabenzonorbornadienes showed good tolerance. Applications of the present co-catalytic system in the asymmetric transfer hydrogenation of other unsaturated alkenes are currently underway in our laboratory.

Acknowledgements

We thank the National Natural Science Foundation of China (21572198, 21362043, 21302162) and the Department of Education of Yunnan Province (ZD2015012) for financial support.

Notes and references

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12 X-ray crystallographic data of **4** have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 1526719.

