DOI: 10.1002/ejoc.200900726

Efficient Deracemization of Pipecolic Acid Amides through Enantioselective Protonation of Their Lithium Enolates: Insights into the Origin of the Transferred Proton

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Keywords: Asymmetric synthesis / Protonation / Deracemization / Amides / Lithium enolates / Enantioselectivity

A detailed study of the deracemization of pipecolic acid amides is reported. Enantioselective protonation of the lithium enolates of these amides with use of commercially available ephedrines led to enantiomeric excesses (*ee* values) higher than 99 %. The success of the reaction was strongly dependent on the following parameters: the base, the reaction temperature, the structure of the chiral source, and the achiral quenching reagent. *s*BuLi and the bimetallic base "potassium alkoxide/*n*BuLi" were the only bases to allow complete formation of the enolate in conjunction with high stereocontrol of the protonation. Experiments with (+)- or (–)-ephedrine derivatives as chiral sources and deuteriated reagents gave evidence that both the OH and NH protons of ephedrine were involved in the stereoinduction. *External* delivery of the proton was mainly operative with the aniline derivative (+)-**5**, as shown by deuterium labeling experiments, whereas *internal* quenching was the major pathway observed with ephedrine (**6**). Finally, the deracemization procedure was successfully applied to prepare both enantiomers of *N*-protected pipecolic acid from racemic pipecolic acid (51 % overall yield, 99 % *ee*).

Introduction

Deracemization of ketones, acids, amino acid derivatives, esters, thioesters, or phosphane oxides through enantioselective protonation of their corresponding enolates or enolate equivalents is well documented,[1–3] and some catalytic versions[4] have been developed. In the case of amides, however, this methodology remains limited; the only reported examples involve γ,δ unsaturated substrates[5,6] or a particular lactam.[7] Vedejs et al.[8,5c,5d] demonstrated in an in-depth study that the enantiomeric excesses (*ee* values) are strongly dependent on the substrate, on the base used to generate the enolate, and on the temperature of the reaction.

As a part of our ongoing program on the synthesis of ligands for the study of muscarinic receptors in the central nervous system, we prepared both enantiomers of AF-DX 384 (**1**) via amides **2** derived from (*S*)-(–)- or (*R*)-(+)-pipecolic acids (**3**, Figure 1).[9] However, the high cost of these homochiral acids was an important drawback to their use as starting materials on a large scale. Moreover, because of the ubiquitous structural feature of the piperidine-2-carboxyl unit in peptides,[10] immunosuppressor agents,[11] and biologically active compounds,[12] there is still a demand for alternatives to the numerous routes[13] to the enantio-enriched acids (+)- or (–)-**3**. A few years ago we successfully tested the deracemization of pipecolamides[14] through enantioselective protonation of their enolates (Scheme 1). In this paper we summarize our efforts to address the key issues of this reaction to define the roles of the various reaction parameters and to gain insight into

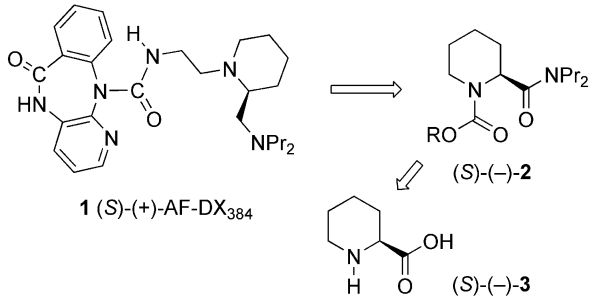

Figure 1. (*S*)-(+)-AF-DX 384 from (*S*)-(–)-pipecolic acid (**3**).

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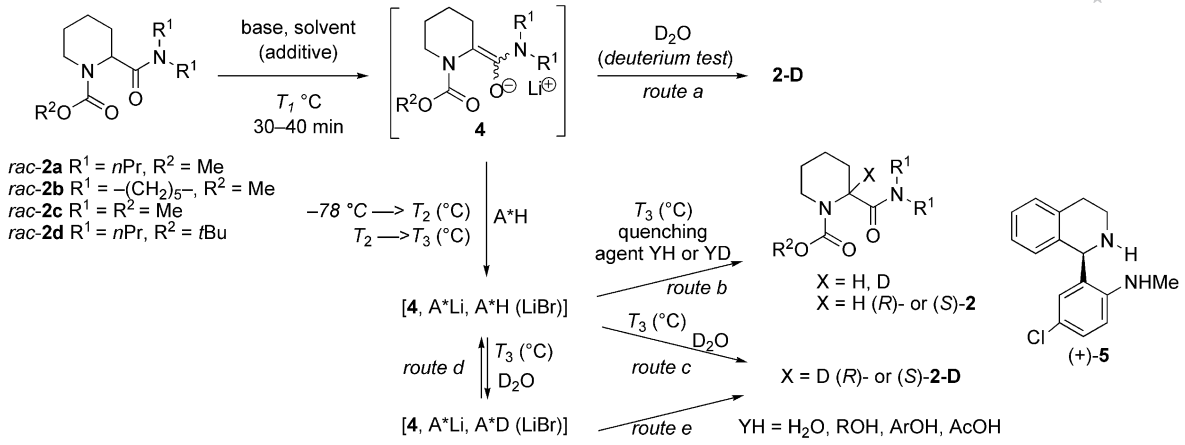
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900726.



Scheme 1. Deracemization of pipecolamides **2**.

the identities of the proton donors. The efficiency of the methodology was demonstrated in the synthesis of *N*-protected (*S*)- or (*R*)-pipecolic acids.

Results and Discussion

The amide **2a** (Scheme 1) was used as a model substrate for detailed deracemization optimization experiments. From Vedejs' studies[5,8] and our preliminary results,[14] we chose the aniline derivative (+)-**5** as the chiral "acid" for the enantioselective protonation of the enolate **4a**. For the sake of reproducibility[8] we used 2 equiv. of chiral source. Moreover, in this study and for each experiment, the extent of amide enolization was evaluated by ^{1}H NMR measurement of deuterium incorporation ("deuterium test", Scheme 1, route *a*; see Exp. Sect.).

Influence of Temperature

The temperatures of the different reaction steps are crucial parameters in enantioselective protonations.[2,5,8] In Table 1 we report some data relating to the influence of the temperature on the obtained *ee* values of amide **2a**. The enolate **4a** was generated at temperature T_1 (–78 °C) and the chiral source (+)-**5** was added. After 60 min at T_1, the solution was warmed to temperature T_2 over a 30 min period. After 5–10 min at T_2, the mixture was allowed to reach T_3 and the quenching agent was added. Comparison of Entries 1 and 4 suggests that a reorganization of the "*s*BuLi/enolate/chiral source" complex was necessary for high *ee* values to be achieved. The enantioselection decreased dramatically with a higher temperature T_2 (Entries 3 and 4), particularly when T_3 was also high (Entry 2). These results could be explained by reversible deprotonation of the amide **2a** at temperatures above 0 °C.[5b]

Table 1. Obtained *ee* values of **2a** as a function of temperature.

Entry[a]	T_1 [°C] Enolate formation and (+)-**5** addition	T_2 [°C] Reaction mixture	T_3 [°C] H_2O addition	*ee* [yield] [%][b]
1	–78	–78	–78	1 [88]
2	–78	+15	+15	5 [77]
3	–78	+15	–78	54 [75]
4	–78	–30 or –20	–78	96 [78]

[a] *s*BuLi (1.75 equiv.), LiBr (1.75 equiv.), amide **2a**, chiral source (+)-**5** (2 equiv.). [b] Isolated yields; *ee* values were determined by chiral HPLC. Major isomer: (*S*)-(–)-**2a**.

Choice of Base

The *ee* values being strongly dependent on the quality of the *s*BuLi,[15] we searched for an alternative base for the preparation of intermediate **4a**. No enantioselection was observed with lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS) whatever the number of equivalents used. Because an exchange of proton between the lithiated reagent and the amine is known to occur,[16,17] we did not pursue our investigations with these bases. No asymmetric induction was observed with any of *n*BuLi, MeLi, or *t*BuLi, although complete deprotonation of amide **2a** was observed (deuterium test). Addition of $BF_3{\cdot}Et_2O$ (2 equiv.), known to increase electron demand in the amine/anion complex and to force internal proton return,[18] gave low *ee* values (<27%). Addition of lithium chloride, which is able to form mixed aggregates and to modify the reaction intermediate,[17] was no more successful (*ee* values <8%).

*s*BuLi in THF, however, yielded the amide (*S*)-(–)-**2a** in 87% *ee* (Table 2, Entry 1). No improvement was observed in the presence of $BF_3{\cdot}Et_2O$ (Entry 2), but when LiBr[19–22] (1.75 equiv.) was added the *ee* reached 95% (Entry 3). The use of *s*BuLi (1.75 equiv.) was necessary to achieve complete deprotonation. Indeed, under the same conditions as in Entry 1 but with 1 equiv. of base, only a 54% yield of the enolate (deuterium test) was formed and no enantioselection was observed (Entry 4). Similar results were observed when the reaction was performed with *s*BuLi (1 equiv.) at –30 °C rather than –78 °C (data not shown). Attempts to carry out the reaction in other solvents (diethyl ether or toluene or a diethyl ether/THF mixture) failed (Entry 5).

Table 2. Deracemization of pipecolamide **2a**. Influences of base and additives.

Entry	Base [equiv.][a]	Added reagent [equiv.][b]	A*H [2 equiv.]	Solvent	**2a** Yield [%][c]	*ee* [%][d,e]
1	*s*BuLi [1.75]	no	(+)-**5**	THF	87	87
2	*s*BuLi [1.75]	BF_3·Et_2O [2]	(+)-**5**	THF	26	86
3	*s*BuLi [1.75]	LiBr [1.75]	(+)-**5**	THF	78	95
4	*s*BuLi [1]	no	(+)-**5**	THF	n.d.[g]	0
5	*s*BuLi [1.75]	LiBr [1.75]	(+)-**5**	Et_2O, toluene, or Et_2O/THF[f]	62–68	0
6	KH/*n*BuLi/(–)-ephedrine [1.25:2.25:1.25]	no	no	THF	67	0
7	KH/*n*BuLi/(+)-ephedrine [1.25:2.25:1.25]	no	(+)-**6**	THF	65	92
8	KH/*n*BuLi/(–)-ephedrine [1.25:2.25:1.25]	no	(–)-**6**	THF	53	88

[a] Amide **2a** and the additive in the solvent were cooled to –78 °C and stirred at this temperature for 40–60 min. The base was added and after 15 min a deuterium incorporation test was carried out on an aliquot (see Exp. Sect.). The chiral source (2 equiv.) was then added. After 30 min at –78 °C (T_1) the mixture was warmed over a 30 min period to –20 or –30 °C and then, after 5–10 min, cooled again to –78 °C before quenching with H_2O. [b] Number of equivalents vs. amide **2a**. [c] Isolated yields. [d] Determined by chiral HPLC. [e] The enantiomer (*S*)-(–)-**2a** was formed from (+)-**5** or (+)-**6**. [f] Ratio 1:1 v/v. [g] Because only 54% enolate generation had occurred, the yield of the reaction was not determined.

It is noteworthy that no deracemization occurred when the enolate **4a** was not completely formed. This observation was checked by addition of amide **2a** (0.2 equiv.) to a preformed enolate before addition of the chiral source (+)-**5**. Under standard conditions of temperature and time (Table 2, Entry 3), amide **2a** was isolated as a racemate. This result suggests either an equilibrium between enolate **4a** and amide **2a** or the participation of amide **2a** in the complex formed in the transition state.

Finally, in order to test strong deprotonating agents, we prepared a mixed lithium/potassium base by treatment of (+)- or (–)-ephedrine [(+)- or (–)-**6**] with KH (1.2 equiv., room temp., 5 min) in THF followed by *n*BuLi (2.25 equiv., –40 °C, 30 min) under Schlosser conditions.[23] No chiral induction was observed, as shown in Entry 6. Treatment, however, of amide **2a** (–78 °C, 30 min) with the "superbase" followed by addition of ephedrine to enolate **4a** prior to quenching with H_2O at –78 °C yielded (*S*)- or (*R*)-amide **2a** in 92 and 88% *ee*s, respectively (Table 2, Entries 7, 8). The *ee* values in these asymmetric protonations were similar to those obtained with *s*BuLi (Entries 1–3). The alkoxide-amide "superbase" thus appeared to be a good alternative to *s*BuLi for deracemization of pipecolamides.

Attempts to trap the enolate intermediates **4a** (Figure 2) by treatment variously with chlorotrimethylsilane, chlorodimethyl-*tert*-butylsilane, or acetic anhydride failed.[8] Few data for lithium enolates of amides are available,[24–27] so we undertook $^1H/^1H$ COSY and $^1H/^1H$ NOESY NMR experiments. Carried out at –60 °C in [D_8]THF, these showed strong cross-couplings between the protons of the methoxy group (9-H) and the protons of the methyl (12-H) and methylene (10-H) units of the propyl chain on the hand and between 6-H and 9-H on the other hand. However, no cross-coupling between protons 10-H and 3-H was observed. The observed correlations suggested that the major enolate had the *E* configuration (Figure 3).[28] A relative 60:40 ratio for the rotamers (similar to that observed for the amide **2a**) was deduced from the ^1H NMR spectrum.

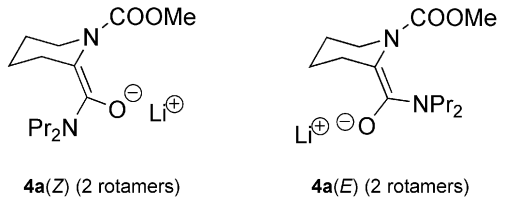


Figure 2. Enolate intermediates **4a**.

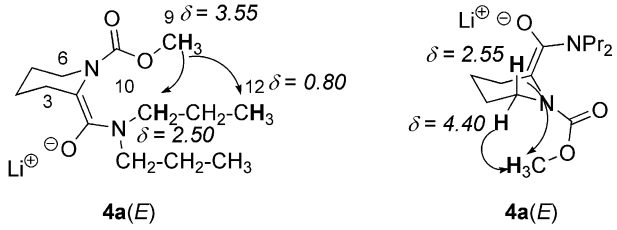


Figure 3. Cross-couplings observed in NMR of enolates **4a** (*E*).

Influence of Nitrogen Substituents

Amides **2b**, **2c**, and **2d** were prepared in order to allow comparison of the steric demands of the nitrogen systems. The results of all the experiments performed under the best conditions (Table 2, Entry 3) are presented in Table 3. The

Table 3. Influence of nitrogen substitutions on the obtained *ee* values of amides **2**.

Entry[a]	Amide	R^1	R^2	A*H	Product	Yield[b] [%]	*ee*[c] [%]
1	**2b**	$–(CH_2)_5–$	Me	(+)-**5**	(*S*)-**2b**	65	>99
2	**2b**	$–(CH_2)_5–$	Me	(–)-**6**	(*R*)-**2b**	56	>99
3	**2c**	Me	Me	(+)-**5**	(*S*)-**2c**	74	96
4	**2c**	Me	Me	(–)-**6**	(*R*)-**2c**	65	95
5	**2d**	*n*Pr	*t*Bu	(+)-**5**	(*S*)-**2d**	85	86[d]
6	**2d**	*n*Pr	*t*Bu	(–)-**6**	(*R*)-**2d**	89	85[d]

[a] Standard conditions: Table 2, Entry 3. [b] Isolated yield. [c] Determined by chiral HPLC. [d] From optical rotations of the *N*-deprotected compound.

piperidinyl amide **2b** was obtained in *ee* values higher than 99% whereas the dimethyl amide **2c** gave the same selectivity as its *n*-propyl analogue **2a**. A small erosion of the *ee* values was observed when the methoxycarbonyl component was substituted by the easily removable *tert*-butoxycarbonyl group in compound **2d** (Entries 5, 6).

The excellent *ee* values obtained with amide **2b** are noteworthy. The moderate yields observed in Entries 1 and 2 were significantly improved when working with amide **2b** on a gram scale (see below). However, one could not exclude contamination by a side-product resulting from a reaction between *s*BuLi and the carbamate.[6]

Influence of the Amount of Chiral Source

In a few experiments, the amount of chiral source was decreased while the 1.75 equiv. of *s*BuLi was maintained. Under the standard conditions (Table 2, Entry 3), the highest *ee* values were obtained with 2 or 3 equiv. of chiral source (+)-**5**. These results (Table 4, Entries 1, 3, 4) suggested that two molecules either of aniline (+)-**5** or of ephedrine (**6**) could be involved in the mixed aggregates.[26,27]

Table 4. Effect of the amount of the chiral source.

Entry[a]	A*H	A*H [equiv.]	*ee* [%][a,b]
1	(+)-**5**	2	95
2	(+)-**5**	1 or 1.75	0
3	(+)-**5**	3	96
4	(+)-**6**; (–)-**6**	2	89; 93
5	(+)-**6**	1.25	87
6	(+)-**6**	1	61

[a] Standard conditions Table 2, Entry 3, isolated yields: 68–87%. [b] Determined by chiral HPLC.

The two chiral sources appear to behave differently, however: with 1.75 or 1 equiv. of aniline (+)-**5** (Table 4, Entry 2) no induction was observed, whereas with 1.25 and 1 equiv. of (+)-ephedrine [(+)-**6**, Entries 5, 6], **2a** was isolated in 87 and 61% *ee* values, respectively. Deuterium labeling experiments (see below) confirmed that the proton transfer mechanisms with these two proton sources are quite different.

Origin of the Transferred Proton

The asymmetric induction relies on the use either of a chiral protic compound ("*internal quench*") or of an achiral protic agent coupled with a chiral ligand ("*external quench*").[2d,2e,4f] Many effective chiral protonating agents A*H (chiral acids, diols, functionalized alcohols or amines, cinchona alkaloids, hydroxy sulfoxides or selenoxides, imides, phenolic amides) have been developed[2,29,4c] in order to achieve high enantioselectivities in deracemization through asymmetric protonation. In some cases (see, for instance,[8,30l]), deuterium-labeled sources have been used to demonstrate the origin of the proton delivery. The "*external quench*" is far less common than the "*internal quench*". Most of the reports on the "*external quench*" have used the prochiral enolates of 2-alkyltetralones. High *ee* values (91%) were obtained with a triamine/acetic acid pair,[19] whereas a 3-aminopyrrolidine derivative[31] or a C_2-symmetrical cyclohexyldiamine[29] in combination with acetic acid were less efficient (*ee* values around 40%). The use of a catalytic amount of the BINAP·AgF complex with MeOH as the proton source induced enantioselective protonation of silyl enolates of 2-substituted cyclohexanones with *ee* values higher than 99%.[32]

We have shown that both enantiomers of the commercially available and inexpensive ephedrine (**6**) have the same efficiency as aniline (+)-**5**[33] in the asymmetric protonation of pipecolamide enolates **4**. In order to understand the course of the proton transfer, we first examined the role of each proton in the amine and alcohol functions of **6** (Figure 4). Typical results for the asymmetric protonation of enolate **4a** in the presence of the ephedrine derivatives **6**–**10** as sources of chirality are summarized in Table 5. A comparison of experiments performed with aniline (+)-**5** (Table 2, Entries 1–2) and with **6** (Table 5, Entries 1–3) show that the effect of BF_3·Et_2O on the yield was less pronounced with (+)-ephedrine [(+)-**6**]; however, BF_3·Et_2O significantly affected the *ee* (Entry 3 vs. 2). Norephedrine (**7**), *N*-methylephedrine (**8**), and *O*-methylephedrine (**9**) gave no asymmetric induction (Table 5, Entries 4, 5, 6 respectively), and pseudoephedrine (**10**) was less efficient (*ee* = 26%) than ephedrine itself (Entry 7). Thus, both the N–H and the O–H units and the unlike configuration of the stereogenic centers of ephedrine were essential for high induction in the asymmetric protonation of enolate **4a**.

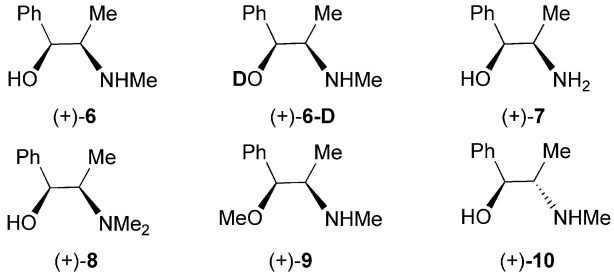


Figure 4. Ephedrine derivatives as chiral sources.

Table 5. Obtained *ee* values of amide **2a** as a function of ephedrine derivatives.

Entry	A*H[a]	Additive	Yield **2a** [%][b]	*ee* [%][c]	Config.
1	(–)-**6**		73	93	*R*-(+)
2	(+)-**6**		74	89	*S*-(–)
3	(+)-**6**	BF_3·Et_2O	68	44	*S*-(–)
4	(+)-**7**		68	0	
5	(+)-**8**		71	0	
6	(+)-**9**		78	5	*S*-(–)
7	(+)-**10**		73	26	*S*-(–)

[a] Reaction conditions: amide **2a** in THF was cooled to –78 °C and *s*BuLi (1.73 equiv.) was added. After 15 min at –78 °C, A*H (2 equiv.) in THF was added and the mixture was warmed to – 20 °C over a 30 min period. After cooling again to –78 °C, H_2O was added. [b] Isolated yield. [c] Determined by chiral HPLC.

In our next investigation, asymmetric protonation of lithium enolate **4a** was performed under the standard conditions, but D_2O was used to quench the reaction mixture in order to evaluate the amount of deuterium incorporation at the α-carbon.[34,35] In a preliminary experiment, we checked that the reaction between D_2O and **4a**, at –78 °C, led to the deuteriated amide **2a-D** in 100% yield (Table 6, Entry 1, Scheme 1, route "*a*"). The results summarized in Table 6 show that, under the same conditions of temperature and time, quenching of the reaction mixture with D_2O led to deuterium levels of 75–80% with diamine (+)-**5** (Entries 2, 3) and 25% with (–)-ephedrine [(–)-**6**, Entry 7]. These tests showed that in the case of aniline (+)-**5** the α-proton in (*S*)-**2a** was delivered mainly from the quenching reagent ("*external quench*"). This process was less important with ephedrine (**6**, Entries 6, 7) or norephedrine (**7**, Entry 9), probably because of the higher acidity of the alcohol function relative to that of the secondary amine of aniline (+)-**5**.[36,37] The 50% deuterium level observed when ephedrine derivative (+)-**6D** was used confirmed the role of the OD/OH and NH groups in the reaction pathway and that of H_2O as source of protonating agent of the enolate. From these observations we were able to suggest that the main process for asymmetric protonation with aniline (+)-**5** involved the formation of a chiral complex including the achiral quenching reagent (H_2O or D_2O; Scheme 1, route *d* and then *e*) whereas with ephedrine (**6**) an *internal quench* (route *b*) was mainly operating.

Table 6. Obtained *ee* values of amide **2a** as a function of the quenching reagent.

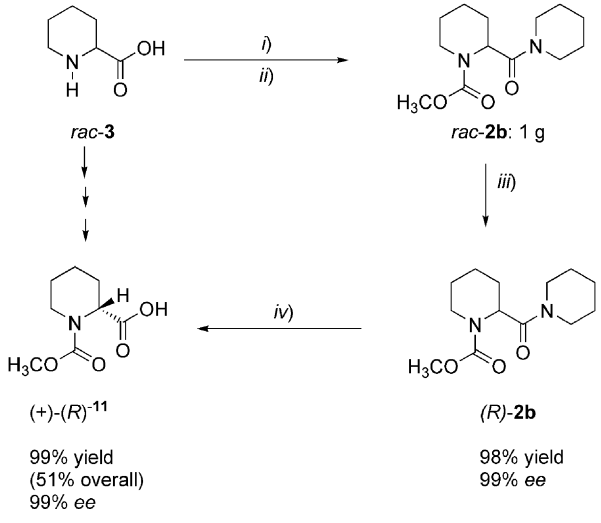
Entry	A*H[a]	Quenching reagent [*T*/°C][b]	**2a-D** deuterium content [%][c]	*ee* [%][d]
1	–	D_2O [–78]	100	–
2	(+)-**5**	D_2O [–78]	80	97
3	(+)-**5**	D_2O [–78]	75	80[e]
4	(+)-**5**[f]	D_2O [–78]	70	0
5	(+)-**5**	D_2O [–20]	95	0
6	(+)-**6D**	H_2O [–78]	50	88[e]
7	(–)-**6**	D_2O [–78]	25	92
8	(+)-**6**	D_2O then AcOH [–78]	50	85[e]
9	(+)-**7**	D_2O [–78]	22	0
10	(+)-**8**	D_2O [–78]	90	0
11	(+)-**9**	D_2O [–78]	50	5
12	(+)-**5**	MeOD [–78]	70	81[e]
13	(+)-**5**	*t*BuOD [–78]	70	87[e]
14	(+)-**5**	*t*BuOD [–78]	60	90
15	(+)-**5**	PhOH [–78]	–	63
16	(+)-**5**	PhOD [–78]	70	66
17	(+)-**5**	AcOD [–78]	50	0[e]

[a] Reaction conditions: the chiral source was added at –78 °C to enolate **4a** prepared from amide **2a** (0.3 mmol), LiBr, and *s*BuLi in THF (see Exp. Sect.). [b] 36 equiv. and temperature of addition. [c] Determined by ^1H NMR, the chemical yields being higher than 70%. [d] Determined by chiral HPLC. The enantiomer (*S*)-(–)-**2a** was formed from (+)-**5** or (+)-**6**. [e] Experiment carried out without LiBr. [f] The reaction was entirely conducted at –78 °C.

The deuterium labeling confirmed our previous observations (Table 1) on the effects of temperature on the obtained *ee* values of amide **2a**. With the chiral aniline derivative (+)-**5**, if the deuterolysis was carried out at –20 °C rather than at –78 °C (Table 6, Entry 5), or if all the reaction was entirely conducted at –78 °C (Entry 4), the deuterium levels reached 90% and 70%, respectively, although no asymmetric induction was observed.

Whereas norephedrine (**7**) and *N*-methylephedrine (**8**) were not efficient in enantioselective protonation of **4a**, they showed different behavior in deuteriation experiments. Indeed, deuterium was transferred with up to 90% effectiveness from *N*-methylephedrine (Table 6, Entry 10) but with only 22% effectiveness from the more acidic norephedrine (Entry 9). Substitution of the ephedrine hydroxy group for a methoxy group in (+)-**9** raised the level of deuterium incorporation over that obtained with (–)-ephedrine [(–)-**6**, 50 vs. 25%, Entries 11 and 7] and similar to that observed when **6-D** was used (Entry 6). This result confirmed the role of the hydroxy group in the delivery of the proton.

Finally we studied the effects of the acidities of the quenching reagents on the *ee* values obtained from the asymmetric protonations. The roles of those reagents are usually to regenerate the chiral sources. Experiments (Entries 12–17; cf. Entries 2 or 3) carried out with aniline (+)-**5** and different protic reagents (alcohols, phenol, acetic acid) showed similar deuterium levels with use of D_2O, ROD, or PhOD, but the degree of enantioselectivity was significantly lower with the more acidic phenol (Entries 15 and 16). On moving to acetic acid, no asymmetric induction was observed (Entry 17). Moreover, in one experiment, AcOH was added immediately after the addition of water (Table 6, Entry 8). In that case a high *ee* was obtained, suggesting that enantioselective protonation had been complete before the addition of AcOH at –78 °C. All these experiments were in good agreement with our previous hypothesis on the par-



Scheme 2. Reagents and conditions. *i*) ClCOOMe, NaOH (2 N), pH 8–9, room temp., 14 h, 97%; *ii*) ClCOO*i*Bu, NEt_3, $CHCl_3$, 1 h, room temp., then piperidine; 56%; *iii*) *s*BuLi (1.75 equiv.), LiBr (1.75 equiv.), *rac*-**2b** (3.94 mmol) –78 °C, (–)-(1*R*,2*S*)-**6** (2 equiv.). –20 °C, then –78 °C, addition of H_2O; 98%; *ee*: 99%. *iv*) HCl (6 N), reflux, 3 d; 99%, *ee*: 99%.

ticipation of the quenching reagent in the enantioselective process. Proton/deuterium exchanges (equilibrium *d* in Scheme 1) have previously been postulated to explain the deuterium levels observed in asymmetric protonations of lactones.[38]

Enantio-Enriched Pipecolic Acids

As a practical application of this method, we prepared the racemic amide **2b** (Scheme 2) on a gram scale and then subjected it to deracemization under the standard conditions (Table 2, Entry 3) in the presence of (–)-ephedrine [(–)-**6**]. The amide (+)-**2b** was obtained in an excellent yield and *ee* (98 and 99%, respectively).

Of the different attempts to hydrolyze the amide **2b**, the acidic conditions (HCl, 6 N, reflux, 3 d) gave the best results in terms both of yields and *ee* values. The enantiomeric purity, checked by HPLC, was completely retained. The *N*-protected pipecolic acid (+)-(*R*)-**11** (Scheme 2) was obtained from (±)-pipecolic acid (**3**) in 51% overall yield and 99% *ee*. The efficiency of this synthetic process makes it attractive for the synthesis of enantio-enriched pipecolic acid derivatives.

Conclusions

An efficient method for deracemization of pipecolamides **2** (*ee* > 95%) has been developed. If several results, such as those relating to the effects of temperature and the choice of the deprotonating base, are reminiscent of those found by Vedejs et al., salient observations have been made. *a*) An "*external quench*" by water, added to hydrolyze the reaction mixture, appeared to be the major process with the aniline derivative (+)-**5**, whereas both *internal* and *external* quenches could be involved with the more acidic ephedrines (**6**). It would be premature to propose a model for the mixed aggregates assumed to undergo the enantioselective protonation at this stage, knowledge about aggregates in solution still being in its infancy. *b*) The enolate **4a** was characterized by ^{1}H and ^{13}C NMR spectroscopy. NOESY and COSY experiments were in favor of the formation of the *E* stereoisomer as two rotamers. The efficiency of the enantioselective protonation did not reflect the ratio of the *E*/*Z* configurations of the enolates. It seems that in this case the approach of the proton is controlled by only one of the two trigonal centers in the enolate (the carbon in the 2-position).[39] *c*) Optimization of the formation of enolate **4a** suggested that a mixed potassium-lithium alkoxide could be an alternative to the use of *s*BuLi. *d*) The asymmetric protonation of pipecolamides was not strongly dependent on the substitution of the exo- or endocyclic nitrogens. Finally, we have shown that deracemization of pipecolamide **2b** with the aid of commercially available (+)- or (–)-ephedrine [(+)- or (–)-**6**] can offer an efficient route to the preparation of both enantiomers of *N*-protected pipecolic acid on a gram scale.

Experimental Section

General Methods: Unless otherwise stated, all reactions were performed under argon in glassware oven-dried overnight at 110 °C. THF was distilled from benzophenone ketyl under argon prior to use. Diisopropylamine and $BF_3{\cdot}Et_2O$ were distilled from calcium hydride and diethyl ether from lithium aluminium hydride. Lithium chloride and lithium bromide were dried in vacuo (0.1 Pa) at 50 °C for 14 h. Zinc bromide was dried at 300 °C in vacuo (1 Pa) for 1 h and was then sublimed (0.1 Pa). *n*BuLi and *s*Buli were titrated by the described methods.[40] (1*S*,2*R*)-(+)-Ephedrine [(+)-**6**], (1*R*,2*S*)-(–)-ephedrine [(–)-**6**], (1*S*,2*R*)-(+)-norephedrine (**7**), (1*S*,2*R*)-(+)-*N*-methylephedrine (**8**), and (1*S*,2*S*)-(+)-pseudoephedrine (**10**) were commercially available. (*R*)-(+)-[5-Chloro-2-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline was obtained from its commercially available tartrate.[5] (1*S*,2*R*)-*O*-Methylephedrine (**9**),[41] methyl 2-(dipropylcarboxamido)piperidine-1-carboxylate (**2a**),[9a,14] and methyl 2-(piperidinecarboxamido)piperidine-1-carboxylate (**2b**)[14] have been described previously. All other reagents or catalysts were used as obtained from commercial sources (purity > 98%). Thin layer chromatography (TLC) was performed on silica gel plates (60 F-254, 0.1 mm) with iodine and/or UV detection. Flash chromatography was carried out on silica gel (SI 60, 0.040–0.063 mm, Merck). Optical rotations were measured with a Perkin–Elmer 241 polarimeter with a sodium lamp (589 nm) as the light source. Infra-red (IR) spectra were recorded with a Perkin–Elmer 684 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 MHz (^{1}H) or 62 MHz (^{13}C) with TMS and residual protic solvent ($CHCl_3$) as the reference and solvent respectively. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). The proton spectra are reported as follows: δ (ppm), number of protons, multiplicity, coupling constant *J* (Hz), assignment. ^{13}C NMR spectra are reported as follows: δ (ppm), assignment. DEPT and two-dimensional NMR spectroscopy were used, where appropriate, to aid in the assignments of signals in the ^{1}H and ^{13}C NMR spectra. Low-resolution mass spectra were recorded on a NermagR10 instrument (EI, 70 eV). Chiral HPLC analyses were performed on a Waters instrument with chiral stationary columns from Chiralcel.

Representative Procedure for the Synthesis of Amides: Triethylamine (0.77 mL, 5.35 mmol, 1 equiv.) and *tert*-butyl chloroformate (0.7 mL, 5.4 mmol, 1.01 equiv.) were added dropwise to a solution of (1-methoxycarbonyl)piperidine-2-carboxylic acid (1 g, 5.35 mmol) in chloroform (15 mL), cooled to 0 °C. The mixture was stirred for 1 h at 0 °C. The secondary amine (5.35 mmol, 1 equiv.) was added and the reaction mixture was stirred for 3 h at 0 °C. The reaction was quenched with water, followed by extraction with dichloromethane. The combined organic layers were washed successively with brine (20 mL), dilute hydrochloric acid (3 N, 2 × 20 mL), aqueous sodium hydrogencarbonate (saturated, 2 × 20 mL), and brine (20 mL) and dried with magnesium sulfate. After concentration in vacuo, the residue was purified by flash column chromatography to afford the desired product (Figure 5).

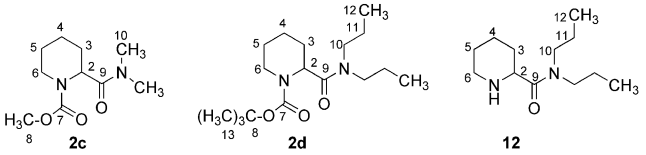


Figure 5. Numbering of carbon atoms of pipecolamides.

Methyl 2-(Dimethylcarboxamido)piperidine-1-carboxylate (2c): Two conformers (38%), colorless oil, b.p. 80 °C (0.1 Pa). $[a]_D^{22}$ = –29.6 (c = 3, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 1.42–1.90 (m, 6 H, 3-H, 4-H, 5-H), 2.94 (s, 3 H, NCH_3), 3.06 (s, 3 H, NCH_3), 3.47–3.68 (m, 1 H, 6-H), 3.70 (s, 3 H, OCH_3), 3.74–3.93 (m, 1 H, 6-H), 5.06 (s, 1 H, 2-H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$, 20 °C): δ = 19.5 (4-C), 24.9 (5-C), 26.5 (3-C), 37.1 and 35.8 (10-C, 10′-C), 42.0 (6-C), 51.0 (2-C), 52.7 (8-C), 156.8 (7-C), 175.4 (9-C) ppm. IR (film): $\tilde{\nu}_{max}$ = 1698 (NCOO), 1652 (CON) cm^{-1}. MS (EI): m/z (%) = 215 [M+1] (2), 214 (11), 142 (100) cm^{-1}. $C_{10}H_{18}N_2O_3$ (214): calcd. C 56.06, H 8.46, N 13.07, O 22.40; found C 55.89, H 8.35, N 13.04, O 22.26.

***tert*-Butyl 2-(Dimethylcarboxamido)piperidine-1-carboxylate (2d):** Di-*tert*-butyl dicarbonate (270 mg, 1.39 mmol, 1.18 equiv.) in dichloromethane (1 mL) was added to *N*,*N*-dipropylpiperidine-2-carboxamide[9a] (222 mg, 1.18 mmol) in dichloromethane (6 mL). The mixture was stirred at room temperature for 24 h and the volatile compounds were evaporated. The residue was diluted with dichloromethane and the solution was washed with diluted hydrochloric acid (3 N, 3 × 10 mL), satd. aqueous sodium hydrogen carbonate (10 mL), and then brine (10 mL). The organic layer was dried with magnesium sulfate. After evaporation of the solvent, amide **2d** was isolated (120 mg, 33% yield) as a colorless liquid. ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 4.90–5.10 (m, 1 H, 2-H), 4.10–3.80 (m, 1 H, 1 6-H), 3.29–3.18 (m, 5 H, 1 6-H, 4 10-H), 1.84–1.47 (m, 10 H, 2 3-H, 2 4-H, 2 5-H, 4 11-H), 0.85 (t, J = 7 Hz, 3 H, 15-H), 0.81 (t, J = 7.3 Hz, 3 H, 15′-H) ppm. ^{13}C NMR (62 MHz, $CDCl_3$, 20 °C): δ = 171.2 (9-C), 157.4 (7-C), 79.6 (8-C) 49.5 (2-C), 47.8 (6-C), 43.8 (2 10-C), 28.5 (3 13-C), 27.2 (3-C), 22.3 (5-C), 21.0 (4-C), 19.7 (2 11-C), 11.4 (2 12-C) ppm. IR (film): $\tilde{\nu}_{max}$ = 1701 (NCOO), 1655 (CON) cm^{-1}.

***N*,*N*-Dipropylpiperidine-2-carboxamide (12)[9] from Amide 2d:** Enantio-enriched amide (+)- or (–)-**2d** (40 mg, 0.13 mmol) in chloroform (2 mL) was cooled to 0 °C. Trifluoroacetic acid (5 mL) was added and the solution was stirred at 0 °C for 30 min. The mixture was allowed to warm to room temp. and the volatile compounds were evaporated. Chloroform was added to the residue. The organic layer was washed with sodium hydroxide (2 N, 2 × 5 mL) and then brine, dried with magnesium sulfate, filtered and concentrated.

From amide (*R*)-(+)-**2d** {$[a]_D^{25}$ = +10 (c = 4, $CHCl_3$) obtained with (–)-ephedrine **6** for the deracemization}, (*R*)-(+)-*N*,*N*-dimethylpiperidine-2-carboxamide [(+)-**12**] was obtained in 89% yield and 85% *ee* {$[a]_D^{25}$ = +8.9 (c = 2.4, in $CHCl_3$)}.

From amide (*S*)-(–)-**2d** {$[a]_D^{25}$ = –12.5 (c = 4.35, in $CHCl_3$) obtained with aniline (+)-**5** for the deracemization}, (*S*)-(–)-*N*,*N*-dipropylpiperidine-2-carboxamide [(–)-**12**] was obtained in 85% yield and 86% *ee* {$[a]_D^{25}$ = –9.0 (c = 2.53, in $CHCl_3$); ref.[9] $[a]_D^{25}$ = –10.4 (c = 4, in $CHCl_3$)}.

Deracemization of Amides 2 through Enantioselective Protonation. Typical Procedure with LiBr as Additive: A solution of amide **2a** (0.15 M, 80 mg, 0.3 mmol) and LiBr (145 mg, 1.75 equiv.) in THF (2 mL) was cooled to –78 °C for 1 h. *s*BuLi (1.3 M in cyclohexane, 1.75 equiv., 0.41 mL) was added over 10 min. After 15 min, a deuterium test (see below) was carried out on an aliquot. The yellow mixture was stirred for 45 min at –78 °C and the chiral proton source (2 equiv., 0.15 M) in THF (4 mL) was then added over 30–40 min at this temperature. After 30 min at –78 °C, the yellow solution was warmed to –30 °C over a 30 min period. The orange-red mixture was stirred for 5 min at –30 °C and then cooled again to –78 °C for addition of water (0.2 mL, 37 equiv.[42]). The mixture was allowed to warm to room temp. The volatile compounds were removed in vacuo and the residue was partitioned between ethyl acetate and dilute hydrochloric acid (3 N). The organic layer was successively washed with dilute hydrochloric acid (3 N), sodium hydroxide (2 N), and brine and was then dried with magnesium sulfate. After filtration, evaporation of the solvent, and purification by flash chromatography (eluent: CH_2Cl_2/MeOH, 97:3), the enantio-enriched amide was isolated. The yields and *ee* values are shown in Tables 1, 2, 3, 4, 5, and 6. The *ee* values were determined by chiral HPLC as follows.

Compound 2a: Chiralcel OD, *n*-heptane/*i*PrOH 95:5; λ = 220 nm, flow rate: 0.6 mL min^{-1}. t_R (+)-(*R*): 11 min; t_R (–)-(*S*): 18 min.

Compound 2b: Chiralcel OD, *n*-heptane/*i*PrOH 95:5; λ = 215 nm, flow rate: 0.6 mL min^{-1}. t_R (+)-(*R*): 27 min; t_R (–)-(*S*): 48 min.

Compound 2c: Chiralcel OB, *n*-hexane/*i*PrOH 99:1; λ = 210 nm, flow rate: 0.6 mL min^{-1}. t_R (+)-(*R*): 35 min; t_R (–)-(*S*): 53 min.

Compound 2d: The *ee* values were determined from the optical rotation of *N*,*N*-dipropylpiperidine-2-carboxamide (**12**, cf. above).

Deuterium Test. Typical Procedure: In the deracemization procedure, an aliquot (0.3 mL) of the reaction mixture (base, amide **2**, and solvent) was removed after 10–15 min stirring at –78 °C and rapidly transferred into a vial containing deuterium oxide (0.5 mL). The mixture was vigorously stirred and then extracted with deuteriochloroform. The solvent was evaporated and the residue was analyzed by ^{1}H NMR spectroscopy. When the proton in the 2-position had completely disappeared in the spectrum, the deracemization experiment was carried out.

Deracemization of 2a with a Bimetallic Base: (–)-Ephedrine [(–)-**6**, 47 mg, 0.28 mmol, 1.25 equiv.] in THF (0.9 mL) was added at room temperature to KH (11 mg, 0.28 mmol, 1.25 equiv.). The mixture was cooled to –40 °C and *n*BuLi was added (0.31 mL, 0.495 mmol, 2.25 equiv.). After stirring for 40 min at this temperature, the mixture was cooled to –78 °C and amide **2a** (60 mg, 0.22 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 30 min and (–)-ephedrine [(–)-**6**, 98 mg, 0.44 mmol, 2 equiv.] in THF (3 mL) was added. The procedure was then identical to that described above for the deracemization.

Li Enolate 4a: Methyllithium in diethyl ether (2.2 M, 0.15 mL, 0.33 mmol, 3 equiv.) was added by syringe to an ^{1}H NMR tube previously dried, stoppered with a rubber septum, and flushed with nitrogen. The diethyl ether was removed under vacuum (2 Pa, 40 min). A white solid was obtained and cooled to –40 °C. [D_8]-THF [0.25 mL, distilled from a few drops of *n*BuLi in hexanes (1.6 M) before use] was added. The mixture was cooled to –70 °C and amide **2a** (30 mg, 0.11 mmol) in [D_8]THF (0.25 mL) was added. ^{1}H NMR spectra of the mixture of rotamers (70:30) were then recorded at –60 °C. The signals were assigned by comparison with those observed in the ^{1}H NMR of amide **2a** recorded under the same conditions. The enolate was stable for 18 h at –60 °C and the ^{1}H NMR signals were not modified upon warming until –40 °C. Signals coalesced at –30 °C.

Supporting Information (see also the footnote on the first page of this article): Preparation and ^{1}H NMR of lithium enolate **4a**. Preparation of amide **2b** on a gram scale.

Acknowledgments

The authors thank P. and L. Duhamel for helpful discussions and H. Oulyadi for NMR experiments at low temperature. The work was supported by the Réseau Interrégional de Chimie Organique Fine (Contrat de Plan Etat-Régions Haute-Normandie, Basse-Nor-

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Received: June 30, 2009
Published Online: September 16, 2009

