Effective construction of quaternary stereocenters by highly enantioselective α-amination of branched aldehydes†

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A highly efficient enantioselective α-amination of branched aldehydes with azadicarboxylates promoted by chiral proline-derived amide thiourea bifunctional catalysts was developed for the first time, affording the adducts bearing quaternary stereogenic centers with excellent yields (up to 99%) and enantioselectivities (up to 97% ee).

Introduction

Optically active nitrogen-containing compounds are versatile and fascinating building blocks in organic synthesis.[1] Particularly, those with chiral quaternary stereogenic centers are widely used in the preparation of natural products, biologically active molecules and pharmaceuticals.[2] Over the past years, numerous strategies have been developed for the construction of these interesting structures, typical examples include the reaction of 2-oxindoles[3] with azadicarboxylates, the enantioselective α-amination of cyanoacetates,[4] alkylidene cyanoacetates[5] and branched aldehydes.[6,7] Among them, the amination of branched aldehydes is one of the straightforward methods to access nitrogen-containing compounds with quaternary stereocenters.[8] In 2003, Bräse and co-workers[6] first reported the α-amination of branched aldehydes with azadicarboxylates catalyzed by 50 mol% L-proline in moderate results, and recently, an improved result was obtained for the same reaction with the aid of microwave irradiation.[7] Barbas[9] applied the α-amination of 3-(4-bromophenyl)-2-methylpropanal catalyzed by chiral L-proline-derived tetrazole to construct LFA-1 antagonist BIRT-377 in 95% yield and 80% ee, and the amino-aldehyde was obtained in >99% ee after recrystallization. To the best of our knowledge, the α-aminations of simple and unsubstituted chain aldehydes are well established,[10] while the highly effective reaction of α,α-disubstituted aldehydes is less exploited and it is still highly challenging and desirable to develop new efficient catalytic systems for this transformation.

Bifunctional thiourea catalysts, which are powerful tools to simultaneously activate both donors and acceptors, have been investigated extensively in asymmetric reactions.[11] Primary and tertiary amine-thioureas have been well identified as powerful catalysts,[12] while the secondary amine-thioureas, especially catalysts **1a–1d** (Fig. 1) with two catalytic sites of chiral thiourea and

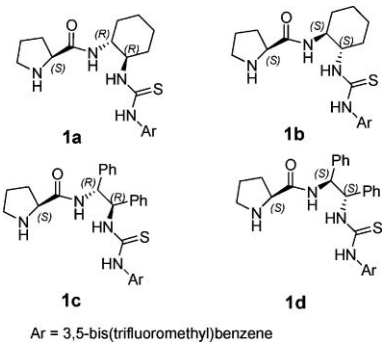

Fig. 1 Secondary amine-thiourea bifunctional catalysts.

L-prolic amide skeleton haven't drawn enough attention[13] except for in our recent works on asymmetric Michael additions and α-amination of simple aldehydes.[14a,14b,14e] As a part of our continuing interest in asymmetric synthesis,[14] herein, we wish to report the further application of these chiral proline amide-thiourea bifunctional catalysts in the promotion of the enantioselective α-amination of branched aldehydes with azodicarboxylates.

Results and discussion

To determine the optimal asymmetric α-amination reaction conditions, 2-phenylpropionaldehyde (**2a**) and diethyl azadicarboxylate (DEAD) (**3a**) were used as model reactants and the results are summarized in Table 1. All catalysts were screened in CH_3CN, moderate to excellent yields (75–96%) and good enantioselectivities (46–85% ee) were achieved (Table 1, entries 1–4). Comparatively, catalyst **1a**, bearing an *R*,*R*-linker, gave a better yield and enantioselectivity (Table 1, entry 1) probably due to the compatibility of the two catalytic chiral centers, and was chosen for further optimization.

Then a series of solvents were evaluated and the results are listed in Table 1. The results revealed that enantioselectivities and yields are highly variable with solvents. In less polar solvents such as CH_2Cl_2, DCE, $CHCl_3$, **1a** delivered excellent yields (up to 96%) and good enantioselectivities (up to 87% ee) (Table 1, entries 5–9). Comparatively, when the reaction was carried out in polar solvent such as MeOH, only poor yield (35%) and moderate enantioselectivity (66% ee) were obtained (Table 1, entry 14). These results indicated that CH_2Cl_2 is a suitable candidate solvent for this reaction (Table 1, entry 7). A wide range of acid and base additives were also investigated.[15] The results indicated that *o*-hydroxybenzoic acid was the most promising additive and afforded the best result in both yield and enantioselectivity (Table 1, entry 15, 99% yield and 90% ee) and was selected for further studies.

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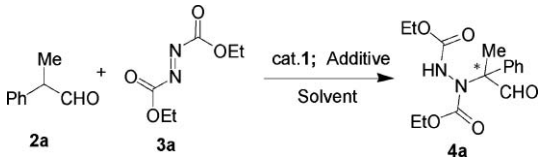
Table 1 Optimizing the reaction conditions[a]



Entry	Catalyst	Solvent	Additive	Temp./°C	Cat. Loading (%)	Time/h	Yield (%)[b]	ee (%)[c]
1	**1a**	CH_3CN	TFA	25	20	20.5	94	85(*R*)
2	**1b**	CH_3CN	TFA	25	20	27	75	49(*R*)
3	**1c**	CH_3CN	TFA	25	20	15.5	84	66(*R*)
4	**1d**	CH_3CN	TFA	25	20	20.5	96	46(*R*)
5	**1a**	toluene	TFA	25	20	11	88	79
6	**1a**	cyclohexane	TFA	25	20	11	99	81
7	**1a**	DCM	TFA	25	20	8.5	96	87
8	**1a**	CH_2ClCH_2Cl	TFA	25	20	21	87	87
9	**1a**	$CHCl_3$	TFA	25	20	11	80	84
10	**1a**	Et_2O	TFA	25	20	3.5	85	79
11	**1a**	THF	TFA	25	20	11	46	72
12	**1a**	dioxane	TFA	25	20	11	84	79
13	**1a**	DMF	TFA	25	20	49	85	70
14	**1a**	MeOH	TFA	25	20	26	35	66
15	**1a**	DCM	2-OHPhCOOH	25	20	1	99	90
16	**1a**	DCM	2-OHPhCOOH	0	20	6	91	93
17	**1a**	DCM	2-OHPhCOOH	0	10	21.5	88	95
18	**1a**	DCM	2-OHPhCOOH	0	5	47.5	77	96
19[d]	**1a**	DCM	2-OHPhCOOH	0	10	23	96	96

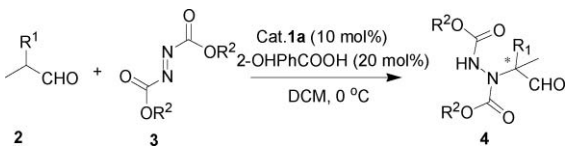
[a] Unless otherwise specified, all reactions were carried out with **2a** (0.30 mmol), **3a** (0.20 mmol), the catalyst **1** in the specified solvent (1.0 mL) and additive (the same eq. as catalyst). [b] Isolated yield. [c] Determined by HPLC with a Chiralpak-AS column and the absolute configuration of **4a** was assigned as *R*[6c] [d] Additive (0.02 mmol).

Other parameters such as temperature, catalyst loading, amount of **2a** and additive loading were also investigated.[15] The reaction temperature has a slight effect on the enantioselectivities. When the reaction was carried out at 0 °C, the enantioselectivity increased slightly (Table 1, entry 16). Decreasing the catalyst loading to 10 mol% (Table 1, entry 17), the enantioselectivity was increased to 95% ee. Acid additive loading also affected the yields, and 20 mol% *o*-hydroxybenzoic acid gave the best result (Table 1, entries 17 *vs.* 19, 96% yield, 96% ee). Through those screenings, the optimized reaction conditions were found to be reaction of 1.0 eq. azodicarboxylate with 1.5 eq. **2a**, in the presence of 10 mol% of **1a** and 20 mol% of *o*-hydroxybenzoic acid in dichloromethane at 0 °C.

Finally, the scope of the branched aldehydes with different azodicarboxylates under the optimized reaction conditions were evaluated and the results are shown in Table 2. Excellent yields (up to 99%) and enantioselectivities (up to 97% ee) were obtained for a wide range of aldehydes bearing electron-withdrawing or donating groups on different sites.

Generally, aliphatic substituted aldehydes afforded lower yields (Table 2. entries 3, 4) than aromatic substituted aldehydes (Table 2, entries 5–20). The electronic properties on the aromatic ring of aldehydes have no obvious effects on the enantioselectivities (Table 2, entries 5–20), whereas steric hindrances of the substituents on the aromatic ring greatly affected the enantioselectivities (Table 2, entries 11 *vs.* 13, 16 *vs.* 18). With diisopropyl azodicarboxylate (DIAD) in hand, we also investigated its effect on this reaction, good yields (up to 94%) and enantioselectivities (up to 97% ee) were also obtained.

Table 2 Scope of substrates[a]



Entry	R^1	R^2	Time/h	Product	Yield (%)[b]	Ee (%)[c]
1	Ph (**2a**)	Et	23	**4a**-Et	96	96
2	Ph (**2a**)	*i*-Pr	32	**4a**-*i*-Pr	87	97
3	*n*-Pr (**2b**)	Et	45	**4b**-Et	52	—[d]
4	*n*-Pr (**2b**)	*i*-Pr	45	**4b**-*i*-Pr	54	—[d]
5	*p*-NO_2Ph (**2c**)	Et	50	**4c**-Et	93	81
6	*p*-NO_2Ph (**2c**)	*i*-Pr	32	**4c**-*i*-Pr	81	80
7	*p*-BrPh (**2d**)	Et	24	**4d**-Et	86	93
8	*p*-BrPh (**2d**)	*i*-Pr	32	**4d**-*i*-Pr	92	97
9	*p*-FPh (**2e**)	Et	20	**4e**-Et	99	94
10	*p*-FPh (**2e**)	*i*-Pr	32	**4e**-*i*-Pr	94	96
11	*m*-ClPh (**2f**)	Et	20	**4f**-Et	99	94
12	*m*-ClPh (**2f**)	*i*-Pr	32	**4f**-*i*-Pr	90	94
13	*o*-ClPh (**2g**)	Et	50	**4g**-Et	trace	nd
14	*o*-ClPh (**2g**)	*i*-Pr	56	**4g**-*i*-Pr	30	97
15	*p*-CH_3OPh (**2h**)	Et	22	**4h**-Et	80	93
16	*p*-CH_3Ph (**2i**)	Et	22	**4i**-Et	80	93
17	*p*-CH_3Ph (**2i**)	*i*-Pr	20	**4i**-*i*-Pr	85	96
18	*o*-CH_3Ph (**2j**)	Et	72	**4j**-Et	nr	nd
19	2-Naph (**2k**)	Et	10	**4k**-Et	92	90
20	2-Naph (**2k**)	*i*-Pr	15.5	**4k**-*i*-Pr	90	95

[a] Unless otherwise specified, all reactions were carried out with **2** (0.3 mmol), **3** (0.20 mmol), the catalyst **1a** (0.02 mmol) and 2-OHPhCOOH (0.04 mmol) in DCM (1.0 mL) at 0 °C. [b] Isolated yield. [c] Determined by HPLC with Chiralpak column. [d] The ee could not be determined by GC or HPLC with chiral stationary phase.

Conclusion

In summary, we have successfully applied the secondary amine-thiourea bifunctional catalysts **1a–1d** to promote the direct asymmetric α-amination of various branched aldehydes with azodicarboxylates in excellent yields (up to 99%) and enantioselectivities (up to 97% ee) and provided an effective and enantioselective method for the construction of quaternary stereocenters. Further applications of these catalysts in other reactions are currently underway in our laboratory.

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15 The results are listed in supporting information†.

