Construction of Quaternary Stereocenters: Asymmetric α-Amination of Branched Aldehydes Catalyzed by Monoimide Substituted Cyclohexane-1,2-Diamines

JI-YA FU,[1,2] QI-LIN WANG,[1,3] LIN PENG,[1] YONG-YUAN GUI,[1,3] XIAO-YING XU,[1*] AND LI-XIN WANG[1*]

[1]*Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, P.R. China*

[2]*College of Chemistry and Chemical Engineering, Henan University, Kaifeng, Henan, P.R. China*

[3]*University of Chinese Academy of Sciences, Beijing, P.R. China*

ABSTRACT A highly efficient enantioselective α-amination of branched aldehydes catalyzed by chiral imide monosubstituted 1,2-diamine derivatives was reported to afford the quaternary stereogenic centers in excellent yields (up to 99%) and enantioselectivities (up to 97% ee). *Chirality 25:668–672, 2013.*

KEY WORDS: asymmetric amination; branched aldehydes; primary amine

INTRODUCTION

Asymmetric amination is one of the most important methods for the direct asymmetric formation of C-N bonds and widely applied in organic synthesis.[1–4] In particular, α-amination of branched aldehydes is an efficient method to access optically active nitrogen-containing compounds with chiral quaternary stereogenic centers, which are versatile synthetic motifs for the preparation of biologically active natural products and pharmaceuticals.[5–8] Typically, α,α-disubstituted amino aldehydes are important building blocks and key intermediates to construct α-amino alcohols and unnatural α-amino acids.[9,10] Since Bräse and colleagues reported the first example of amination of branched aldehyde in moderate enantioeslectivities,[11] several asymmetric protocols have been reported.[12–15] However, there were still no efficient and satisfactory asymmetric methods until our group reported a highly effective α-amination of branched aldehydes promoted by chiral proline-derived amide thiourea bifunctional catalysts in excellent yields (up to 99%) and enantioselectivities (up to 97% ee).[16] After that, an ion pair catalyst of 9-amino(9-deoxy)epi-quinine and (-)-CSA was applied in this transformation.[17] And in 2011, our group disclosed that the simple primary amino acid of 3-(1-naphthyl) alanine may catalyze the amination of branched aldehydes with high enantioselectivities.[18] Even so the direct enantioselective preparations of unnatural chiral α-amino acids, especially chiral quaternary amino acids, are still challenges. Considering asymmetric α-amination of branched aldehydes, easily and cheaply available, may be one of the most efficient and direct means to fulfill this goal and for further and deep understanding and expanding this useful asymmetric transformation, it is still desirable to develop simple, easily available catalysts for various multifunctional preparations of optically active chiral α,α-disubstituted amino compounds.

RESULTS AND DISCUSSION

Chiral amines have emerged as powerful tools in asymmetric catalysis.[19–24] Among them, 1,2-diphenylethane-1,2-diamine and cyclohexane-1,2-diamine are widely used as starting materials for the preparation of chiral reagents, ligands, and catalysts, such as Jacobsen's salen ligands,[25–27] Trost's ligand,[28–32] and chiral thioureas.[33–35] Imide monosubstituted-1,2-diamines, the key intermediates in the preparation of those chiral molecules, have drawn our attention and were successfully applied to asymmetric double Michael reaction[36] and enantioselective Diels-Alder reaction of anthrone with maleimide.[37] On the other hand, our group is interested in developing new methods to construct substituted amino aldehydes and successfully applied chiral thioureas, amino acids in the amination of aldehydes with excellent results.[16, 18, 15j] Based on these achievements and our continuing interests in asymmetric synthesis promoted by chiral amine catalysis,[16,18,38–42] herein we report the asymmetric α-amination of branched aldehydes with azodicarboxylates catalyzed by simple chiral imide monosubstituted 1,2-diamine derivatives in excellent enantioselectivities.

In the course of our deep and systematic study on asymmetric amination of aldehydes, we found that the imide monosubstituted and unsymmetric chiral cyclohexane 1,2-diamine **1a**, not the C_2 symmetric counterpart **1i**, showed high reactivity and enantioselectivity in this transformation, which might be attributed to the introduction of bulkier substituents. Encouraged by the primary outstanding results, imide monosubstituted-1,2-diamines catalysts **1a-1f** bearing different chiral diamine skeletons were synthesized,[34,35,43,44] and primary thiourea bifunctional catalysts **1g**, **1h**, and 1,2-diaminocyclo-hexane were also chosen as the counterparts (Fig. 1). 2-Phenyl-propionaldehyde (**2a**) and diethyl azadicarboxylate (DEAD) (**3a**) were used as the model substrates and the results were summarized in Table 1.

All the cases gave the desired amination products **4a** in moderate to excellent yields (61–99%) and poor to good enantioselectivities (29–89% ee; Table 1, entries 1–9). Catalysts

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*Correspondence to: X.-Y. Xu or L.-X. Wang, Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 61004, P.R. China. E-mail: wlxioc@cioc.ac.cn or xuxy@cioc.ac.cn

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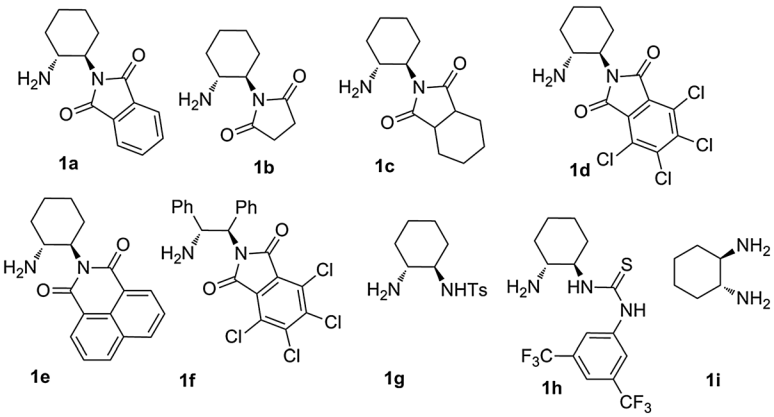
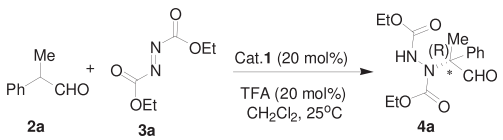


Fig. 1. Screened primary amine catalysts.

1a-1f afforded the α,α-disubstituted amino compounds in moderate to excellent yields and enantioselectivities (61–99% yield, 49–89% ee; Table 1, entries 1–6). Catalyst **1d** with a cyclohexanediamine chiral scaffold afforded better yield and enantioselectivity than **1f** with a diphenyldiamine scaffold, and it seemed that introduction of a bulkier group or more conjugated aromatic ring would be beneficial to the reaction. Catalyst **1c** with a bulkier group gave better enantioselectivity than **1b**, which revealed that the catalytic activities and enantioselectivities are highly dependent on steric hindrances of imide monosubstituted groups (Table 1, entry 2 vs. 3). When catalyst **1e** with naphthyl group was employed, an obvious increase in enantioselectivity was observed (Table 1, entry 5).

TABLE 1. Reaction of 2-phenyl-propionaldehyde with DEAD catalyzed by 1a-1i [a]



Entry	Cat.	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1a**	2	88	78
2	**1b**	2	98	56
3	**1c**	1	96	80
4	**1d**	2	99	86
5	**1e**	1	85	89(R)
6	**1f**	16	61	49
7	**1g**	30	65	40
8	**1h**	4	76	66
9	**1i**	4	87	29

[a]Unless otherwise specified, all reactions were carried out with 2-phenyl-propionaldehyde (**2a**, 0.30 mmol), diethyl azodicarboxylate (**3a**, 0.20 mmol), the catalyst (20 mol%) and TFA (20 mol%) in CH_2Cl_2 (1.0 mL) at 25°C.
[b]Isolated yield.
[c]Determined by HPLC with a Chiralpak-AS column and the absolute configuration of **4a** was assigned as R.[5h]

To further optimize the reaction conditions, a number of solvents and additives were also examined in the presence of 20 mol% **1d** or **1e** at 25°C, and the results are described in Table 2. The reaction media significantly affected the yields and enantioselectivities. Almost all the solvents gave moderate to good yields and enantioselectivities (up to 90% ee). Less polar solvents gave high yields and enantioselectivities (Table 2, entries 4–7), whereas a polar solvent such as DMF afforded poor yield and enantioselectivity (Table 2, entry 10). Chlorinated solvents were found to be more suitable for both **1d** and **1e** (Table 2, entries 4–7). Especially 1,2-dichloroethane (DCE) afforded the best results (99% yield, 90% ee; Table 2, entry 6) in the presence of catalyst **1e**, and was chosen as the optimal solvent.

To further increase the enantioselectivities, a series of acid additives and the reaction temperature were evaluated (Table 2, entries 12–16). As shown in Table 2, TFA was the most favorable additive. the reaction temperature slightly affected the enantioselectivities, and lower temperatures had almost no effect on the enantioselectivity, while dramatically decreasing the yield and reaction rate (Table 2, entries 6, 17, 18); better yields and enantioselectivities were observed at 25°C. Subsequently, the amount of additive and catalyst was also examined. Better results were obtained when 20 mol% additive was added (99% yield and 90% ee; Table 2, entry 6), as well as when the catalyst loadings were reduced to 10 mol % (91% ee) (Table 2, entry 21). Based on the comprehensive screenings, the optimal reaction conditions were established as shown in Table 2, entry 21.

Under the optimized conditions, various azodicarboxylates and branched aldehydes were also examined and the results are summarized in Table 3. Substituents on azodicarboxylates and branched aldehydes were well tolerated, affording the desired adducts in moderate to excellent yields (up to 99%) and excellent enantioselectivities (up to 97% ee). Basically, the steric hindrance of azodicarboxylates had no obvious effects on the enantioselectivities and yields, and all the cases gave good results (91–96% yield and 88–93% ee; Table 3, entries 1–4). A range of substituted aromatic aldehydes were also studied, and the substituents on the phenyl ring showed no evident effects on the yields and enantioselectivities (Table 3, entries 5–13). Both electron-withdrawing and -donating substituents afforded poor to excellent yields (38–99% yields; Table 3, entries 5–13) and good to excellent enantioselectivities (81–97% ee; Table 3; entries 5, 6, 8–13) except 4-nitrophenyl

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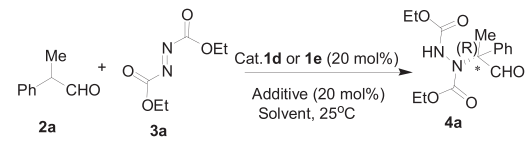
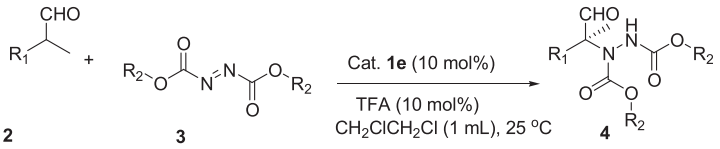
TABLE 2. Optimization of reaction parameters[a]



Entry	Cat.	Solvent	Additive	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1d (1e)**	toulene	TFA	4 (6)	99 (92)	80 (81)
2	**1d (1e)**	*n*-henxane	TFA	24 (28)	85 (65)	59 (74)
3	**1d (1e)**	acetonitrile	TFA	16 (7)	96 (92)	77 (79)
4	**1d (1e)**	CH_2Cl_2	TFA	2 (1)	99 (85)	86 (89)
5	**1d (1e)**	$CHCl_3$	TFA	4 (3)	99 (99)	86 (86)
6	**1d (1e)**	CH_2ClCH_2Cl	TFA	4 (3)	66 (99)	84 (90)
7	**1d (1e)**	$CHCl_2CH_2Cl$	TFA	4 (3)	95 (99)	88 (89)
8	**1d (1e)**	Et_2O	TFA	7 (6)	99 (87)	70 (84)
9	**1d (1e)**	THF	TFA	16 (3)	93 (82)	67 (81)
10	**1d (1e)**	DMF	TFA	4 (36)	33 (22)	29 (21)
11	**1e**	CH_2ClCH_2Cl	—	22	90	52
12	**1e**	CH_2ClCH_2Cl	$PhCO_2H$	8	86	62
13	**1e**	CH_2ClCH_2Cl	2-$OHPhCO_2H$	0.3	90	87
14	**1e**	CH_2ClCH_2Cl	3-$OHPhCO_2H$	22	91	58
15	**1e**	CH_2ClCH_2Cl	4-NO_2PhCO_2H	2	95	57
16	**1e**	CH_2ClCH_2Cl	CF_3SO_3H	64	85	30
17[d]	**1e**	CH_2ClCH_2Cl	TFA	23.5	60	85
18[e]	**1e**	CH_2ClCH_2Cl	TFA	94	39	85
19[f]	**1e**	CH_2ClCH_2Cl	TFA	22	96	86
20[g]	**1e**	CH_2ClCH_2Cl	TFA	3	96	89
21[h]	**1e**	CH_2ClCH_2Cl	TFA	5	96	91
22[i]	**1e**	CH_2ClCH_2Cl	TFA	5	94	90

[a]Unless otherwise specified, all reactions were carried out with 2-phenyl-propionaldehyde (**2a**, 0.30 mmol), diethyl azodicarboxylate (**3a**, 0.20 mmol), **1d** or **1e** (20 mol%) and additive (20 mol%) in solvent (1.0 mL) at 25°C.
[b]Isolated yield.
[c]Determined by HPLC with a Chiralpak-AS column.
[d]The reaction was stirred at 0°C.
[e]The reaction was stirred at -10°C.
[f]40 mol% additive was used.
[g]10 mol% additive was used.
[h]10 mol% catalyst and 10 mol% additive were used.
[i]5 mol% catalyst and 5 mol% additive were used.

TABLE 3. Asymmetric amination of branched aldehydes[a]



2 3 4

Entry	R_1	R_2	Time (h)	Product	Yield (%)[b]	ee (%)[c]
1	Ph	Et	5	(+)-**4a**	96	91
2	Ph	*i*-Pr	4	(+)-**4b**	94	93
3	Ph	*t*-Bu	4	(+)-**4c**	92	90
4	Ph	Bn	1.5	(+)-**4d**	91	88
5	4-CH_3OPh	Et	48	(+)-**4e**	88	91
6	4-CH_3Ph	Et	155	(+)-**4f**	38	97
7	4-NO_2Ph	Et	48	(+)-**4g**	94	54
8	4-BrPh	Et	3	(+)-**4h**	>99	95
9	4-FPh	Et	18	(+)-**4i**	62	93
10	4-ClPh	Et	144	(+)-**4j**	38	81
11	3-ClPh	Et	3	(+)-**4k**	94	89
12	2-ClPh	Et	24	(-)-**4l**	47	78
13	2-naphthyl	Et	3	(+)-**4m**	95	93
14	2-CH_3Ph	Et	48	(-)-**4n**	75	76
15	3-CH_3OPh	Et	2	(+)-**4o**	90	90
16	n-Pr	Bn	3	(+)-**4p**	77	57

[a]Unless otherwise specified, all reactions were carried out with branched aldehydes (**2**, 0.30 mmol), azodicarboxylate (**3**, 0.20 mmol), **1e** (10 mol%) and TFA (10 mol%), $ClCH_2CH_2Cl$ (1.0 mL) at 25°C.
[b]Isolated yield.
[c]Determined by HPLC with a Chiralpak column.

substituted aromatic aldehydes (54% ee; Table 3, entry 7). Electron-donating substituents phenyl and 2-naphthyl aldehydes gave better enantioselectivities, and the electron-rich of aromatic ring was beneficial to the reaction (Table 3, entries 5, 6, 13). The position of the substitutents was also tested. The enantioselectivities were not obviously sensitive to the position of the substituents on the aromatic aldehydes, although the para substitutents gave slightly lower ee values compared with the corresponding meta- and ortho-substituted counterparts (Table 3, entries 10 vs. 11 vs. 12).

CONCLUSION

In conclusion, we have disclosed the asymmetric amination of branched aldehydes catalyzed by simple imide monosubstituted-primary amine and afforded the optically active α,α-disubstituted amino aldehydes in excellent yields (up to 99%) and enantioselectivities (up to 97% ee). This protocol provided a potential and effective method for the construction of optically active chiral α,α-disubstituted amino aldehydes with quaternary stereocenters. Further applications of these catalysts in other reactions and new pharmaceutical preparations are currently under way in our laboratory.

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