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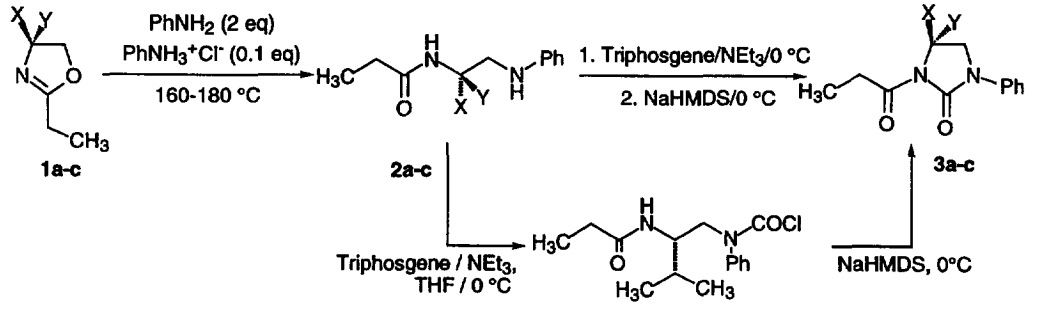
N-Acylimidazolidin-2-ones: new chiral auxiliaries for carboxylic acid alkylation

Kurt Königsberger, Kapa Prasad,* Oljan Repic and Thomas J. Blacklock

Process Research and Development, Chemical and Analytical Development, Novartis Pharmaceuticals Corporation, 59 Route 10, East Hanover, NJ 07936, USA

Abstract: Chiral *N*-acylated imidazolidin-2-ones, readily available from aminoethanols in three steps through the nucleophilic opening of oxazoline intermediates, have been demonstrated to undergo highly diastereoselective benzylations and methylations via their sodium enolates. In most cases, the resulting products are highly crystalline, and the chiral auxiliaries can be readily recycled. © 1997 Elsevier Science Ltd

Chiral aminoethanols, which are easily accessible from the reduction of α-aminoacids, are widely used in asymmetric transformations. Diastereoselective aldol and alkylation reactions with aminoethanol derived *N*-acyloxazolidin-2-ones are the result of the pioneering work of Evans and coworkers.[1] Oxazolines resulting from the condensation of 1,2-aminoalcohols with carboxylic acids have been utilized by Meyers' group for the modification of the carboxy part of the molecule both in asymmetric and nonasymmetric transformations.[2] In the course of our studies on the synthesis of substituted 1,2-diaminoalkanes and 1,3-diaminoalkanes we investigated the nucleophilic opening of 5,6-dihydro-4*H*-1,3-oxazines and chiral aminoalcohol derived oxazolines (4,5-dihydrooxazoles) as a method of preparing diaminoalkanes, already functionalized at the primary amine. Although the opening of simple oxazolines by amines, resulting in acylated 1,2-diamines, was reported earlier by Fazio,[3] the opening of chiral aminoalcohol derived oxazolines is not well documented.[4] These chiral 1,2-diamines can be transformed into new imidazolidin-2-one based chiral auxiliaries.[5,12–16] In the present work we open chiral oxazolines with aniline, and cyclize the intermediates to form the corresponding *N*-acylimidazolidin-2-ones. The synthetic details and the use of these novel chiral auxiliaries in diastereoselective alkylations are reported in this communication.



Our sequence started from commercially available, enantiopure aminoethanols. In consideration of several routes to the key diamino-derivatives **2**, we decided that *N*-acylation of the aminoethanol and activation of the hydroxy function with a leaving group, followed by displacement with aniline in a reaction which may proceed via an oxazoline,[2] appeared to be inferior to the chosen strategy of utilizing a preformed oxazoline.[6] Thus, the easily prepared[7] oxazolines **1** were reacted by a slow addition to aniline at 160–180°C, in the presence of a catalytic amount of aniline hydrochloride, to

* Corresponding author.

Table 1. Synthesis of *N*-acyl-*N'*-phenyl-1,2-diamines

Cpd.	X	Y	% yield[a]	mp (°C)	$[\alpha]_D$ ($CHCl_3$)
(*S*)-**2a**	$CH(CH_3)_2$	H	45	oil	–62.4 (*c* 1.1, 20 °C)
rac-**2a**	$CH(CH_3)_2$	H	53	63-64	-
(*S*)-**2b**	$PhCH_2$	H	60	93-94	–7.5 (*c* 0.9, 22 °C)
rac-**2b**	$PhCH_2$	H	57	121-121	-
(*S*)-**2c**	Ph	H	54	106-107	+34.3 (*c* 1.2, 22 °C)
(*R*)-**2c**	H	Ph	50	105-110	–33.1 (*c* 1.7, 22 °C)

[a] Isolated after chromatography

Table 2. Synthesis of 3-acylimidazolidin-2-ones

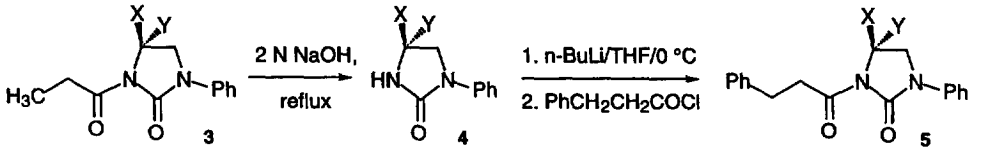
Cpd.	X	Y	% yield[a]	mp (°C)	e.e. % (HPLC)	$[\alpha]_D$ ($CHCl_3$)
(*S*)-**3a**	$CH(CH_3)_2$	H	88 (2 steps)	67-69	>99	+45.3 (*c* 1.5, 20 °C)
(*rac*)-**3a**	$CH(CH_3)_2$	H	90	61-62	-	-
(*S*)-**3b**	$PhCH_2$	H	57	94-95	>99	+48.7 (*c* 0.7, 22°C)
(*rac*)-**3b**	$PhCH_2$	H	55	81-82	-	-
(*S*)-**3c**	Ph	H	74	112-113	>99	–5.9 (*c* 1.2, 22 °C)
(*R*)-**3c**	H	Ph	85	110-112	>99	+6.0 (*c* 1.4, 22 °C)

[a] Isolated after chromatography

afford amides **2** in 45–60% yield (Table 1). Although the reaction is incomplete, the products were isolated easily by chromatography. The amides thus obtained are enantiomerically pure, as shown by chiral-phase HPLC of the cyclized products **3**.

The cyclization of the amides proceeded as expected: triphosgene/NEt_3 at 0°C formed the chloroformamide as an intermediate, which is, interestingly, stable enough for isolation and characterization. It was then cyclized by addition of a strong non-nucleophilic base such as NaHMDS to afford products **3** in 54–90% yield (Table 2). Determination of the *e.e.* of the compounds **3a–c** was performed by HPLC on a Chiracel OD-H column.

Synthesis of the dihydrocinnamoyl-derivatives **5** was accomplished by hydrolysis of **3** with refluxing aqueous NaOH, followed by deprotonation with *n*-butyllithium and acylation with dihydrocinnamoyl chloride (Table 3). No racemization was observed during these operations.



The results of the alkylation reactions are summarized in Table 4. After enolate formation, in THF at −78°C with NaHMDS,[8] the benzylation of the propionyl derivatives with benzyl bromide (3 eq) at −78°C occurs in d.e. >98%, with excellent chemical yields (Table 4). The determination of the diastereomeric ratios was performed by HPLC on a silica column, using the other diastereoisomer (from methylation reactions, see below) as a reference material. Methylation reactions of the dihydrocinnamoyl derivatives **5**, performed under the same conditions with CH_3I (5 eq), exhibited a

Table 3. Synthesis of dihydrocinnamoyl derivatives

Cpd.	X	Y	% yield[a]	mp (°C)	$[\alpha]_D$ ($CHCl_3$)
rac-**5a**	$CH(CH_3)_2$	H	66	67-69	-
(*S*)-**5b**	$PhCH_2$	H	68	134-135	+54.0 (*c* 1.1, 20 °C)
(*R*)-**5c**	H	Ph	76	121-122	+2.5 (*c* 1.06, 20 °C)

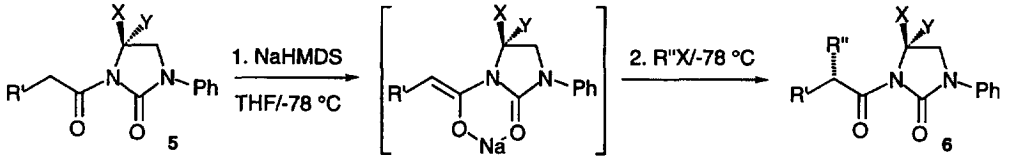
[a] From **3**, isolated after chromatography

Table 4. Alkylations of 3-acylimidazolidin-2-ones

entry	X	Y	R'	R''	d.e.[a]	product[b]	mp (°C)[c]	$[\alpha]_D$ ($CHCl_3$)
(*S*)-**3a**	$CH(CH_3)_2$	H	CH_3	$PhCH_2$	>98%	**6a** (92%)	76-78	+32.0 (*c* 0.4, 20 °C)
(*S*)-**3b**	$PhCH_2$	H	CH_3	$PhCH_2$	>98%	**6b** (91%)	121-122	+57.0 (*c* 0.7, 22 °C)
(*S*)-**3c**	Ph	H	CH_3	$PhCH_2$	>98%	**6c** (92%)	oil	+5.4 (*c* 1.0, 20 °C)
rac-**5a**	$CH(CH_3)_2$	H	$PhCH_2$	CH_3	78%	**6d** (62%)	110-111	-
(*S*)-**5b**	$PhCH_2$	H	$PhCH_2$	CH_3	89%	**6e** (84%)	113-115	+65.8 (*c* 1.0, 20 °C)
(*R*)-**5c**	H	Ph	CH_3	$PhCH_2$	72%	**6f** (54%)	oil	–29.1 (*c* 1.1, 20 °C)

[a] Determined by HPLC and ^1H NMR before purification. [b] Yield of the main diastereoisomer after purification. The yield of product mixture was generally >95%. [c] Of the main diastereoisomer.

strong dependence of the observed diastereomeric excess on the side chain of the chiral auxiliary, the benzyl residue furnishing 89% d.e.



Products can be cleaved to the acid with $LiOH/H_2O_2$ at 25°C over 12 h or, faster, with refluxing 2 M NaOH/dioxane (1:1) (30 min). The auxiliary can be recovered in >95% yield by extracting the reaction mixture with CH_2Cl_2. Isolation of the acid by extraction with EtOAc after acidification to pH 2 was almost quantitative. No racemization was observed in either case, as shown by GC analysis of the corresponding methyl esters on an Astec Chiraldex β-TA chiral capillary column.

In conclusion, the opening of easily accessible chiral oxazolines **1** with aniline appears to be a viable way of preparing *N*-acylated chiral 1,2-diamines **2**, and thus-derived imidazolidin-2-ones have been shown to perform diastereoselective alkylations similarly to the corresponding oxazolidin-2-ones. The main advantages of compounds of type **3** are high crystallinity of the products in most cases, enabling facile purification of the main diastereoisomer, as well as the ease of cleavage of the products with aqueous base. Whereas for the bulky electrophile benzyl bromide, a d.e. >98% was obtained in alkylation for all auxiliary side chains, the methylation of the dihydrocinnamoyl derived enolate afforded very good 89% d.e. only with the chiral auxiliary from phenylalaninol (benzyl side chain, entry **5b**). Although examples of higher values of diastereoselection in chiral auxiliary controlled methylation have been recently reported,[9–11] the polycyclic auxiliaries employed are synthesized in several steps and involve the resolution of racemates.

Experimental

General

Air- and/or moisture sensitive reactions were performed under argon in glassware dried by heating under vacuum. Anhydrous THF was distilled from Na–benzophenone, other solvents were purchased in anhydrous quality or were of HPLC grade purity, as necessary. ^{1}H NMR coupling constants are given in Hz.

General procedure for the synthesis of oxazolines (1)

A solution of aminoalcohol (1 eq) and triethoxypropane (1 eq) in 1,2-dichloroethane (1 mL/mmol) was held at reflux for 14 h. Distillation of the resulting yellow solution under the appropriate vacuum afforded the product as a clear liquid.

General procedure for the synthesis of N-*acyl*-N′-*phenyl-1,2-diamines (2)*

To the stirred mixture of aniline (2 eq) and aniline hydrochloride (0.1 eq), heated in a 180°C oil bath, the oxazoline (1 eq) was added over 1 h. The mixture was heated for another 2 h, cooled to 40°C, and excess aniline was removed under high vacuum. Chromatography (silica gel, toluene/EtOAc, 4:1) of the dark residue afforded a crystalline material of >95% purity (by ^{1}H NMR), of which an analytical sample was derived by recrystallization from hexanes/EtOAc. For physical data see Table 1.

N-*[3-Methyl-1-(phenylamino)but-2-yl]propionamide (2a)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J=7.9, 2H); 6.69 (t, J=7.7, 1H); 6.59 (d, J=8.4, 2H); 5.40 (br, 1H); 4.0–4.12 (m, 2H); 3.27 (dd, J=12.1, 3.9, 1H); 3.10 (dd, J=12.1, 8.8, 1H); 2.21 (q, J=7.5, 2H); 1.88 (oct, J=6.6, 1H); 1.16 (t, J=7.6, 3H); 0.99 (d, J=6.7, 3H); 0.97 (d, J=6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 148.3, 129.2 (2C), 117.2, 112.5 (2C), 54.0, 46.7, 30.2, 29.8, 19.5, 18.2, 9.9. MS (CI) 235 (MH^+). HRMS (FAB) calcd for $C_{14}H_{22}N_2O$+Na^+ 257.1630, found 257.1615.

N-*[1-Phenyl-3-(phenylamino)prop-2-yl]propionamide (2b)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12–7.36 (m, 7H); 6.69 (t, J=8.3, 1H); 6.58 (d, J=8.5, 2H); 5.43 (br d, J=8.1, 1H); 4.45 (m, 1H); 4.00 (s, 1H); 3.27 (dd, J=12.4, 4.6, 1H); 3.15 (dd, J=12.4, 7.6, 1H); 2.91 (m, 2H); 2.13 (q, J=7.6, 2H); 1.07 (t, J=7.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 148.1, 137.1, 129.24 (2C), 129.15 (2C), 128.6 (2C), 126.7, 117.5, 112.7 (2C), 50.0, 47.7, 38.7, 29.7, 9.7. HRMS calcd for $C_{18}H_{22}N_2O$+Na^+ 305.1630, found 305.1635. Anal. calcd for $C_{18}H_{22}N_2O$: C 76.56, H 7.85, N 9.92; found: C 76.34, H 7.67, N 9.92.

N-*[1-Phenyl-2-(phenylamino)ethyl]propionamide (2c)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.43 (m, 5H); 7.17 (t, J=7.9, 2H); 6.72 (t, J=7.6, 1H); 6.63 (d, J=8.5, 2H); 5.43 (br d, J=7.4, 1H); 5.28 (q, J=6.8, 1H); 3.88 (br s, 1H); 3.50 (m, 2H); 2.23 (q, J=7.6, 2H); 1.14 (t, J=7.6, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 147.8, 139.6, 129.3 (2C), 129.0 (2C), 127.9, 126.6 (2C), 117.9, 113.0 (2C), 52.8, 49.2, 29.7, 9.7. MS (CI) 269 (MH^+). Anal. calcd for $C_{17}H_{20}N_2O$: C 76.09, H 7.51, N 10.44; found: C 76.26, H 7.43, N 10.44.

General procedure for the synthesis of 4-substituted 1-phenyl-3-propionylimidazolidin-2-ones (3)

To a stirred solution of the amide **2** (1 eq) and triethylamine (1.8 eq) in anhydrous THF (5 mL/mmol) at 0°C was added slowly triphosgene (0.45 eq) as a solution in anhydrous THF (2 mL/mmol). The mixture was stirred for 10 min at 0°C, then sodium hexamethyldisilazide (2.5 eq) was added. After 30 min at 0°C no more starting material or intermediates could be detected by TLC. After addition of sodium phosphate buffer (0.2 M, pH 7), the mixture was brought to pH 7 with HCl (2 N) and extracted with EtOAc (4×50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. Chromatography and/or crystallization afforded the pure imidazolidin-2-one. For physical data see Table 2. The optical purity of the material was determined after chromatography by

HPLC on a Chiracel OD–H column, eluting with 1 mL/min hexanes/isopropanol, 95:5, detection at 256 nm.

*4-Isopropyl-1-phenyl-3-propionylimidazolidin-2-one (**3a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 2H); 7.38 (m, 2H); 7.16 (t, J=7.2, 1H); 4.43 (ddd, J=9.2, 3.7, 2.5, 1H); 3.90 (t, J=9.3, 1H); 3.55 (dd, J=9.5, 2.5, 1H); 2.87–3.14 (m, 2H); 2.43 (m, 1H); 1.19 (t, J=7.4, 3H); 0.97 (d, J=7.0, 3H); 0.84 (d, J=7.0, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 153.0, 138.6, 128.9 (2C), 124.3, 119.0 (2C), 54.6, 43.1, 29.5, 28.8, 18.0, 14.5, 8.8. MS (CI) 261 (MH^+). HRMS (FAB) calcd for $C_{15}H_{20}N_2O_2$+Na^+ 283.1422, found 283.1420. Anal. calcd for $C_{15}H_{20}N_2O_2$: C 69.20, H 7.74, N 10.76; found: C 69.15, H 7.75, N 10.88.

*4-Benzyl-1-phenyl-3-propionylimidazolidin-2-one (**3b**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.42 (m, 9H); 7.13 (tm, J=7.0, 1H); 4.68 (tdd, J=9.1, 3.1, 2.0, 1H); 3.84 (t, J=8.9, 1H); 3.53 (dd, J=9.6, 2.0, 1H); 3.31 (dd, J=13.3, 3.1, 1H); 2.9–3.15 (m, 2H); 2.77 (dd, J=13.3, 9.4, 1H); 1.23 (t, J=7.3, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 152.5, 138.7, 136.1, 129.4 (2C), 128.9 (2C), 128.7 (2C), 127.0, 124.4, 119.2 (2C), 51.6, 46.4, 38.6, 29.5, 8.7. MS (CI) 309 (MH^+). HRMS calcd for $C_{19}H_{20}N_2O_2$+Na^+ 331.1422, found 331.1420. Anal. calcd for $C_{19}H_{20}N_2O_2$: C 74.00, H 6.54, N 9.08; found: C 73.81, H 6.45, N 9.14.

*1,4-Diphenyl-3-propionylimidazolidin-2-one (**3c**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.60 (m, 2H); 7.25–7.43 (m, 7H); 7.16 (t, J=7.3, 1H); 5.42 (dd, J=9.4, 2.8, 1H); 4.32 (t, J=9.4, 1H); 3.71 (dd, J=9.4, 2.8, 1H); 2.23 (q, J=7.4, 2H); 1.14 (t, J=7.4, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 152.8, 141.0, 138.6, 129.0 (4C), 128.2, 125.6 (2C), 124.4, 119.0 (2C), 53.6, 50.7, 29.6, 8.5. MS (CI) 295 (MH^+). Anal. calcd for $C_{18}H_{18}N_2O_2$: C 73.45, H 6.16, N 9.52; found: C 73.55, H 6.12, N 9.56.

*General procedure for the synthesis of 4-substituted 1-phenylimidazolidin-2-ones (**4**)*

A suspension of the 3-acylimidazolidin-2-one **3** in aqueous NaOH (2 N) was heated at reflux with vigorous stirring until TLC indicated complete consumption of starting material. After extraction of the mixture with CH_2Cl_2 (4×), the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to dryness to afford the pure imidazolidin-2-one **4** as a white solid.

*(RS)-4-Isopropyl-1-phenylimidazolidin-2-one (**4a**)*

White solid; mp 124.5–126°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dm, J=8.0, 2H); 7.34 (m, 2H); 7.16 (tm, J=7.3, 1H); 5.60 (s, 1H); 3.94 (m, 1H); 3.48–3.62 (m, 2H); 1.77 (oct, J=6.7, 1H); 0.99 (d, J=6.6, 3H); 0.97 (d, J=6.7, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 140.0, 128.8 (2C), 122.4, 117.6 (2C), 54.8, 49.0, 33.1, 18.1, 17.7. MS (CI) 205 (MH^+). HRMS (FAB) calcd for $C_{12}H_{16}N_2O$+Na^+ 227.1160, found 227.1165. Anal. calcd for $C_{12}H_{16}N_2O$: C 70.56, H 7.89, N 13.71; found: C 70.51, H 7.94, N 13.73.

*(S)-4-Benzyl-1-phenylimidazolidin-2-one (**4b**)*

White solid; mp 119–123°C; $[\alpha]_D^{22}$ −50.8 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.57 (m, 2H); 7.18–7.40 (m, 7H); 7.05 (tm, J=7.3, 1H); 5.30 (s, 1H); 3.90–4.10 (m, 2H); 3.63 (m, 1H); 2.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 139.9, 136.6, 129.05 (2C), 128.85 (2C), 128.77 (2C), 127.0, 122.6, 117.7 (2C), 50.38, 50.35, 42.2. MS (CI) 253 (MH^+). Anal. calcd for $C_{16}H_{16}N_2O$: C 76.16, H 6.39, N 11.10; found: C 75.91, H 6.32, N 11.07.

*(R)-1,4-Diphenylimidazolidin-2-one (**4c**)*

White solid; mp 135–137°C; $[\alpha]_D^{20}$ −15.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.56 (m, 2H); 7.27–7.45 (m, 7H); 7.04 (t, J=7.3, 1H); 5.65 (s, 1H); 4.89 (ddd, J=8.6, 7.0, 1.1, 1H); 4.24

(t, J=9.1, 1H); 3.72 (dd, J=9.1, 7.0, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 141.2, 139.7, 129.0 (2C), 128.8 (2C), 128.4, 126.0 (2C), 122.7, 117.8 (2C), 53.7, 52.9. MS (CI) 238 (MH^+). Anal. calcd for $C_{15}H_{14}N_2O$: C 75.61, H 5.92, N 11.76; found: C 75.38, H 5.81, N 11.75.

*General procedure for the synthesis of 4-substituted 1-phenyl-3-(dihydrocinnamoyl)-imidazolidin-2-ones (**5**)*

To a solution of the imidazolidin-2-one **4** (1 eq) in anhydrous THF (6 mL/mmol) at 0°C was added *n*-BuLi (1.05 eq, 2.5 M solution). After stirring for 15 min at 0°C, dihydrocinnamoyl chloride (1.2 eq) was added, and the mixture was stirred for 3 h at 0°C, when TLC indicated consumption of the starting material. After addition of sodium phosphate buffer (0.2 M, pH 7) the mixture was extracted with CH_2Cl_2 (4×), the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to dryness. Chromatography and recrystallization afforded the pure compound. For physical data see Table 3.

*(RS)-4-Isopropyl-1-phenyl-3-(3-phenylpropionyl)imidazolidin-2-one (**5a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dm, J=7.0, 2H); 7.37 (tm, J=8.0, 2H); 7.24–7.30 (m, 4H); 7.12–7.24 (m, 2H); 4.42 (ddd, J=9.2, 3.7, 2.5, 1H); 3.87 (t, J=9.3, 1H); 3.53 (dd, J=9.6, 2.4, 1H); 3.22–3.48 (m, 2H); 2.93–3.11 (m, 2H); 2.40 (dsept, J=2.8, 7.0, 1H); 0.95 (d, J=7.0, 3H); 0.81 (d, J=7.0, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 153.0, 141.0, 138.6, 129.0 (2C), 128.5 (2C), 128.3 (2C), 126.0, 124.4, 119.2 (2C), 54.7, 43.1, 37.5, 30.8, 28.9, 18.1, 14.5. MS (CI) 337 (MH^+). HRMS (FAB) calcd for $C_{21}H_{24}N_2O_2$+Na^+ 359.1736, found 359.1725.

*(S)-4-Benzyl-1-phenyl-3-(3-phenylpropionyl)imidazolidin-2-one (**5b**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08–7.42 (m, 15H); 4.67 (m, 1H); 3.91 (t, J=9.0, 1H); 3.51 (dd, J=9.5, 2.0, 1H); 3.22–3.47 (m, 3H); 2.97–3.17 (m, 2H); 2.77 (dd, J=13.3, 9.2, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 152.4, 140.9, 138.5, 136.0, 129.4 (2C), 128.9 (2C), 128.7 (2C), 128.5 (2C), 128.3 (2C), 127.0, 126.0, 124.4, 119.2 (2C), 51.5, 46.3, 38.5, 37.5, 30.5. MS (CI) 385 (MH^+). Anal. calcd for $C_{25}H_{24}N_2O_2$: C 78.10, H 6.29, N 7.29; found: C 78.33, H 6.24, N 7.28.

*(R)-1,4-Diphenyl-3-(3-phenylpropionyl)imidazolidin-2-one (**5c**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.58 (m, 2H); 7.12–7.43 (m, 13H); 5.43 (dd, J=9.3, 2.8, 1H); 4.31 (t, J=9.4, 1H); 3.71 (dd, J=9.4, 2.9, 1H); 3.37 (m, 2H); 2.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 152.8, 140.89, 140.79, 138.6, 129.1 (4C), 128.54 (2C), 128.34 (2C), 128.24, 126.0, 125.6 (2C), 124.5, 119.1 (2C), 53.6, 50.7, 37.6, 30.4. MS (CI) 371 (MH^+). Anal. calcd for $C_{24}H_{22}N_2O_2$: C 77.81, H 5.98, N 7.56; found: C 77.57, H 5.96, N 7.52.

*General procedure for the alkylation of 4-substituted 1-phenyl-3-acylimidazolidin-2-ones (**3** or **5**)*

To a solution of amide **3** or **5** (1.0 eq) in anhydrous THF (10 mL/mmol) was added NaHMDS (1.0 M in THF, 1.1 eq) at −78°C. Stirring was continued for 1 h. After addition of the alkyl halide (3 eq of BnBr, or 5 eq of CH_3I), stirring was continued at −78°C until the starting material was completely consumed (3–5 h). The mixture was quenched with sodium phosphate buffer (pH 7, 0.2 M), extracted with CH_2Cl_2 (4×), the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. HPLC analysis (100×4.6 mm Spherisorb silica 3 μm; 0.8 mL/min hexanes/EtOAc 90:10; UV detection 262 nm) allowed determination of the diastereomeric ratio. Confirmation of the diastereomeric excess was obtained by ^{1}H NMR, where applicable. Chromatography (silica gel, hexanes/EtOAc, 5/1) afforded the pure alkylation product, which was recrystallized (series **a** and **b**) from hexane/EtOAc. For physical data see Table 4.

*(S)-4-Isopropyl-3-[(R)-2-methyl-3-phenylpropionyl]-1-phenylimidazolidin-2-one (**6a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dm, J=7.8, 2H); 7.37 (tm, J=8.0, 2H); 7.22–7.34 (m, 4H); 7.12–7.22 (m, 2H); 4.43 (dt, J=9.2, 2.8, 1H); 4.33 (hex, J=7.1, 1H); 3.87 (t, J=9.4, 1H); 3.49 (dd, J=9.5, 2.5, 1H); 3.20 (dd, J=13.2, 7.1, 1H); 2.64 (J=13.2, 7.1, 1H); 2.22 (dsept, J=2.8, 7.0, 1H); 1.16 (d, J=6.7, 3H); 0.89 (d, J=7.0, 3H); 0.69 (d, J=7.0, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 152.7, 139.7, 138.6, 129.3 (2C), 129.0 (2C), 128.2 (2C), 126.1, 124.4, 119.3 (2C), 54.6, 42.8, 40.3, 39.7, 28.8, 18.0, 16.6, 14.2. MS (CI) 351 (MH^+). HRMS (FAB) calcd for $C_{22}H_{26}N_2O_2$+Na^+ 373.1892, found 373.1905.

*(S)-4-Benzyl-3-[(R)-2-methyl-3-phenylpropionyl]-1-phenylimidazolidin-2-one (**6b**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05–7.42 (m, 15H); 4.69 (tt, J=7.9, 1.6, 1H); 4.31 (sex, J=7.1, 1H); 3.82 (t, J=9.0, 1H); 3.48 (dd, J=9.5, 2.1, 1H); 3.26 (dd, J=13.2, 7.2, 1H); 3.08 (dd, J=13.3, 3.2, 1H); 2.69 (dd, J=13.2, 7.7, 1H); 2.61 (dd, J=13.2, 8.9, 1H); 1.18 (d, J=6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 152.1, 139.8, 138.5, 135.9, 129.43 (2C), 129.37 (2C), 128.90 (2C), 128.66 (2C), 128.21 (2C), 127.0, 126.2, 124.5, 119.4 (2C), 51.4, 46.1, 39.95, 39.84, 38.4, 16.9. MS (CI) 399 (MH^+). Anal. calcd for $C_{26}H_{26}N_2O_2$: C 78.36, H 6.58, N 7.03; found: C 78.52, H 6.26, N 6.96.

*(S)-1,4-Diphenyl-3-[(R)-2-methyl-3-phenylpropionyl]imidazolidin-2-one (**6c**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dm, J=8.2, 2H); 7.10–7.45 (m, 13H); 5.42 (dd, J=9.4, 3.2, 1H); 4.33 (sex, J=7.2, 1H); 4.27 (t, J=9.4, 1H); 3.54 (dd, J=9.4, 3.2, 1H); 3.15 (dd, J=13.2, 6.9, 1H); 2.53 (dd, J=13.3, 7.9, 1H); 1.13 (d, J=6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 152.4, 140.7, 139.4, 138.5, 129.22 (2C), 129.02 (2C), 128.94 (2C), 128.16 (2C), 127.92, 126.0, 125.4 (2C), 124.5, 119.2 (2C), 53.7, 50.5, 39.78, 39.76, 16.4. MS (CI) 385 (MH^+). HRMS (FAB) calcd for $C_{25}H_{24}N_2O_2$+Na^+ 407.1735, found 407.1740.

*(RS)-4-Isopropyl-3-[(RS)-2-methyl-3-phenylpropionyl]-1-phenylimidazolidin-2-one (**6d**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (dm, J=7.8, 2H); 7.37 (tm, J=7.5, 2H); 7.10–7.26 (m, 6H); 4.24–4.47 (m, 2H); 3.68 (t, J=9.4, 1H); 3.44 (dd, J=9.5, 2.3 1H); 3.04 (dd, J=13.3, 7.9, 1H); 2.68 (J=13.3, 7.2, 1H); 2.38 (dsept, J=4.0, 7.0, 1H); 1.27 (d, J=6.8, 3H); 0.94 (d, J=7.0, 3H); 0.82 (d, J=7.0, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 152.6, 139.8, 138.6, 129.2 (2C), 129.0 (2C), 128.1 (2C), 126.0, 124.4, 119.3 (2C), 54.8, 43.0, 9.70, 39.62, 29.0, 18.0, 17.8, 14.7. MS (CI) 351 (MH^+). HRMS (FAB) calcd for $C_{22}H_{26}N_2O_2$+Na^+ 373.1892, found 373.1905.

*(S)-4-Benzyl-3-[(S)-2-methyl-3-phenylpropionyl]-1-phenylimidazolidin-2-one (**6e**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.40 (m, 15H); 4.67 (tm, J=9.0, 1H); 4.28 (hex, J=7.1, 1H); 3.63 (t, J=9.0, 1H); 3.43 (dd, J=9.4, 1.7, 1H); 3.24 (dd, J=13.3, 3.1, 1H); 3.06 (dd, J=13.3, 7.6, 1H); 2.77 (dd, J=13.3, 9.3, 1H); 2.72 (dd, J=13.3, 7.5, 1H); 1.29 (d, J=6.8, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 152.2, 139.7, 138.6, 136.1, 129.45 (2C), 129.18 (2C), 128.91 (2C), 128.72 (2C), 128.15 (2C), 127.0, 126.0, 124.5, 119.4 (2C), 51.8, 46.2, 40.02, 39.65, 38.6, 17.3. MS (CI) 399 (MH^+). HRMS (FAB) calcd for $C_{26}H_{26}N_2O_2$+Na^+ 421.1892, found 421.1900.

*(R)-1,4-Diphenyl-3-[(R)-2-methyl-3-phenylpropionyl]imidazolidin-2-one (**6f**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dm, J=8.2, 2H); 7.09–7.40 (m, 13H); 5.28 (dd, J=9.3, 2.7, 1H); 4.32 (sex, J=7.2, 1H); 4.07 (t, J=9.3, 1H); 3.56 (dd, J=9.3, 2.8, 1H); 3.05 (dd, J=13.4, 7.7, 1H); 2.65 (dd, J=13.4, 7.3, 1H); 1.19 (d, J=6.8, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 152.3, 140.9, 139.8, 139.4, 129.2 (2C), 128.96 (2C), 128.93 (2C), 128.10 (2C), 128.06, 126.0, 125.2 (2C), 124.4, 119.1 (2C), 53.6, 50.4, 39.8, 39.4, 17.3. MS (CI) 385 (MH^+). HRMS (FAB) calcd for $C_{25}H_{24}N_2O_2$+Na^+ 407.1735, found 407.1740.

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