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Primary amine catalyzed electrophilic amination of α,α-disubstituted aldehydes

Alaric Desmarchelier, Hasret Yalgin, Vincent Coeffard, Xavier Moreau *, Christine Greck *

Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles-Saint-Quentin-en-Yvelines, 45, Avenue des Etats-Unis, 78035 Versailles Cedex, France

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ABSTRACT

Organocatalytic α-amination of α,α-disubstituted aldehydes promoted by 9-amino-(9-deoxy)-epi-quinine is described. α-Hydrazino aldehydes bearing a quaternary stereogenic center are obtained in good to excellent yields and enantioselectivities.

Over the last decade, organocatalytic α-amination of aldehydes and ketones has emerged as one of the most powerful methods for stereoselective C—N bond formation.[1] While electrophilic amination of simple aliphatic carbonyl compounds is well documented in the literature,[2] the use of α,α-disubstituted aldehydes to form quaternary stereocenter-containing products bearing a nitrogen atom still remains scarce. In 2003, Bräse and co-workers reported the first example of this transformation using proline as a catalyst.[3] In 2005, Barbas and co-workers applied this strategy to the synthesis of three biologically active products namely, BIRT-377,[4] AIDA and APICA.[5] More recently, Wang et al. have shown that the same reaction could be efficiently promoted by chiral secondary amine derived from proline.[6] Primary amine catalysts were also found to be effective for this transformation. Melchiorre and co-workers developed a cascade reaction involving an electrophilic amination catalyzed by a primary amine derived from hydroquinine.[7] Finally, our group has recently described an organocatalytic sequence combining Michael addition/α-amination promoted by an aminated cinchonine derivative.[8] In this letter, we would like to report our results about the enantioselective amination of α,α-disubstituted aldehydes catalyzed by primary amines derived from cinchona alkaloids.

Electrophilic amination of commercially available 2-phenylpropionaldehyde with diisopropyl azodicarboxylate (0.83 equiv) was examined as the reaction model and the results are summarized in Table 1. Combination of 9-amino-(9-deoxy)-epi-cinchonidine **I** (5 mol %) and TFA (15 mol %) in chloroform was first investigated (entry 1) since this catalyst system was successfully applied for such a transformation by our group.[8] While the reactivity was excellent (full conversion within 3 h at rt and 94% of isolated yield), the enantioselectivity was disappointing (68% ee). When the reaction was run in CH_2Cl_2 or toluene (entries 2 and 3) the reactivity remained good but the selectivity was lower (respectively 58% and 50% ee). If more polar or protic polar solvents such as MeCN or *i*PrOH (entries 4 and 5) were used for this reaction, both reactivity and selectivity dropped (after 3 h, the conversion was not complete and the selectivity was poor). As the stereoselectivity was not improved by lowering the temperature to 0 °C (entry 6), we then screened various primary amine catalysts derived from cinchona alkaloids. Moving from 9-amino-(9-deoxy)-epi-cinchonidine **I** to 9-amino-(9-deoxy)-epi-quinine **II** greatly enhanced the ee (entry 7). The expected product was obtained in 95% yield and 90% ee. Pseudo-enantiomers of these catalysts were not effective for this transformation (entries 8 and 9). 9-Amino-(9-deoxy)-epi-cinchonine **III** almost led to a racemic sample and 9-amino-(9-deoxy)-epi-quinidine **IV** delivered the product as the opposite enantiomer in 95% yield and only 55% ee. Finally the influence of the amount of acid co-catalyst was also investigated. Slow conversion and poor selectivity were observed when the reaction was carried out without TFA (entry 10) while using 7.5 mol % TFA required longer reaction time and the product was obtained in 84% yield and 92% ee (entry 11).

With the optimized conditions in hands[9] (1 equiv DIAD, 1.2 equiv aldehyde, 5 mol % catalyst **II**, 15 mol % TFA in $CHCl_3$ at rt), we then turned our attention to the influence of the electrophilic nitrogen source and the reaction was conducted with different azodicarboxylates (Table 2). As expected, less hindered

* Corresponding authors. Tel.: +33 (0) 1 39 25 44 05; fax: +33 (0) 1 39 25 44 52 (X.M.).
E-mail addresses: moreau@chimie.uvsq.fr, xavier.moreau@chimie.uvsq.fr (X. Moreau), greck@chimie.uvsq.fr (C. Greck).

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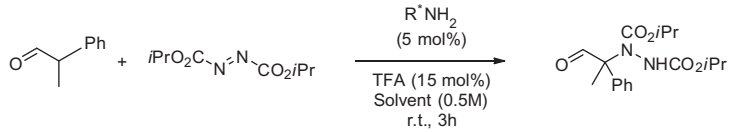
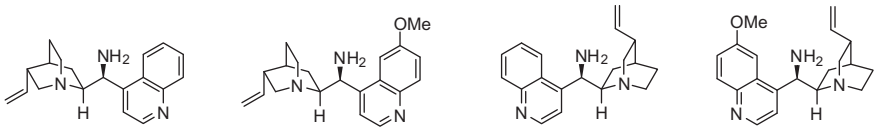
Table 1
Catalyst and solvent screening

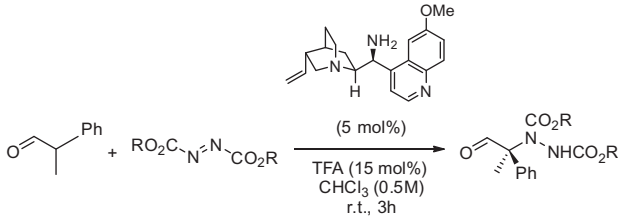




Entry	Catalyst	Solvent	Yield[a] (%)	ee[b] (%)
1	**I**	$CHCl_3$	94	68 (*S*)
2	**I**	CH_2Cl_2	82	58 (*S*)
3	**I**	Toluene	94	50 (*S*)
4	**I**	CH_3CN	36	28 (*S*)
5	**I**	*i*PrOH	56	40 (*S*)
6[c]	**I**	$CHCl_3$	91	60 (*S*)
7	**II**	$CHCl_3$	95	90 (*S*)
8	**III**	$CHCl_3$	86	4 (*R*)
9	**IV**	$CHCl_3$	95	55 (*R*)
10[d]	**II**	$CHCl_3$	59	19 (*R*)
11[e]	**II**	$CHCl_3$	84	92 (*S*)

[a] Isolated yield after column chromatography.
[b] Ee was determined by chiral phase HPLC analysis (AS-H column, 10% *i*PrOH/heptane, 0.8 mL/min, 30 °C).
[c] Reaction run at 0 °C during 24 h.
[d] Reaction run without TFA during 56 h.
[e] Reaction run with 7.5 mol % TFA during 8 h.

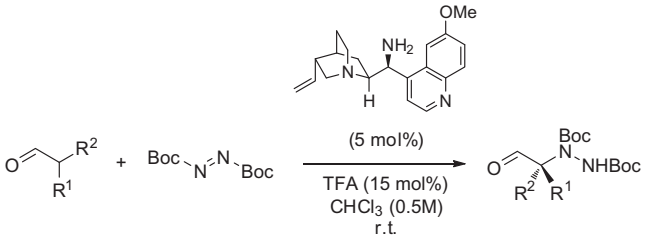
Table 2
Azodicarboxylate screening



Entry	Azodicarboxylate	Yield[a] (%)	ee[b] (%)
1	$iPrO_2C{-}N{=}N{-}CO_2iPr$	95	90
2	$EtO_2C{-}N{=}N{-}CO_2Et$	88	84
3	$BnO_2C{-}N{=}N{-}CO_2Bn$	72	82
4	$tBuO_2C{-}N{=}N{-}CO_2tBu$	96	95

[a] Isolated yield after column chromatography.
[b] Ee was determined by chiral phase HPLC analysis.

Table 3
Aldehyde screening



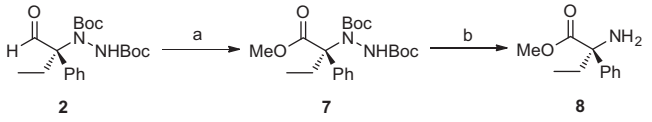
Entry	R^1	R^2	Product	Yield[b] (%)[a]	ee (%)
1	Ph	Me	**1**	96	95[c]
2	Ph	Et	**2**	82	94[c]
3	*p*-$MeOC_6H_4$	Me	**3**	87	88[d]
4	*o*-$MeOC_6H_4$	Me	**4**	95	99[d]
5	*o*-$NO_2C_6H_4$	Me	**5**	83	94[e]
6	Bn	Me	**6**	72	36[c]

[a] Isolated yield after column chromatography.
[b] Ee was determined by chiral phase HPLC analysis.
[c] AD-H column, 10% *i*PrOH/heptane, 0.8 mL/min, 30 °C.
[d] OD-H column, 2% *i*PrOH/heptane, 0.9 mL/min, 30 °C.
[e] AS-H column, 5% *i*PrOH/heptane, 0.9 mL/min, 30 °C.

azodicarboxylates such as diethyl or dibenzyl (DEAD or DBAD) afforded the aminated product with slightly lower selectivity. In contrast, more hindered di-*tert*-butylazodicarboxylate (D*t*BAD) afforded the expected α-aminoaldehyde with excellent yield (96%) and selectivity (95% ee).

Various branched aldehydes were tested for this reaction and the results are listed in Table 3. Switching from 2-phenylpropionaldehyde to 2-phenylbutyraldehyde afforded the expected α-hydrazino aldehyde in 82% yield and 94% ee (entry 2). Lower yield and enantioselectivity due to the increasing steric demand were not observed as reported previously.[3b] Electron-rich and electron-deficient aryl groups substituted in *ortho*- or *para*-position were well tolerated and provided good to excellent results in terms of reactivities and selectivities (entries 3–5). However, if the phenyl group was replaced by a benzyl group, the product was obtained in 72% yield but the enantioselectivity dropped to 36% ee (entry 6).

Finally, this methodology was applied to the synthesis of a quaternary α-aminoester (Scheme 1).[10] The α-hydrazino aldehyde **2** was oxidized under smooth conditions and esterified to provide the α-hydrazino methyl ester **7** in 67% yield over two steps. Boc protecting groups were removed under acidic conditions and the



2 7 8

Scheme 1. Reagents and conditions: (a) (i) KH_2PO_4, $NaClO_2$, H_2O_2, MeOH/MeCN/H_2O (1/1/1), 0 °C to rt, 2 h; (ii) $TMSCHN_2$, MeOH, rt, 0.5 h, 67% (over two steps); (b) (i) TFA, DCM, 0 °C to rt, 3 h; (ii) H_2, Ni-Raney, MeOH, rt, 48 h, 76% (over two steps).

hydrazine bond was hydrogenated in the presence of Ni-Raney to afford (*S*)-ethyl phenylglycine methyl ester **8**[11] in 76% yield over two steps.

In summary, we have developed an organocatalytic α-amination of α,α-disubstituted aldehydes promoted by 9-amino-(9-deoxy)-epi-quinine. α-Hydrazino aldehydes bearing a tetrasubstituted stereocenter were obtained in good to excellent yields and enantioselectivities. This methodology was successfully applied to the synthesis of a quaternary α-aminoester.

Acknowledgment

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The reaction has been scaled up 10-fold for the synthesis of (*S*)-ethyl phenylglycine methyl ester **8** without changes in the procedure.
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Compound **8**: $[\alpha]_D^{25}$ +13,0 (*c* 1; CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.48–7.53 (m, 2H), 7.25–7.38 (m, 3H), 3.72 (s, 3H), 2.15-2.27 (m, 3H), 1.99–2.11 (m, 1H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.2, 143.0, 128.5, 127.5, 125.6, 64.3, 52.6, 32.8, 8.5; IR υ (cm^{-1}): 3385, 3317, 2952, 1731, 1447, 1228; HRMS. Anal. calcd for $C_{11}H_{16}NO_2$ [M^+H^+]: 194.1181. Found: 194.1184.