Received: 15 September 2016 | Revised: 13 December 2016 | Accepted: 19 December 2016

DOI: 10.1002/chir.22699

REGULAR ARTICLE

WILEY

An efficient and enantioselective Michael addition of aromatic oximes to α,β-unsaturated aldehydes promoted by a chiral diamine catalyst derived from α,α-diphenyl prolinol

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Abstract

Chiral diamine catalysts 11a–e derived from α,α-diphenyl prolinol were prepared and successfully applied to the Michael addition of aromatic oximes to α,β-unsaturated aldehydes in mediocre to good yields (up to 78%) and good to high enantioselectivities (up to 93% *ee*).

KEYWORDS

aromatic oxime, diamine catalyst, Michael reaction, organocatalysis, α,β-unsaturated aldehyde

1 | INTRODUCTION

Over the past years, asymmetric organocatalysis has made significant progress in the field of organic synthesis.[1-10] Discovery of new catalysts has drawn much attention from chemists. Among those organic catalysts, proline-derived catalysts, such as α,α-diaryl-(*S*)-prolinol[11] and the corresponding silyl ether derivatives,[12,13] as well as secondary amine-(thio)ureas or squaramides,[14] have been extensively applied in the field of aminocatalysis, especially the diaryl prolinol silyl ethers, which were used as general catalysts in activating aldehydes via the enamine or iminium transition state.[15-18] Generally, this privileged skeleton included second amine as a single catalytic center and diaryl prolinol silyl ether as a special steric and regioselective controlling group. In recent years, diamine catalysts derived from (*S*)-proline have been widely used in asymmetric organocatalysis.[19-25] Based on the diaryl segment of α,α-diaryl-(*S*)-prolinol with good enantioinducing ability,[26,27] combined with our work[28-32] with the secondary amine catalysis, we envisioned that chiral diamine catalysts derived from α,α-diphenyl prolinol would be a better new type of catalyst for asymmetric reactions and chiral ligands for organometallic catalysis (Figure 1). As far as we know, the synthesis and applications of such diamine catalysts derived from α,α-diphenyl prolinol skeleton were still rare.[33] In 2008, Juaristi[34] reported the reduction of prochiral ketones promoted by oxazaborolidine derivatives prepared from α,α-diphenyl-(*S*)-prolinol. In 2013, a similar work was accomplished by Asami's group.[35] Compared to the single catalytic center and regioselective controlling group of α,α-diphenyl-(*S*)-prolinol silyl ether, we recognized the diamine catalysts derived from α,α-diphenyl prolinol, bearing a secondary amine of pyrrolidine moiety, diphenyl segment, and another amino group on the chiral scaffold, in which the pyrrolidine amine might activate the reaction substrate via an enamine or an iminium mechanism, the diphenly segment having good enantioinducing ability and the diamine would activate substrate with good stereoselectivity (Figure 1).

Enantioselective Michael addition is one of the most important reactions in new bond (C-C, C-O, C-S, C-P, etc.) formations, and many kinds of efficient chiral organocatalysts

FIGURE 1 From α,α-diphenylprolinol silyl ether to diamine catalysts, general activation mode of diamine catalyst

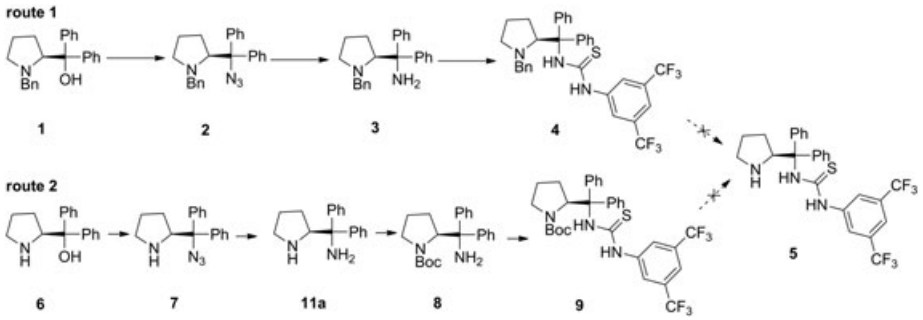


FIGURE 2 Efforts for the preparations of second amine thiourea bifunctional catalyst **5**

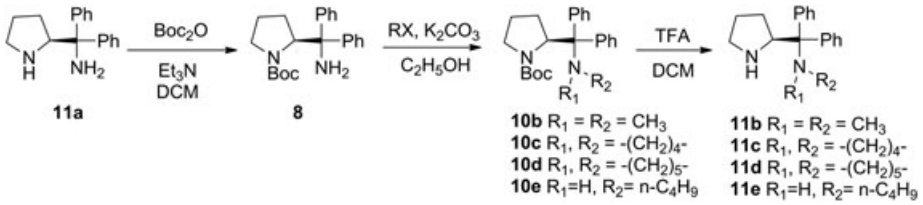
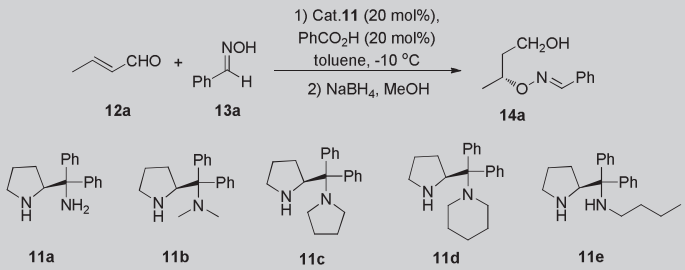


FIGURE 3 Preparation of diamine catalysts **11**

TABLE 1 Catalyst screenings[a]



Entry	Cat.	Time (d)	Yield[b] (%)	*ee*[c] (%)
1	**11a**	4	54	71
2	**11b**	1	73	22
3[d]	**11b**	4	79	48
4	**11c**	1	97	25
5	**11d**	4	93	25
6	**11e**	4	72	93

[a]Unless otherwise specified, all the reactions were performed with crotonaldehyde **12a** (0.25 mmol), (*E*)-benzaldehyde oxime **13a** (0.75 mmol), $PhCO_2H$ (0.05 mmol) and **cat. 11** (0.05 mmol) in toluene (1 ml) at –10 °C, after completion of the reaction, MeOH (0.5 mL) and $NaBH_4$ (0.375 mmol) was added, after 20 min, the reduction was quenched with NH_4Cl (aq.) and extracted with DCM (3 x 1 mL).

[b]Isolated yield after silica gel column chromatography.

[c]Determined by chiral HPLC analysis.

[d]The reaction was conducted at –30 °C.

have been developed for such reactions,[36-39] and Oxa-Michael reaction is a good way to build new chiral C-O bonds. Jørgensen's group[40,41] first reported the enantioselective Michael reaction of aromatic oximes to α,β-unsaturated aldehydes catalyzed by α,α-diaryl prolinol silyl ether, and subsequent in situ reduction to give optically active β-diols in excellent enantioselectivities. In 2010, Pihko's group[42] reported the enantioselective Michael reaction of aromatic oximes to α,β-unsaturated aldehydes catalyzed by α,α-diaryl prolinol silyl ether to obtain the addition products, which rapidly cyclized into stable isoxazoline under acidic conditions with good to excellent enantioselectivities. In those reactions, aromatic oximes are good nucleophiles[43] and α,β-unsaturated aldehydes are good Michael receptors.[44] We envisioned that the diamine catalysts, bearing α,α-diphenyl prolinol silyl ether and diamine catalysts, would catalyze aromatic oximes and α,β-unsaturated aldehydes with good results. To our knowledge, diamine catalysts derived from α,α-diphenyl prolinol have not drawn enough attention on asymmetric organocatalysis yet. Herein, we report the enantioselective Michael reaction of aromatic oximes to α,β-unsaturated aldehydes catalyzed by secondary–secondary diamine catalyst.

2 | RESULTS AND DISCUSSION

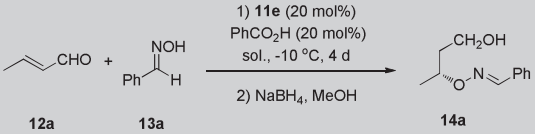
Before our study, we tried for years and failed to prepare the "ideal" second amine thiourea bifunctional catalyst **5** which was derived from α,α-diphenyl prolinol. At the beginning of our work, we designed two routes to synthesize catalyst **5**. We first used N-Bn protected α,α-diphenyl prolinol[45] as a starting material and N-Bn protected thiourea was obtained. However, no desired thiourea bifunctional catalyst **5** was obtained by hydrogenation deprotection of **4** (Figure 2, route 1). When prepared according to route 2, N-Boc protected thiourea **9** was smoothly obtained. Deprotection of thiourea **9** also failed to give the title compound **5** (Figure 2, route 2). The result was consistent with that of Juaristi's group.[33]

Then we turned our attention to prepare chiral diamine catalysts. We first prepared the secondary–primary diamine catalyst **11a** according to the literature.[46,47] N-Boc protected diamine **8** was prepared according to the literature.[48] Treating **8** with halides,[49] **10b–e** were obtained. When **8** was reacted with iodomethane, 1,4-dibromobutane, or 1,5-dibromopentane, the disubstituted **10b–d** were obtained as expected. However, when 1-bromobutane was used as reactant, only monosubstituted catalyst **10e** was obtained even if a large quantity of 1-bromobutane (4 equiv.) was used. The possible reason might be the steric hindrances of the diphenyl segment and *n*-butyl group. Finally, the title catalysts **11b–e** were successfully obtained by deprotection with trifluoroacetic acid in dichloromethane, as expected (Figure 3).

We initiated our work by evaluating the model reaction between crotonaldehyde **12a** and (*E*)-benzaldehyde oxime **13a** in the presence of diamine catalysts **11a–e** and the results are summarized in Table 1. Catalysts **11b–d** gave good to excellent yields while poor enantioselectivities (73–97% yield, 22–25% enantiomeric excess, *ee*; Table 1, entries 2, 4–5) at –10 °C. Decreasing the temperature to –30 °C, catalyst **11b** gave only moderate enantioselectivity (48% *ee*; Table 1, entry 3). Catalyst **11a** gave moderate result (54% yield, 71% *ee*; Table 1, entry 1). Secondary–secondary diamine catalyst **11e** gave good yield and excellent enantioselectivity (72% yield, 93% *ee*; Table 1, entry 6) and was chosen for further investigations.

To further optimize the reaction conditions, a series of solvents were evaluated. Arene solvents afforded moderate

TABLE 2 Solvent screenings[a]



12a 13a 14a

Entry	Sol.	Yield[b] (%)	*ee*[c] (%)
1	Toluene	72	93
2	Chlorobenzene	57	87
3	*o*-xylene	78	90
4	*m*-xylene	79	91
5	Mesitylene	77	91
6	DCM	51	85
7	$CHCl_3$	47	89
8	DCE	48	84
9	Hexane	56	71
10	THF	5	92
11	Et_2O	9	93
12	MTBE	9	93
13	MeCN	14	61
14	DMF	Trace	nd[d]
15	Diethyl carbonate	40	90

[a]Unless otherwise specified, all the reactions were performed with crotonaldehyde **12a** (0.25 mmol), (*E*)-benzaldehyde oxime **13a** (0.75 mmol), $PhCO_2H$ (0.05 mmol) and **11e** (0.05 mmol) in solvent (1 ml) at –10 °C for 4 days, after completion of the reaction, MeOH (0.5 mL) and $NaBH_4$ (0.375 mmol) was added, after 20 min, the reduction was quenched with NH_4Cl (aq.) and extracted with DCM (3 x 1 mL).

[b]Isolated yield after silica gel column chromatography.

[c]Determined by chiral HPLC analysis.

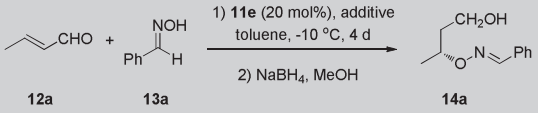
[d]Not determined.

to good yields and good to excellent enantioselectivities (57–79% yield, 87–93% *ee*; Table 2, entries 1–5). Halohydrocarbon solvents, such as DCM, $CHCl_3$, DCE, gave moderate yields and good enantioselectivities (47–51% yield, 84–89% *ee*; Table 2, entries 6–8). Excellent enantioselectivities were obtained when the reaction was performed in ether solvents with poor yields (5–9% yield, 92–93% *ee*; Table 2, entries 10–12). No desired product was detected when performed in DMF (Table 2, entry 14). The possible reason might be the strong polarity of DMF. Diethyl carbonate gave moderate yield and excellent enantioselectivity (40% yield, 90% *ee*; Table 2, entry 15). Toluene gave the highest enantioselectivity and good yield (72% yield, 93% *ee*; Table 2, entry 1) and was chosen as the most suitable solvent.

Amine activations are generally via an enamine or an iminium transition state. So a series of acid additives were also studied and the results were shown in Table 3. The reaction gave 63% yield and 89% *ee* without any additive (Table 3, entry 1). Strong Brønsted acid additives such as TFA and CF_3SO_3H gave relatively lower yields and enantioselectivities (41–78% yield, 32–33% *ee*; Table 3, entries 2, 3). A wide range of benzoic acids were also investigated and the results indicated that benzoic without substituent on the phenyl was the most promising additive and the best result was afforded (72% yield, 93% *ee*; Table 3, entry 5), benzoic acid with electron-withdrawing groups or electron-donating groups gave both lower yields and enantioselectivities (28–63% yield, 65–90% *ee*; Table 3, entries 6–11). Chiral acids such as (*R/S*)-BINOL-phosphoric acid and (*D/L*)-camphorsulfonic acid afforded relatively poor yields and lower enantioselectivities (10–31% yield, 59–88% *ee*; Table 3, entries 12–15). The loading of additive was also studied and increasing or lowering the amount had little effect on the enantioselectivities (63–80% yield, 86–93% *ee*; Table 3, entries 1, 5, 16–18).

Based on those positive results, other reaction parameters, such as the molar ratio of substrate **12a** to **13a**,

TABLE 3 Additive screenings[a]



12a 13a 14a

Entry	Additive	Yield[b] (%)	*ee*[c] (%)
1	No	63	89
2	TFA	78	32
3	CF_3SO_3H	41	33
4	AcOH	61	89
5	$PhCO_2H$	72	93
6	2-OH-$PhCO_2H$	42	80
7	2-NO_2-$PhCO_2H$	28	65
8	4-MeO-$PhCO_2H$	63	90
9	2,3-*di*-OH-$PhCO_2H$	38	80
10	2,6-*di*-F-$PhCO_2H$	39	78
11	3,5-*di*-NO_2-$PhCO_2H$	42	67
12	(*R*)-BINOL-phosphoric acid	10	59
13	(*S*)-BINOL-phosphoric acid	12	77
14	(*D*)-Camphorsulfonic acid	26	87
15	(*L*)-Camphorsulfonic acid	31	88
16[d]	$PhCO_2H$	80	90
17[e]	$PhCO_2H$	75	88
18[f]	$PhCO_2H$	77	86

[a]Unless otherwise specified, all the reactions were performed with crotonaldehyde **12a** (0.25 mmol), (*E*)-benzaldehyde oxime **13a** (0.75 mmol), additive (0.05 mmol) and **11e** (0.05 mmol) in toluene (1 ml) at –10 °C for 4 days, after completion of the reaction, MeOH (0.5 mL) and $NaBH_4$ (0.375 mmol) was added, after 20 min, the reduction was quenched with NH_4Cl (aq.) and extracted with DCM (3 x 1 mL).

[b]Isolated yield after silica gel column chromatography.

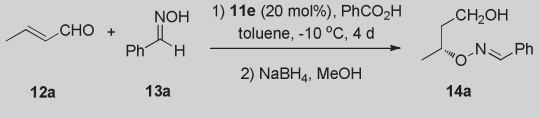
[c]Determined by chiral HPLC analysis.

[d]0.025 mmol $PhCO_2H$ was added.

[e]0.075 mmol $PhCO_2H$ was added.

[f]0.1 mmol $PhCO_2H$ was added.

TABLE 4 Optimization of reaction conditions[a]



12a 13a 14a

Entry	12a:13a	T (°C)	Yield[b] (%)	*ee*[c] (%)
1	1:3	-10	72	93
2	1:2	-10	60	89
3	1:1	-10	35	89
4	2:1	-10	39	89
5	3:1	-10	40	88
6[d]	1:3	-10	70	86
7[e]	1:3	-10	65	90
8	1:3	0	90	87
9	1:3	-20	38	87

[a]Unless otherwise specified, all the reactions were performed with crotonaldehyde **12a**, (*E*)-benzaldehyde oxime **13a**, additive (0.05 mmol) and **11e** (0.05 mmol) in toluene (1 ml) at –10 °C for 4 days, after completion of the reaction, MeOH (0.5 mL) and $NaBH_4$ was added, after 20 min, the reduction was quenched with NH_4Cl (aq.) and extracted with DCM (3 x 1 mL).

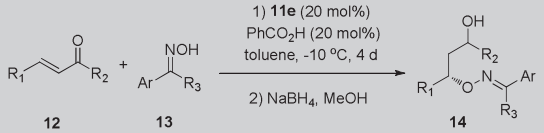
[b]Isolated yield after silica gel column chromatography.

[c]Determined by chiral HPLC analysis.

[d]0.5 ml toluene was added.

[e]2 ml toluene was added.

TABLE 5 Scope of substrates[a]



Entry	R_1	R_2	Ar	R_3	14	Yield[b] (%)	ee[c] (%)
1	CH_3	H	C_6H_5	H	**14a**	72	93
2	CH_3	H	2-FC_6H_4	H	**14b**	61	84
3	CH_3	H	2-ClC_6H_4	H	**14c**	77	83
4	CH_3	H	2-$MeOC_6H_4$	H	**14d**	41	89
5	CH_3	H	3-ClC_6H_4	H	**14e**	74	83
6	CH_3	H	3-BrC_6H_4	H	**14f**	65	84
7	CH_3	H	3-$MeOC_6H_4$	H	**14g**	62	86
8	CH_3	H	4-MeC_6H_4	H	**14h**	74	89
9	CH_3	H	4-$MeOC_6H_4$	H	**14i**	78	89
10	CH_3	H	4-$NO_2C_6H_4$	H	-	Trace	nd[e]
11	CH_3	H	4-FC_6H_4	H	**14k**	61	85
12	CH_3	H	4-ClC_6H_4	H	**14l**	48	85
13	CH_3	H	3,4,5-$(MeO)_3C_6H_2$	H	**14m**	29	92
14	CH_3	H	4-Py	H	-	Trace	nd[e]
15	CH_3	H	C_6H_5	Me	**14o**	19	85
16	C_2H_5	H	C_6H_5	H	**14p**	65	84
17	*n*-C_3H_7	H	C_6H_5	H	**14q**	59	85
18	$CO_2C_2H_5$	H	C_6H_5	H	**14r**	14	73
19	C_6H_5	H	C_6H_5	H	-	nr[d]	nd[e]
20	CH_3	CH_3	C_6H_5	H	-	nr[d]	nd[e]

[a]Unless otherwise specified, all the reactions were performed with **12** (0.25 mmol), **13** (0.75 mmol), $PhCO_2H$ (0.05 mmol) and **11e** (0.05 mmol) in toluene (1 ml) at –10 °C for 4 days, after completion of the reaction, MeOH (0.5 mL) and $NaBH_4$ (0.375 mmol) was added, after 20 min, the reduction was quenched with NH_4Cl (aq.) and extracted with DCM (3 x 1 mL).

[b]Isolated yield after silica gel column chromatography.

[c]Determined by chiral HPLC analysis.

[d]No reaction.

[e]Not determined.

concentrations of reactants and temperature were further studied. As shown in Table 4, tuning the molar ratio of substrate **12a** to **13a** significantly affected the yields, while slightly affecting the *ee* values (35–72% yield, 88–93% *ee*; Table 4, entries 1–5). Increasing or lowering concentrations have less effect on the results (65–72% yield, 86–93% *ee*; Table 4, entries 1, 6, 7). Raising the temperature to 0 °C, the yield was increased to 90% with a lower enantioselectivity (87% *ee*; Table 4, entry 8). Lowering the temperature to –20 °C, the yield decreased (38% yield, 87% *ee*; Table 4, entry 9). On the basis of those results, we conducted the reaction under the optimal conditions as: 3 equiv. of **13**, 20 mol% $PhCO_2H$ as acid additive, with 20 mol% catalyst **11e** in toluene at –10 °C for 4 days.

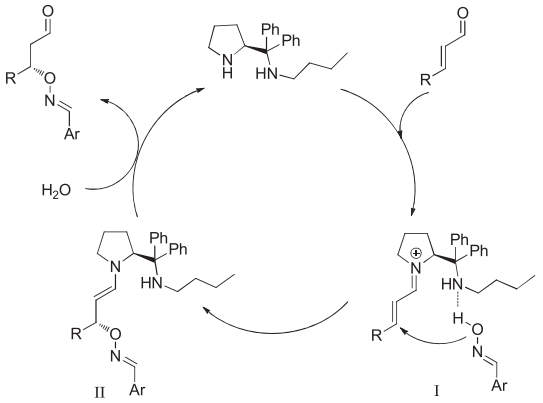


FIGURE 4 A probable bifunctional mechanism for the reaction

Under the optimized conditions, the substrate scope was further evaluated, and the results are summarized in Table 5. The positions of the substituents on the oximes aromatic ring have some influence on the enantioselectivities. The ortho- and meta-position substituted oximes gave moderate to good yields and good to excellent enantioselectivities (41–77% yield, 83–89% *ee*; Table 5, entries 2–7). Electron donating substituents at para-position oximes gave good results (74–78% yield, 89% *ee*; Table 5, entries 8, 9); electron-withdrawing substituents such as F- and Cl- at para-position gave moderate yields and good enantioselectivities (48–61% yield, 85% *ee*; Table 5, entries 11, 12). No desired product was detected with 4-NO_2-benzaldehyde oxime and 4-pyridinecarboxaldehyde oxime as reactants, and the possible reason might be their poor solubilities in toluene (Table 5, entries 10, 14). Acetophenone oxime gave relatively lower yield and good enantioselectivity (19% yield, 85% *ee*; Table 5, entry 15). Several α,β-unsaturated aldehydes were evaluated under the optimized conditions. Crotonaldehyde, trans-2-pentenal and trans-2-hexenal gave moderate to good yields and good to excellent enantioselectivities (59–72% yield, 84–93% *ee*; Table 5, entries 1, 16, 17). Ethyl trans-4-oxo-2-butenoate also gave good enantioselectivity, but poor yield (14% yield, 73% *ee*; Table 5, entry 18). It should be noted that cinnamaldehyde and 3-penten-2-one did not react under the optimized conditions (Table 5, entries 19–20).

A probable bifunctional mechanism for the reaction was proposed (Figure 4). We presumed that the secondary amine of pyrrolidine moiety of catalyst **11e** might activate the α,β-unsaturated aldehydes via the formation of an iminium ion **I** while the another secondary amine might activate the nucleophilic oxime via hydrogen bonding. Then **I** undergoes the conjugate addition and thus renders an enamine intermediate **II**. A final hydrolysis step releases both the Michael addition product and the amine catalyst. We determined the specific rotation of the Michael products and compared it with previous the literature,[40] the absolute stereochemistry of the products is *R* configuration.

3 | CONCLUSION

In conclusion, we synthesized a series of chiral diamine catalysts derived from α,α-diphenyl prolinol, and those catalysts were well applied to the Michael reaction of aromatic oximes to α,β-unsaturated aldehydes. The products were obtained in mediocre to good yields (up to 78%) and good to excellent enantioselectivities (up to 93% *ee*).

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SUPPORTING INFORMATION

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How to cite this article: Chen F, Ren H-X, Yang Y, et al. An efficient and enantioselective Michael addition of aromatic oximes to *α,β*-unsaturated aldehydes promoted by a chiral diamine catalyst derived from *α,α*-diphenyl prolinol. *Chirality*. 2017. https://doi.org/10.1002/chir.22699