Pergamon

Tetrahedron 56 (2000) 3951–3961

TETRAHEDRON

Et_3B- and Et_2Zn-Mediated Radical Additions to Glyoxylate Imines, Compared Stereoinductions

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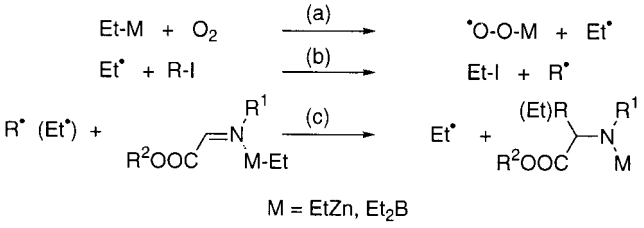
Received 20 January 2000; accepted 25 April 2000

Abstract—1,3-Stereoinduction in the addition of alkyl radicals to glyoxylic imines derived from various chiral amines has been investigated. New synthetic methodologies involving Et_3B and Et_2Zn as mediators have been compared. Dihydro-1,4-oxazin-2-one (**2b**) gave the highest d.e. but no chemoselectivity. Open chain analogues derived from β-alkoxyamines led to good stereoinduction when the reaction was performed with Et_2Zn which is a bidentate complexing reagent.

Radical additions to C═N bonds have been far less developed than their ionic counterparts. The latter reactions involve mainly organometallic species,[1] or enolates[2,3] and suffer some limitations inherent to the low reactivity of the C═N bond and to the basicity of most organometallic reagents. Radical additions performed under strictly non basic conditions offer an alternative to the above mentioned nucleophilic reactions. The studies devoted to intermolecular additions to C═N bonds are few compared to those dealing with intramolecular processes.[4] It can be inferred from literature data that intermolecular radical additions to C═N bonds are successful when either the carbon atom is not sterically hindered,[5] or the carbon is rendered more electrophilic by a substituent.[6] The third possibility is to activate the substrate through complexation with a Lewis acid.[7]

We have recently reported that triethylborane,[8a] and diethylzinc[8b] were particularly well suited to achieve radical additions onto the imino group (Scheme 1). Both reagents are able to initiate radical processes by reacting with oxygen (step a).[9] This results in the production of ethyl radicals which can either add to the imine (step c) or transfer an iodine atom from an alkyl iodide[10] (step b) thus generating an alkyl radical which adds to the C═N bond (step c). During this step, ethyl radical which is the chain carrier is regenerated. Therefore, both Et_3B and Et_2Zn play simultaneously the role of initiator, the role of chain transfer agent and the role of activating complexing reagent.

Performing stereoselective addition to imines, under mild conditions, is still a challenging problem. The results of experiments conducted on a series of glyoxylate imines (**1**, **2**, Figs. 1 and 2), prepared from various chiral amines, are reported in Tables 1–3. The structures of the products are shown in Figs. 3 and 4. The comparison of triethylborane- with diethylzinc-mediated reactions gives an insight



Scheme 1.

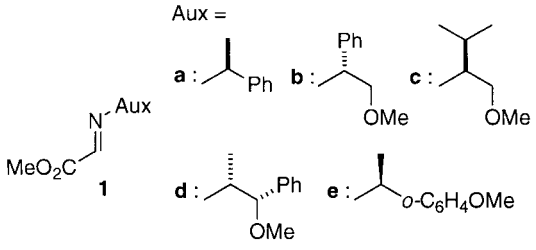
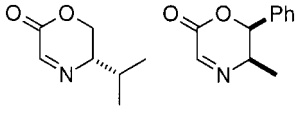


Figure 1.



2a **2b**

Figure 2.

Keywords: radical additions; glyoxylate imines; triethylborane diethylzinc.
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0040–4020/00/$ - see front matter
PII: S0040-4020(00)00327-6

Table 1. Et_3B- and Et_2Zn-mediated radical additions to **1a**–**d**: (i) Et_3B (3 equiv.), RI (none or 6 equiv.), substrate (0.2 M solution in CH_2Cl_2), air (5 mL); (ii) Et_2Zn (2 equiv.), RI (none or 6 equiv.), substrate (0.2 M solution in CH_2Cl_2), air (5 mL); (iii) Et_2Zn (2 equiv.), RI (none or 6 equiv.), substrate (0.2 M solution in CH_2Cl_2 degassed, 4 cycles); (iv) Et_2Zn (2 equiv.), RI (none or 6 equiv.), substrate (0.2 M solution in CH_2Cl_2), air (20 mL)

Entry	Substrate	RI	Conditions	T°C	Products	Relative ratio	Yield (%)
1	**1a**	None	(i)	−78	**3a**: **4a**	60: 40	60
2	**1a**	*t*-BuI	(i)	−78	**7a**: **8a**	70: 30	48
3	**1a**	None	(i)	−40	**3a**: **4a**	58: 42	56
4	**1a**	*t*-BuI	(i)	20	**7a**: **8a**	69: 31	41
5	**1a**	None	(ii)	20	**3a**: **4a**: **11a**	42.5: 42.5: 15	57
6	**1a**	None	(iii)	20	**3a**: **4a**: **11a**	30.5: 30.5: 39	55
7	**1a**	*c*-HexI	(ii)	20	**5a**: **6a**	47: 53	48
8	**1a**	*t*-BuI	(ii)	20	**7a**: **8a**	40: 60	41
9	**1a**	*t*-BuI	(ii)	−40	**7a**: **8a**	40: 60	66
10	**1b**	None	(i)	20	**3b**: **4b**	59: 41	72
11	**1b**	*t*-BuI	(i)	20	**7b**: **8b**	58: 42	48
12	**1b**	None	(ii)	20	**3b**: **4b**	38: 62	40
13	**1b**	None	(ii)	−40	**3b**: **4b**	31: 69	62
14	**1b**	*t*-BuI	(ii)	20	**7b**: **8b**	30: 70	43
15	**1b**	*t*-BuI	(ii)	−40	**7b**: **8b**	23: 77	66
16	**1c**	None	(i)	20	**3c**: **4c**	56: 44	39
17	**1c**	*t*-BuI	(i)	20	**7c**: **8c**	55: 45	42
18	**1c**	None	(ii)	20	**3c**: **4c**	80: 20	40
19	**1c**	None	(ii)	−40	**3c**: **4c**	85: 15	70
20	**1c**	*c*-HexI	(ii)	−40	**5c**: **6c**	87: 13	66
21	**1c**	*t*-BuI	(ii)	20	**7c**: **8c**	87: 13	41
22	**1c**	*t*-BuI	(ii)	−40	**7c**: **8c**	92: 8	67
23	**1d**	None	(i)	20	**3d**: **4d**	58: 42	40
24	**1d**	*t*-BuI	(i)	20	**7d**: **8d**	65: 35	42
25	**1d**	None	(ii)	20	**11d**		35
26	**1d**	None	(iv)	20	**3d**: **4d**	34: 66	45
27	**1d**	*c*-HexI	(ii)	−40	**5d**: **6d**	13: 87	62[12]
28	**1d**	*t*-BuI	(ii)	20	**7d**: **8d**	22: 78	39
29	**1d**	*t*-BuI	(ii)	−40	**7d**: **8d**	7: 93	69

into the factors controlling the diastereoselectivity in these reactions.

Results and Discussion

The reactions were carried out by adding Et_3B or Et_2Zn (1 M solutions in hexane) to a solution containing the imine and an alkyl iodide (if needed) under inert atmosphere. Air was then injected throughout the solution (generally over 1 h). The initial experiments were conducted with imine **1a** (Table 1; entries 1–9). The reaction products were assigned respectively the *like* (**3a**, **5a**, **7a**) and the *unlike* (**4a**, **6a**, **8a**) structures. These assignments follow from literature data[11] according to which, the proton α to both the amino group and the carboxylate is more shielded (0.2–0.3 ppm) in the *like* isomers.

It can be noted that lowering the temperature improved the overall yield significantly in the case of the zinc-promoted reactions. Further experiments, conducted in the presence of triethylborane, were performed only at room temperature. As expected, the diastereomeric ratio increased with the steric bulk of the attacking radical. The difference between the two modes of initiation is not important as regard to the diastereomeric excess which is only slightly better under conditions (i). However it is worth noting that the stereoselectivity is reversed going from boron- to zinc-mediated reactions.

Assuming a substrate controlled stereoinduction, it seems obvious that the origin of the reversal of selectivity resides into the nature of the preferred conformation of the substrate depending upon whether it is associated with triethylborane or with diethylzinc (Scheme 2). Et_3B is a monodentate complexing agent, whereas Et_2Zn is bidentate.

It is noteworthy that the selectivity observed for Et_3B-mediated reactions is similar to that observed using tin methodology,[8a] as if Et_3B does not change the preferred

Table 2. Et_3B-mediated radical additions to **2b**. Reactions of **2b** (0.2 M solution in CH_2Cl_2) with Et_3B (3 equiv.), RI (6 equiv.), air (5 mL), −40°C

Entry	RI	Products (diastereomeric ratio, yield)
1	*c*-HexI	**12**:**13** (75:25, 27%); **14**:**15** (90:10, 25%)
2	*t*-BuI	**12**:**13** (75:25, 25%); **16**:**17** (>99:<1), 25%)

Table 3. Et_3B- and Et_2Zn-mediated additions to **1e**: Reactions of **1e** (0.2 M solution in CH_2Cl_2) with RI (none or 6 equiv.), air (5 mL), −40°C; (i) Et_3B (3 equiv.), (ii) Et_2Zn (2 equiv.)

Entry	RI	Conditions	Products	Diastereomeric ratio	Yield (%)
1	None	(i)	**3e**:**4e**	55:45	80
2	None	(ii)	**3e**:**4e**	42:58	95
3	*i*-PrI	(i)	**9e**:**10e**	57:43	72
4	*i*-PrI	(ii)	**9e**:**10e**	44:56	82
5	*t*-BuI	(i)	**7e**:**8e**	62:38	84
6	*t*-BuI	(ii)	**7e**:**8e**	30:70	87

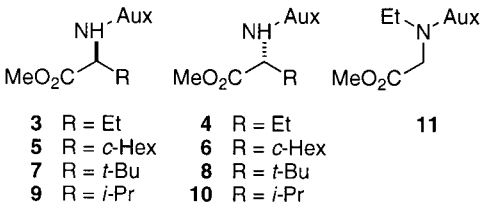


Figure 3.

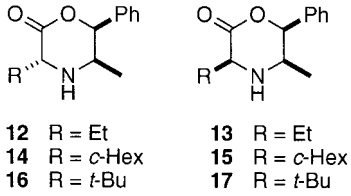


Figure 4.

conformation with respect to the free imine.[13] In this model, due to the minimization of $A^{1,3}$-strain, the C–H bond lies close to the plane of the C=N bond, the relative shielding of the two faces, respectively by the methyl and the phenyl group, determines the selectivity. A slight preference for approach *syn* to the phenyl group is observed (Scheme 2).

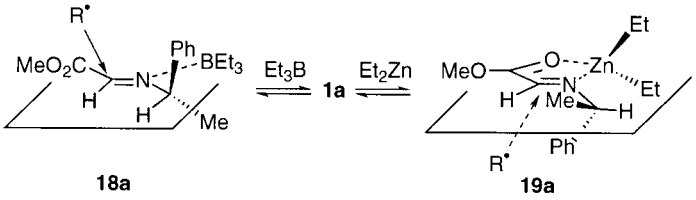
In the case of diethylzinc, a chelate is formed with the substrate which forces the imine to adopt a *s-cis* conformation. We tentatively suggest that the conformation around the C–N bond of the amine moiety is reversed so that, in this first generation model, the preferred attack now would take place at the *re*-face. It must be recalled that previous work of van Koten et al[14] had shown that under inert atmosphere the reaction of diethylzinc with glyoxylic imines led to zinc enolates (Scheme 3). Chelation activates 1,4-nucleophilic addition, the ethyl group migrates from zinc to nitrogen.

Compound **11a** was formed in variable amounts depending on the reaction conditions when diethylzinc was the source of ethyl radical (entries 5 and 6). In the absence of alkyl iodide, low stationary concentrations of ethyl radical allows the nucleophilic pathway to compete with the radical pathway leading to **3a** and **4a**.

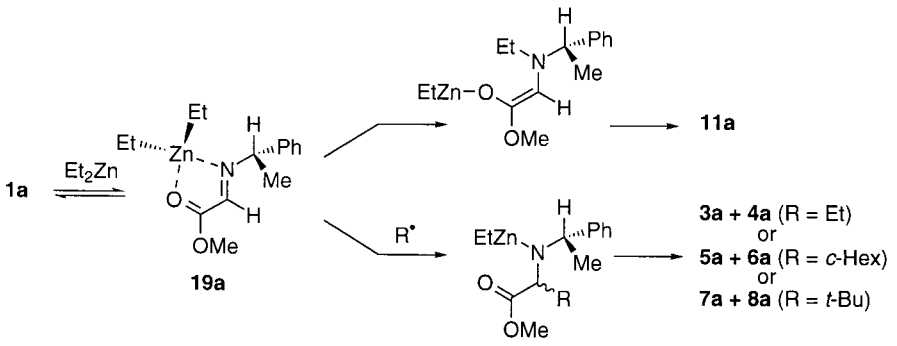
Experiments conducted with triethylborane preceded those involving diethylzinc. The rather poor level of diastereoselectivity, that was accounted for by the conformational flexibility of the starting material, led us to prepare a series of cyclic imines (**2**). The mono-substituted imine (**2a**) did not bring a significant improvement of the diastereomeric ratio. The most interesting results were obtained with imine **2b**, for which, whatever the conformation, one of the faces is shielded either by the phenyl or by the methylgroup.[8a] This substrate is more reactive than the acyclic imines.[15] As reported in Table 2, the d.e reached 80% for the addition of *cyclo*-hexyl radical, and only one diastereoisomer was detected for the addition of *tert*-butyl radical. There is however some drawback to increasing the reactivity: the lack of chemoselectivity. The addition of ethyl radical competes severely with the addition of the alkyl radical issued from the alkyl iodide.

We have investigated the behaviour of imines **1b–d** which are open-chain analogues of imines **2**. The guess was that interesting selectivities could be observed with diethylzinc owing to the possibility offered by these substrates to form two types of chelates. For the sake of comparison, radical additions initiated with triethylborane were studied in parallel. The assignments follow from mechanistic analogy with literature data concerning the addition of various organometallics to closely related compounds,[16] they were also supported by NMR data correlations.[17]

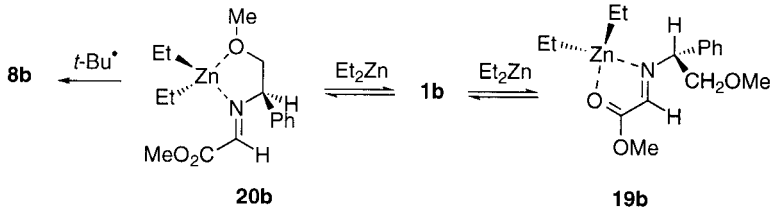
The structure of imine **1b** is very close to that of imine **1a**. As regard to boron-mediated reactions, the selectivities



Scheme 2.



Scheme 3.



Scheme 4.

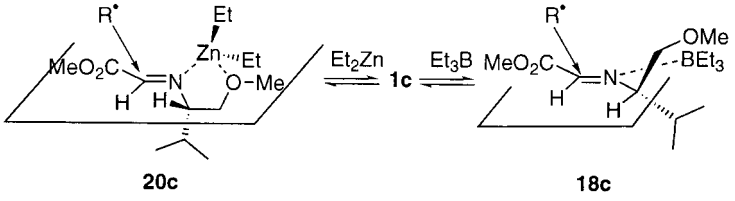
observed with these two substrates were very similar (Table 1: entries 10 and 11/3 and 4).

The reaction of **1b** with diethylzinc exhibited a higher selectivity (Table 1: entries 12–15). Again the selectivity was reversed compared to the reactions involving triethylborane. Two different chelates could result from interaction with the metal (Scheme 4). Due to the greater basicity of the ether oxygen atom, the equilibrium is likely to be shifted towards **20b**, which would result in clean preferential attack at the *re*-face. However, the phenyl group is not bulky enough to shield completely the *si*-face, higher diastereomeric ratios were obtained with the auxiliary derived from L-valinol (**1c**) (Table 1: entries 18–22). In this case, it is to be noted that there was no reversal of selectivity going from boron- to zinc-mediated reactions (Table 1: entries 16 and 17/18–22). Whichever complex was involved, preferential attack occurred opposite to the *iso*-propyl group (Scheme 5). If one refers to the selectivity observed in the additions of organometallic compounds to related imines,[1,16] the radical additions exhibit a lower stereoinduction, although they are easy to carry out and they allow the use of functional alkyl iodides. This might be ascribed either to an earlier transition state for the radical reaction, or more likely to the steric bulk of the attacking species.

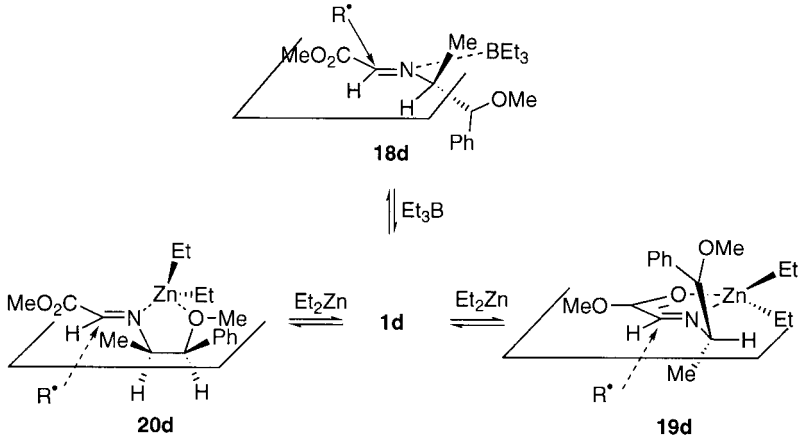
Imine **1d** derived from (*d*,*l*)-norephedrine confirmed the mechanistic hypothesis. The triethylborane-mediated reactions led to a low diastereoselectivity (Table 1: entries 23 and 24) which can be accounted for by the rather small differentiation between the two diastereotopic faces in **18d** like in **18c** (Scheme 6).

As expected, a reversal of selectivity was observed when the radical additions were carried out in the presence of diethylzinc (Table 1: entries 25–29). As shown in Scheme 6, due to steric interactions between the phenyl and the methyl group in chelate **20d**, the equilibrium is shifted towards **19d**.

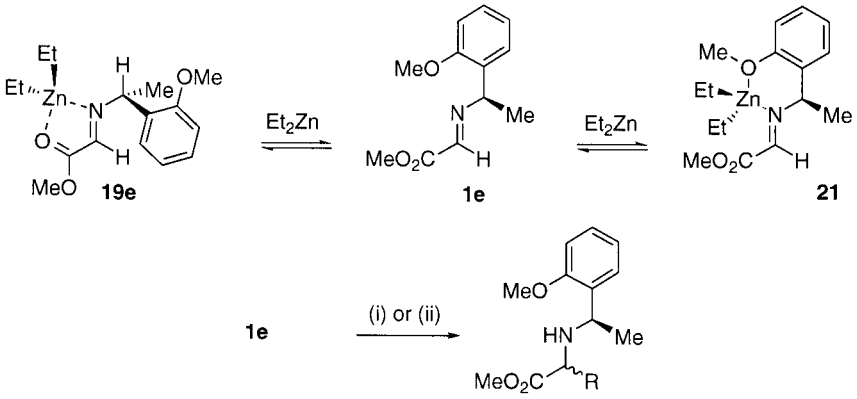
This was confirmed by adding variable amounts of air to the reaction medium. Only the preferential formation of complex **19d** could activate 1,4-nucleophilic addition leading to **11d** as the single product. No competitive radical pathway was observed when 5 mL of air (conditions ii) were introduced over 1 h (Table 1: entry 25). When the volume of air was increased up to 20 mL (conditions iv), even when diethylzinc was the source of ethyl radical, only the products resulting from the radical reaction were isolated (Table 1: entry 26).[18] The introduction of a secondary or a tertiary alkyl iodide resulted in the production of the corresponding radicals, the addition of which was faster



Scheme 5.



Scheme 6.



Scheme 7. Reactions of **1e** (0.2 M solution in CH_2Cl_2) with RI (none or 6 equiv.), air (5 mL), −40°C; (i): Et_3B (3 equiv.), (ii): Et_2Zn (2 equiv.)

than the ionic pathway, even under conditions (ii) (Table 1: entries 27–29).

The diastereomeric ratio observed for the addition of *tert*-butyl radical is as high as that observed with **1c** (Table 1: entries 22/29). Either **19d** or **20d** could account for the preferential attack at the *re*-face. Although disfavoured, **20d** might react much faster than **19d** with the alkyl radical since there is no steric hindrance to approach the *re*-face in this conformation.

It has been shown in the literature, that the alkoxyamines derived from valinol or norephedrine, could be used as 'chiral source' of nitrogen atoms to prepare primary amines,[19] however benzylic amines look still more attractive owing to the formally easy removal of the benzyl group via hydrogenolysis. We had a look at the behaviour of imine **1e** that might be expected to lead to a six-membered chelate (**21**) with diethylzinc (Scheme 7). Very good selectivities were registered for the addition of organolithium to related imines prepared from aromatic aldehydes.[20]

Though this substrate resulted in particularly high yields of adducts, the selectivity was rather low whatever the reaction conditions (Table 3).

No reversal of the d.e. was registered going from boron- to zinc-mediated reactions. If chelate **21** were to be involved, one would have expected a clean preferential attack at the *re*-face and what is more, no reversal of selectivity with respect to boron. The results show that **19e** is likely to be preferred. This was not obvious on the ground of the close basicities of the oxygen atoms. The size of the ring in the chelate by no means can displace the equilibrium in the expected direction. No further attempts to prepare more hindered analogues of **1e** were made.

In conclusion, the screening of the reactivity of a series of imines derived from chiral amines in triethylborane- and diethylzinc-mediated radical additions led to the following observations. Open-chain flexible substrates give poor selectivity. Good stereoinductions are obtained with cyclic imines, but the major drawback in these reactions is that their greater reactivity results in a lack of chemoselectivity (the addition of ethyl radical derived from the mediator competes with the addition of the alkyl radical issued from the added alkyl iodide). Imines derived from alkoxyamines lead to the highest diastereomeric ratios under chelation controlled conditions i.e. when the reactions are performed with diethylzinc as chain transfer agent.

Experimental

All chemicals and reagents were purchased from Aldrich Chemical Co. NMR spectra (^1H, ^{13}C, and DEPT) were registered in $CDCl_3$; chemical shifts are relative to TMS as internal reference. Coupling constants are reported in Hz.

Starting materials were prepared as racemates unless otherwise stated; **1a**[21] and **2a**[22] were prepared according to known procedures, and spectral data were in accordance with literature.

General procedures for radical addition

Method A (conditions i): The alkyl iodide (6 equiv.) was added (when necessary), under argon at a given temperature, to a 0.2 M solution of substrate, in dichloromethane. Triethylborane (3 equiv., 1 M solution in hexane) was then introduced, and the reaction was stirred at the same temperature while air (5 mL) was injected through a needle into the solution over 1 h. The reaction was monitored by TLC and GPC. After completion, the solvent was evaporated under reduce pressure and the crude product was purified by FC.

Method B (conditions ii): The alkyl iodide (6 equiv.) was added (when necessary), under argon at a given temperature, to a 0.2 M solution of substrate, in dichloromethane. Diethylzinc (2 equiv., 1 M solution in hexane) was then introduced, and the reaction was stirred at the same temperature while air (5 mL) was injected through a needle into the solution over 1 h. The reaction was monitored by TLC and GPC. The reaction mixture was treated with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (×3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by FC.

Method C (conditions iii): The experimental conditions were similar to method B except that the reaction was degassed before introducing Et_2Zn.

Method D (conditions iv): The experimental conditions were similar to method B except that a higher volume of oxygen was introduced in the solution (air: 20 mL/5 mL)

Methyl 2-(1-phenylethylamino)butanoate (3a and 4a).[8c] Treating **1a** (222 mg, 1.16 mmol) according to method A, at −40°C, in the absence of any alkyl iodide, led to a mixture of **3a** and **4a** (143 mg, 0.65 mmol, 56%), isolated as a colorless oil after purification by FC (5% EtOAc/pentane). The diastereomeric ratio (58:42) was determined by ^{1}H NMR on the crude reaction mixture. When treated according to method B, at 20°C **1a** (200 mg, 1.05 mmol) led to **3a**, **4a**, and **11a** (132 mg, 0.59 mmol, 57%) as an inseparable mixture. The ratio **3a**:**4a**:**11a** (42.5:42.5:15) was determined by GPC and ^{1}H NMR on the crude reaction mixture. When treated according to method C, at 20°C, **1a** (100 mg, 0.52 mmol) led to **3a**:**4a**:**11a** (64 mg, 0.28 mmol, 55%) in a 30.5:30.5:39 ratio.

Methyl 2-cyclohexyl-2-(1-phenylethylamino)ethanoate (5a and 6a). Treating **1a** (200 mg, 1.05 mmol) according to method B, at 20°C, in the presence of cyclohexyl iodide, led to a mixture of **5a** and **6a** (137 mg, 0.5 mmol, 48%), isolated as a colorless oil after purification by FC (5% EtOAc/pentane). The diastereomeric ratio (47:53) was determined from ^{1}H NMR. ^{1}H NMR (400 MHz): (major isomer: **6a**) δ 0.90–1.85 (m, 12H), 1.29 (d, 3H, J=6.5 Hz), 3.09 (d, 1H, J=6.5 Hz), 3.54 (s, 3H), 3.65 (q, 1H, J=6.5 Hz), 7.16–7.31 (m, 5H); (minor isomer: **5a**) δ 0.90–1.85 (m, 11H), 1.30 (d, 3H, J=6.5 Hz), 2.78 (d, 1H, J=6.5 Hz), 3.59 (q, 1H, J=6.5 Hz), 3.68 (s, 3H), 7.16–7.31 (m, 5H). ^{13}C NMR (50 MHz): (major isomer: **6a**) δ 22.5 (CH_3), 26.2 (2×CH_2), 29.03 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 41.5 (CH), 51.2 (CH_3), 56.9 (CH), 64.6 (CH), 126.7 (CH), 126.8 (CH), 128.1 (CH),145.7 (C), 175.7 (C═O); (minor isomer: **5a**) δ 25.6 (CH_3), 26.1 (2×CH_2), 29.03 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 41.4 (CH), 51.2 (CH_3), 56.8 (CH), 64.2 (CH), 126.8 (CH), 126.9 (CH), 128.2 (CH),145.1 (C), 176.3 (C). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 73.95; H, 9.15.

Methyl 3,3-dimethyl-2-(1-phenylethylamino)butanoate (7a and 8a).[8c] Treating **1a** (132 mg, 0.70 mmol) according to method A, at 20°C, in the presence of *t*-butyl iodide, led to a mixture of **7a** and **8a** (71 mg, 0.28 mmol, 41%), isolated as a colorless oil after purification by FC (3% EtOAc/pentane). The diastereomeric ratio (69:31) was determined from ^{1}H NMR on the crude reaction mixture. Treating **1a** (160 mg, 0.84 mmol) according to method A, at −78°C, in the presence of *t*-butyl iodide, led to **7a** and **8a** (93 mg, 0.38 mmol, 48%) in a 70:30 ratio. When treated according to method B, at 20°C, in the presence of *t*-butyl iodide, **1a** (136 mg, 0.71 mmol) led to **7a** and **8a** (72 mg, 0.29 mmol, 41%) in a 40:60 ratio. Treating **1a** (100 mg, 0.52 mmol) according to method B, at −40°C, in the presence of *t*-butyl iodide, led to **7a** and **8a** (85 mg, 0.34 mmol, 66%) in a 40:60 ratio.

Methyl (2-methoxy-1-phenylethylimino)acetate (1b). A solution of (*R*)-(−)-2-amino-2-phenylethanol (1 g, 7.3 mmol) in THF (2 mL) was added dropwise to a suspension of sodium hydride 60% in mineral oil (600 mg, 14.6 mmol, 2 equiv.) in THF (12 mL) at room temperature. After stirring at 60°C for 2 h, the mixture was cooled, treated dropwise with methyl iodide (480 μL, 7.6 mmol, 1.05 equiv.), and then heated at reflux for 1 h. The reaction mixture was cooled, and then methanol was added to destroy the excess of NaH. The mixture was washed with brine and the aqueous solution was extracted with diethyl ether (×3). The combined extracts were dried and concentrated. The residue was dissolved in dichloromethane (10 mL). Molecular sieves (4 Å) and methyl glyoxylate (871 mg, 9.9 mmol, 1.5 equiv.) were added and the reaction was stirred at room temperature for 1 h. After concentration, purification by FC (20% EtOAc/pentane) gave the desired product **1b** (705 mg, 3.2 mmol, 43%). $[\alpha]_D^{21}$=−32.5 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (200 MHz): δ 3.34 (s, 3H), 3.67 (dd, 1H, J=3.9 and 10.2 Hz), 3.82 (t, 1H, J=9.0 Hz), 3.86 (s, 3H), 4.56 (dd, 1H, J=3.9 and 8.8 Hz), 7.23–7.40 (m, 5H), 7.77 (s, 1H). ^{13}C NMR (50 MHz): δ 52.5 (CH_3), 58.8 (CH_3), 74.4 (CH), 76.1 (CH_2), 127.2 (CH), 127.8 (CH), 128.6 (CH), 138.6 (C), 153.8 (CH), 163.3 (C═O). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 65.03; H, 6.59.

Methyl 2-(2-methoxy-1-phenylethylamino)butanoate (3b and 4b). Treating **1b** (150 mg, 0.68 mmol) according to method A, at 20°C, led to a mixture of **3b** and **4b** (120 mg, 0.48 mmol, 72%), isolated as a colorless oil after purification by FC (10% EtOAc/pentane). The diastereomeric ratio (59:41) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (200 MHz): (major isomer: **3b**): δ 0.91 (t, 3H, J=7.3 Hz), 1.57 (quint, 2H, J=7.1 Hz), 2.85 (br s, 1H), 2.91 (t, 1H, J=6.8 Hz), 3.38 (s, 3H), 3.20–3.60 (m, 2H), 3.70 (s, 3H), 3.87 (dd, 1H, J=4.6 and 8.6 Hz), 7.24–7.36 (m, 5H); (minor isomer: **4b**): δ 0.88 (t, 3H, J=7.3 Hz), 1.65 (quint, 2H, J=7.1 Hz), 2.85 (br s, 1H), 3.28 (t, 1H, J=6.8 Hz), 3.34 (s, 3H), 3.20–3.60 (m, 2H), 3.53 (s, 3H), 3.92 (dd, 1H, J=5.1 and 7.6 Hz), 7.24–7.36 (m, 5H). ^{13}C NMR (50 MHz): (major isomer: **3b**): δ 10.3 (CH_3), 27.0 (CH_2), 51.4 (CH_3), 58.4 (CH_3), 59.5 (CH), 60.3 (CH), 77.7 (CH_2), 127.6 (CH), 127.7 (CH), 128.3 (CH), 139.9 (C), 176.0 (C═O); (minor isomer: **4b**): δ 9.4 (CH_3), 26.2 (CH_2), 51.4 (CH_3), 58.8 (CH_3), 59.5 (CH), 60.7 (CH), 77.3 (CH_2), 127.6 (CH), 127.7 (CH), 128.3 (CH), 139.9 (C), 175.9 (C═O). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42. Found: C, 66.94; H, 8.47. When treated according to method B, at 20°C, **1b** (150 mg, 0.68 mmol) led to **3b** and **4b** (68 mg, 0.27 mmol, 40%) in a 38:62 ratio. Treating **1b** (150 mg, 0.68 mmol) according to method B, at −40°C, led to **3b** and **4b** (105 mg, 0.42 mmol, 62%) in a 31:69 ratio.

Methyl 3,3-dimethyl-2-(2-methoxy-1-phenylethylamino)-butanoate (7b and 8b). Treating **1b** (150 mg, 0.68 mmol) according to method A, at 20°C, in the presence of *t*-butyl iodide, led to a mixture of **7b** and **8b** (92 mg, 0.33 mmol, 48%), isolated as a colorless oil after purification by FC (10% EtOAc/pentane). The diastereomeric ratio (58:42) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (200 MHz): (major isomer: **7b**): δ 0.85 (s, 9H), 2.20 (br s, 1H), 2.66 (s, 1H), 3.29 (s, 3H), 3.20–3.70 (m, 3H), 3.62 (s, 3H), 7.17–7.26 (m, 5H); (minor isomer: **8b**): δ 0.88 (s, 9H), 2.20 (br s, 1H), 2.94 (s, 1H), 3.24 (s, 3H), 3.20–3.70 (m, 3H), 3.35 (s, 3H), 7.17–7.26 (m, 5H). ^{13}C NMR (50 MHz): (major isomer: **7b**): δ 26.7 (3×CH_3), 33.8 (C), 50.9 (CH_3), 58.5 (CH_3), 60.7 (CH), 67.1 (CH),

77.8 (CH_2), 127.6 (CH), 127.9 (CH), 128.3 (CH), 141.4 (C), 175.6 (C═O); (minor isomer: **8b**): δ 26.6 (3×CH_3), 34.5 (C), 50.9 (CH_3), 58.9 (CH_3), 63.1 (CH), 69.2 (CH), 77.3 (CH_2), 127.4 (CH), 127.7 (CH), 128.2 (CH), 140.2 (C), 175.4 (C═O). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02. Found: C, 68.72; H, 9.13. When treated according to method B, at 20°C, in the presence of *t*-butyl iodide, **1b** (150 mg, 0.68 mmol) led to **7b** and **8b** (81 mg, 0.29 mmol, 43%) in a 30:70 ratio. Treating **1b** (150 mg, 0.68 mmol) according to method B, at −40°C, in the presence of *t*-butyl iodide, led to **7b** and **8b** (125 mg, 0.45 mmol, 66%) in a 23:77 ratio.

Methyl (1-methoxymethyl-2-methylpropylimino)acetate (1c). 1-Methoxymethyl-2-methylpropylamine[23] (390 mg, 3.31 mmol) prepared from L-valinol was dissolved in dichloromethane (15 mL). Molecular sieves (4 Å) and methyl glyoxylate (436 mg, 4.96 mmol, 1.5 equiv.) were added and the reaction was stirred at room temperature for 1 h. After concentration, a purification by FC (20% EtOAc/pentane) gave the desired product **1c** (464 mg, 2.48 mmol, 75%). $[\alpha]_D^{21}=-31.3$ (*c* 1.0, CH_2Cl_2). ^{1}H NMR (200 MHz): δ 0.88 (d, 3H, *J*=6.6 Hz), 0.94 (d, 3H, *J*=6.6 Hz), 1.96 (oct, 1H, *J*=6.6 Hz), 3.09 (ddd, 1H, *J*=9.5, 6.6, and 3.7 Hz), 3.30 (s, 3H), 3.54 (t, 1H, *J*=9.5 Hz), 3.62 (dd, 1H, *J*=9.5 and 3.7 Hz), 7.64 (s, 1H). ^{13}C NMR (50 MHz): δ 18.9 (CH_3), 19.3 (CH_3), 29.7 (CH), 52.3 (CH_3), 58.6 (CH_3), 73.2 (CH_2), 76.5 (CH), 153.1 (CH), 163.2 (C═O). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15. Found: C, 57.65; H, 9.08.

Methyl 2-(1-methoxymethyl-2-methylpropylamino)-butanoate (3c and 4c). Treating **1c** (150 mg, 0.80 mmol) according to method A, at 20°C, led to a mixture of **3c** and **4c** (68 mg, 0.31 mmol, 39%), isolated as a colorless oil after purification by FC (5% EtOAc/pentane). The diastereomeric ratio (56:44) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (400 MHz): (major isomer: **3c**): δ 0.91 (d, 3H, *J*=6.8 Hz), 0.92 (t, 3H, *J*=7.2 Hz), 0.93 (d, 3H, *J*=6.8 Hz), 1.60–1.72 (m, 3H), 1.78 (dsept, 1H, *J*=5.1 and 6.8 Hz), 2.43 (dt, 1H, *J*=5.1 and 5.5 Hz), 3.28 (dd, 1H, *J*=5.8 and 9.8 Hz), 3.31 (s, 3H), 3.34–3.40 (m, 2H), 3.71 (s, 3H); (minor isomer: **4c**): δ 2.49 (dt, 1H, *J*=4.1 and 8.1 Hz), 3.29 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (50 MHz): (major isomer: **3c**): δ 10.2 (CH_3), 18.5 (CH_3), 18.7 (CH_3), 27.0 (CH_2), 29.7 (CH), 51.5 (CH_3), 58.9 (CH_3), 61.2 (2×CH), 73.8 (CH_2), 176.3 (C═O); (minor isomer: **4c**): δ 10.4 (CH_3), 17.8 (CH_3), 18.5 (CH_3), 28.8 (CH), 28.9 (CH_2), 51.5 (CH_3), 58.7 (CH_3), 60.8 (CH), 61.3 (CH), 73.7 (CH_2), 176.0 (C═O). Anal. Calcd for $C_{11}H_{23}NO_3$: C, 60.80; H, 10.67. Found: C, 60.91; H, 10.70. When treated according to method B, at 20°C, **1c** (144 mg, 0.77 mmol) led to **3c** and **4c** (67 mg, 0.31 mmol, 40%) in a 80:20 ratio. Treating **1c** (150 mg, 0.80 mmol) according to method B, at −40°C, led to **3c** and **4c** (120 mg, 0.55 mmol, 70%) in a 85:15 ratio.

Methyl 2-cyclohexyl-2-(1-methoxymethyl-2-methylpropylamino)ethanoate (5c and 6c). Treating **1c** (150 mg, 0.80 mmol) according to method B, at −40°C, in the presence of cyclohexyl iodide, led to a mixture of **5c** and **6c** (143 mg, 0.53 mmol, 66%), isolated as a colorless oil after purification by FC (5% EtOAc/pentane). The diastereomeric ratio (87:13) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (200 MHz): (major isomer: **5c**): δ 0.91 (d, 6H, *J*=6.8 Hz), 0.95–1.58 (m, 13H), 2.35 (q, 1H, *J*=5.1 Hz), 3.18 (d, 1H, *J*=6.3 Hz), 3.22–3.37 (m, 2H), 3.30 (s, 3H), 3.69 (s, 3H); (minor isomer: **6c**): δ 0.89 (d, 6H, *J*=6.8 Hz), 0.95–1.58 (m, 13H), 2.44 (q, 1H, *J*=4.2 Hz), 3.05 (d, 1H, *J*=6.3 Hz), 3.22–3.37 (m, 2H), 3.28 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (50 MHz): (major isomer: **5c**): δ 18.1 (CH_3), 18.8 (CH_3), 26.1(2×CH_2), 26.3 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.8 (CH), 41.4 (CH), 51.2 (CH_3), 58.8 (CH_3), 61.4 (CH), 65.3 (CH), 73.9 (CH_2), 176.0 (C═O); (minor isomer: **6c**): δ 17.6 (CH_3), 18.8 (CH_3), 26.1 (2×CH_2), 26.3 (CH_2), 28.7 (CH), 29.3 (CH_2), 29.8 (CH_2), 41.9 (CH), 50.8 (CH_3), 58.6 (CH_3), 60.9 (CH), 65.3 (CH), 73.4 (CH_2), 174.1 (C═O). Anal. Calcd for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77. Found: C, 66.51; H, 10.81.

Methyl 3,3-dimethyl-2-(1-methoxymethyl-2-methylpropylamino)butanoate (7c and 8c). Treating **1c** (150 mg, 0.80 mmol) according to method A, at 20°C, in the presence of *t*-butyl iodide, led to a mixture of **7c** and **8c** (128 mg, 0.52 mmol, 42%), isolated as a colorless oil after purification by FC (3% EtOAc/pentane). The diastereomeric ratio (55:45) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (400 MHz): (major isomer: **7c**): δ 0.87 (d, 3H, *J*=6.8 Hz), 0.88 (d, 3H, *J*=6.8 Hz), 0.91 (s, 9H), 1.61 (br s, 1H), 1.76 (dsept, 1H, *J*=4.9 and 6.8 Hz), 2.27 (q, 1H, *J*=4.9 Hz), 3.05 (s, 1H), 3.23–3.32 (m, 2H), 3.28 (s, 3H), 3.66 (s, 3H); (minor isomer: **8c**): δ 2.36 (q, 1H, *J*=4.1 Hz), 2.91 (s, 1H). ^{13}C NMR (50 MHz): (major isomer: **7c**): δ 17.9 (CH_3), 18.9 (CH_3), 26.6 (3×CH_3), 29.8 (CH), 34.1 (C), 51.0 (CH_3), 58.8 (CH_3), 61.6 (CH), 68.7 (CH), 74.2 (CH_2), 175.9 (C═O); (minor isomer: **8c**): δ 17.9 (CH_3), 18.8 (CH_3), 26.7 (3×CH_3), 29.0 (CH), 34.6 (C), 51.0 (CH_3), 58.7 (CH_3), 61.7 (CH), 68.3 (CH), 73.7 (CH_2), 175.0 (C═O). Anal. Calcd for $C_{13}H_{27}NO_3$: C, 63.64; H, 11.09. Found: C, 63.60; H, 11.00. When treated according to method B, at 20°C, in the presence of *t*-butyl iodide, **1c** (150 mg, 0.80 mmol) led to **7c** and **8c** (80 mg, 0.33 mmol, 41%) in a 87:13 ratio. Treating **1c** (150 mg, 0.80 mmol) according to method B, at −40°C, in the presence of *t*-butyl iodide, led to **7c** and **8c** (130 mg, 0.53 mmol, 67%) in a 92:8 ratio.

Methyl (2-methoxy-1-methyl-2-phenylethylimino)acetate (1d). A solution of (*d*,*l*)-norephedrine (1 g, 6.6 mmol) (prepared from the commercially available hydrochloride salt (Aldrich Chemical Co.) by neutralization and then CH_2Cl_2 extraction) in THF (2 mL) was added dropwise to a suspension of sodium hydride 60% in mineral oil (530 mg, 13.2 mmol, 2 equiv.) in THF (12 mL) at room temperature. After stirring at 60°C for 2 h, the mixture was cooled, treated dropwise with methyliodide (430 μL, 6.9 mmol, 1.05 equiv.), and then heated at reflux for 1 h. The reaction mixture was cooled, and then methanol was added to destroy the excess of NaH. The mixture was washed with brine and the aqueous solution was extracted with diethyl ether (×3). The combined extracts were dried and concentrated. The residue was dissolved in dichloromethane (10 mL). Molecular sieves (4 Å) and methyl glyoxylate (871 mg, 9.9 mmol, 1.5 equiv.) were added and the reaction was stirred at room temperature for 1 h. After concentration, purification by FC (20% EtOAc/pentane) gave the desired

product **1d** (620 mg, 2.6 mmol, 40%). ^{1}H NMR (200 MHz): δ 1.35 (d, 3H, J=6.4 Hz), 3.24 (s, 3H), 3.60 (q, 1H, J=6.4 Hz), 3.80 (s, 3H), 4.27 (d, 1H, J=6.4 Hz), 7.17–7.31 (m, 5H), 7.37 (s, 1H). ^{13}C NMR (50 MHz): δ 17.77 (CH_3), 52.45 (CH_3), 57.04 (CH_3), 71.10 (CH), 86.09 (CH), 127.56 (CH), 127.82 (CH), 128.11 (CH), 138.76 (C), 152.74 (CH), 167.75 (C=O). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.19; H, 7.26.

Methyl 2-(2-methoxy-1-methyl-2-phenylethylamino)-butanoate (3d and 4d). Treating **1d** (150 mg, 0.63 mmol) according to method A, at 20°C, led to a mixture of **3d** and **4d** (65 mg, 0.25 mmol, 40%), isolated as a colorless oil after purification by FC (10% EtOAc/pentane). The diastereomeric ratio (58:42) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (400 MHz): (major isomer: **3d**): δ 0.85 (t, 3H, J=7.3 Hz), 1.06 (d, 3H, J=6.4 Hz), 1.58 (quint, 2H, J=7.3 Hz), 2.80 (quint, 1H, J=6.4 Hz), 3.30 (t, 1H, J=6.6 Hz), 3.22 (s, 3H), 3.57 (br s, 1H), 3.64 (s, 3H), 4.01 (d, 1H, J=5.9 Hz), 7.26–7.35 (m, 5H); (minor isomer: **4d**): δ 0.79 (t, 3H, J=7.3 Hz), 1.04 (d, 3H, J=6.6 Hz), 1.56 (quint, 2H, J=7.3 Hz), 2.75 (quint, 1H, J=6.6 Hz), 3.13 (t, 1H, J=6.4 Hz), 3.24 (s, 3H), 3.57 (br s, 1H), 3.70 (s, 3H), 4.10 (d, 1H, J=5.1 Hz), 7.26–7.35 (m, 5H). ^{13}C NMR (50 MHz): (major isomer: **3d**): δ 10.1 (CH_3), 15.3 (CH_3), 26.8 (CH_2), 51.4 (CH_3), 56.1 (CH_3), 57.4 (CH), 60.7 (CH), 87.2 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 134.0 (C), 175.3 (C=O); (minor isomer: **4d**): δ 9.9 (CH_3), 15.9 (CH_3), 26.3 (CH_2), 51.6 (CH_3), 56.9 (CH_3), 57.1 (CH), 59.8 (CH), 86.5 (CH), 127.3 (CH), 127.8 (CH), 128.1 (CH), 139.7 (C), 179.9 (C=O). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74. Found: C, 67.83; H, 8.71. Treating **1d** (300 mg, 1.27 mmol) according to method D, at 20°C, led to **3d** and **4d** (167 mg, 0.57 mmol, 45%) in a 34:66 ratio.

Methyl (ethyl-(2-methoxy-1-methyl-2-phenylethyl)amino)acetate (11d). Treating **1d** (150 mg, 0.64 mmol) according to method B, at 20°C, led to **11d** (59 mg, 0.23 mmol, 35%), isolated as a colorless oil after purification by FC (10% EtOAc/pentane). ^{1}H NMR (400 MHz): δ 0.96 (d, 3H, J=6.7 Hz), 1.01 (t, 3H, J=7.1 Hz), 2.73 (q, 2H, J=7.1 Hz), 2.92 (dq, 1H, J=3.3 and 6.7 Hz), 3.18 (s, 3H), 3.45 (AB, 2H, J=17.3 Hz, $\Delta\nu$=50 Hz), 3.67 (s, 3H), 4.41 (d, 1H, J=3.3 Hz), 7.18–7.35 (m, 5H). ^{13}C NMR (50 MHz): δ 9.2 (CH_3), 13.8 (CH_3), 47.3 (CH_2), 51.5 (CH_2), 51.6 (CH_3), 56.8 (CH_3), 61.9 (CH), 85.4 (CH), 126.8 (CH), 127.1 (CH), 128.2 (CH), 141.0 (C), 173.6 (C=O). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74. Found: C, 67.81; H, 8.69.

Methyl 2-cyclohexyl-2-(2-methoxy-1-methyl-2-phenylethylamino)ethanoate (5d and 6d). Treating **1d** (70 mg, 0.30 mmol) according to method B, at −40°C, in the presence of cyclohexyl iodide, led to a mixture of **5d** and **6d** (60 mg, 0.19 mmol, 62%), isolated as a colorless oil after purification by FC (5% EtOAc/pentane). The diastereomeric ratio (13:87) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (200 MHz): (major isomer: **6d**): δ 1.02 (d, 3H, J=6.6 Hz), 0.76–1.75 (m, 12H), 2.62 (dq, 1H, J=5.1 and 6.6 Hz), 2.92 (d, 1H, J=6.1 Hz), 3.24 (s, 3H), 3.69 (s, 3H), 4.05 (d, 1H, J=5.1 Hz), 7.25–7.38 (m, 5H); (minor isomer: **5d**): δ 1.00 (d, 3H, J=6.4 Hz), 0.76–1.75 (m, 12H), 2.75 (dq, 1H, J=5.6 and 6.4 Hz), 3.07 (d, 1H, J=6.6 Hz), 3.21 (s, 3H), 3.61 (s, 3H), 3.95 (d, 1H, J=5.6 Hz), 7.25–7.38 (m, 5H). ^{13}C NMR (50 MHz): (major isomer: **6d**): δ 16.4 (CH_3), 26.0 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 29.1 (CH_2), 29.5 (CH_2), 41.4 (CH), 51.4 (CH_3), 57.2 (CH), 58.3 (CH_3), 65.6 (CH), 86.8 (CH), 127.3 (CH), 127.4 (CH), 128.1 (CH), 140.1 (C), 176.2 (C=O); (minor isomer: **5d**): δ 15.8 (CH_3), 26.1 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 41.4 (CH), 51.2 (CH_3), 56.4 (CH), 57.0 (CH_3), 64.2 (CH), 87.6 (CH), 127.3 (CH), 127.8 (CH), 128.2 (CH), 140.1 (C), 175.9 (C=O). Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15. Found: C, 71.28; H, 9.12.

Methyl 3,3-dimethyl-2-(2-methoxy-1-methyl-2-phenylethylamino)butanoate (7d and 8d). Treating **1d** (100 mg, 0.42 mmol) according to method A, at 20°C, in the presence of *t*-butyl iodide, led to a mixture of **7d** and **8d** (53 mg, 0.18 mmol, 42%), isolated as a colorless oil after purification by FC (5% EtOAc/pentane). The diastereomeric ratio (65:35) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (200 MHz): (major isomer: **7d**): δ 0.85 (s, 9H), 0.99 (d, 3H, J=6.4 Hz), 1.56 (br s, 1H), 2.70 (dq, 1H, J=5.4 and 6.4 Hz), 2.96 (s, 1H), 3.21 (s, 3H), 3.60 (s, 3H), 3.92 (d, 1H, J=5.4 Hz), 7.24–7.33 (m, 5H); (minor isomer: **8d**): δ 0.82 (s, 9H), 1.00 (d, 3H, J=6.6 Hz), 1.56 (br s, 1H), 2.59 (dq, 1H, J=5.1 and 6.6 Hz), 2.80 (s, 1H), 3.24 (s, 3H), 3.68 (s, 3H), 4.03 (d, 1H, J=5.4 Hz), 7.24–7.33 (m, 5H). ^{13}C NMR (50 MHz): (major isomer: **7d**): δ 16.1 (CH_3), 26.8 (3×CH_3), 34.1 (C), 51.0 (CH_3), 57.0 (CH_3), 56.7 (CH), 67.6 (CH), 87.6 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 139.3 (C), 175.3 (C=O); (minor isomer: **8d**): δ 17.0 (CH_3), 26.6 (3×CH_3), 34.2 (C), 51.2 (CH_3), 57.3 (CH_3), 59.2 (CH), 69.5 (CH), 87.1 (CH), 127.4 (CH), 127.6 (CH), 128.1 (CH), 140.4 (C), 176.3 (C=O). Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28. Found: C, 69.39; H, 9.25. When treated according to method B, at 20°C, in the presence of *t*-butyl iodide, **1d** (100 mg, 0.42 mmol) led to **7d** and **8d** (46 mg, 0.16 mmol, 39%) in a 22:78 ratio. Treating **1d** (200 mg, 0.85 mmol) according to method B, at −40°C, in the presence of *t*-butyl iodide, led to **7d** and **8d** (172 mg, 0.59 mmol, 69%) in a 7:93 ratio.

5-Methyl-6-phenyl-5,6-dihydro-1,4-oxazin-2-one (2b). 2b was prepared from 2,4-dimethyl-5-phenyl-4,5-dihydro-oxazole according to a procedure described by Molinski et al.[22] H NMR (200 MHz): δ 0.96 (d, 3H, J=7.1 Hz), 4.27 (qdd, 1H, J=1.2, 3.2 and 7.1 Hz), 5.58 (d, 1H, J=3.2 Hz), 7.31–7.48 (m, 5H), 7.93 (d, 1H, J=1.2 Hz). ^{13}C NMR (50 MHz): δ 12.5 (CH_3), 57.6 (CH), 79.8 (CH), 125.3 (CH), 128.4 (CH), 128.6 (CH), 134.9 (C), 151.6 (CH), 155.3 (C=O). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86. Found: C, 69.69; H, 5.54.

3-Cyclohexyl-5-methyl-6-phenyl morpholin-2-one (14 and 15). Treating **2b** (178 mg, 0.94 mmol) according to method A, at −40°C, in the presence of cyclohexyl iodide, led to a mixture of four products: **14**, **15** (63 mg, 0.23 mmol, 27%) and **12**, **13** (51 mg, 0.23 mmol, 25%), isolated as colorless oils after purification by FC (15% EtOAc/pentane). The diastereomeric ratios (**14**:**15**: 90:10 and **12**:**13**: 75:25) were determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (200 MHz): (major isomer: **14**): δ 0.92 (d, 2H, J=6.6 Hz), 1.03–2.30 (m,

12H), 3.46 (dq, 1H, *J*=3.2 and 6.6 Hz), 3.74 (d, 1H, *J*=3.6 Hz), 5.59 (d, 1H, *J*=3.2 Hz), 7.20–7.55 (m, 5H); (minor isomer: **15**): δ 0.85 (d, 3H, *J*=6.6 Hz), 1.03–2.30 (m, 12H), 3.46 (dq, 1H, *J*=4.4 and 6.6 Hz), 3.63 (d, 1H, *J*=3.2 Hz), 5.35 (d, 1H, *J*=4.4 Hz), 7.20–7.55 (m, 5H). ^{13}C NMR (50 MHz): (major isomer: **14**): δ 13.1 (CH_3), 26.0 (CH_2), 26.1 (CH_2), 26.4 (CH_2), 27.6 (CH_2), 29.6 (CH_2), 42.0 (CH), 50.3 (CH), 58.6 (CH), 84.0 (CH), 125.5 (CH), 127.9 (CH), 128.4 (CH), 136.6 (C), 170.1 (C═O); (minor isomer: **15**): δ 17.4 (CH_3), 26.0 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 27.6 (CH_2), 29.9 (CH_2), 39.9 (CH), 52.0 (CH), 64.0 (CH), 84.1 (CH), 125.5 (CH), 127.6 (CH), 128.3 (CH), 136.6 (C), 169.9 (C═O). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.64; H, 8.49.

3-*t*-Butyl-5-methyl-6-phenyl morpholin-2-one (16 and 17). Treating **2b** (184 mg, 0.97 mmol) according to method A, at −40°C, in the presence of *t*-butyl iodide, led to a mixture of four products: **16**, **17** (60 mg, 0.24 mmol, 25%) and **12**, **13** (53 mg, 0.24 mmol, 25%), isolated as colorless oils after purification by FC (10% EtOAc/pentane). The diastereomeric ratios (**16**:**17**: 99>1 and **12**:**13**: 75:25) were determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (200 MHz): (major isomer: **16**): δ 0.85 (d, 3H, *J*=6.8 Hz), 1.05 (s, 9H), 1.50 (br s, 1H), 3.41 (dq, 1H, *J*=2.9 and 6.8 Hz), 3.50 (s, 1H), 5.59 (d, 1H, *J*=2.9 Hz), 7.25–7.40 (m, 5H). ^{13}C NMR (50 MHz): (major isomer: **16**): δ 13.7 (CH_3), 26.8 (3×CH_3), 36.1 (C), 50.9 (CH), 62.5 (CH), 83.5 (CH), 125.5 (CH), 127.6 (CH), 127.7 (CH), 137.3 (C), 169.7 (C═O). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.49; H, 8.35.

3-Ethyl-5-methyl-6-phenyl morpholin-2-one (12 and 13). ^{1}H NMR (200 MHz): (major isomer: **12**): δ 0.91 (d, 3H, *J*=6.8 Hz), 1.12 (t, 3H, *J*=7.1 Hz), 1.73–1.90 (m, 1H), 2.08–2.35 (m, 1H), 3.45–3.59 (m, 1H), 3.85 (ddd, 1H, *J*=4.9, 7.8 and 10.3 Hz), 4.98 (d, 1H, *J*=4.9 Hz), 5.98 (d, 1H, *J*=7.8 Hz, NH), 7.27–7.42 (m, 5H). ^{13}C NMR (50 MHz): (major isomer: **12**): δ 13.0 (CH_3), 13.6 (CH_3), 31.9 (CH_2), 51.0 (CH), 61.9 (CH), 83.5 (CH), 125.6 (CH), 127.3 (CH), 127.9 (CH), 137.9 (C), 171.1 (C═O). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81. Found: C, 71.38; H, 7.78.

Methyl (1-*o*-methoxyphenylethylimino)acetate (1e). 1-(2-Methoxyphenyl)ethylamine (500 mg, 3.31 mmol) prepared[24] from 2-methoxyacetophenone was dissolved in dichloromethane (6 mL). Molecular sieves (4 Å) and methyl glyoxylate (350 mg, 3.97 mmol, 1.5 equiv.) were added and the reaction was stirred at room temperature for 1 h. After concentration, a purification by FC (5% EtOAc/pentane) gave the desired product **1e** (326 mg, 1.47 mmol, 45%). ^{1}H NMR (200 MHz): δ 1.66 (d, 3H, *J*=6.6 Hz), 3.88 (s, 3H), 3.92 (s, 3H), 5.15 (q, 1H, *J*=6.6 Hz), 6.93 (d, 1H, *J*=8.0 Hz), 7.04 (t, 1H, *J*=7.6 Hz), 7.32 (t, 1H, *J*=7.6 Hz), 7.52 (d, 1H, *J*=7.6 Hz), 7.80 (s, 1H). ^{13}C NMR (50 MHz): δ 21.6 (CH_3), 52.3 (CH_3), 55.1 (CH_3), 61.8 (CH), 110.3 (CH), 120.6 (CH), 127.1 (CH), 128.2 (CH), 130.0 (C), 151.8 (CH), 156.3 (C), 163.8 (C═O). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 65.09; H, 6.77.

Methyl 2-(1-*o*-methoxyphenylethylamino)butanoate (3e and 4e). Treating **1e** (100 mg, 0.45 mmol) according to method A, at −40°C, led to a mixture of **3e** and **4e** (90 mg, 0.36 mmol, 90%), isolated as a colorless oil after purification by FC (10% EtOAc/pentane). The diastereomeric ratio (55:45) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (400 MHz): (major isomer: **3e**): δ 0.81 (t, 3H, *J*=7.6 Hz), 1.23 (d, 3H, *J*=6.6 Hz), 1.44–1.64 (m, 2H), 1.95 (br s, 1H), 2.91 (t, 1H, *J*=6.6 Hz), 3.59 (s, 3H), 3.69 (s, 3H), 4.05 (q, 1H, *J*=6.6 Hz), 6.72–6.88 (m, 2H), 7.05–7.39 (m, 2H); (minor isomer: **4e**): δ 0.81 (t, 3H, *J*=7.6 Hz), 1.27 (d, 3H, *J*=6.6 Hz), 1.44–1.64 (m, 2H), 1.95 (br s, 1H), 3.11 (t, 1H, *J*=6.6 Hz), 3.41 (s, 3H), 3.73 (s, 3H), 4.03 (q, 1H, *J*=6.6 Hz), 6.72–6.88 (m, 2H), 7.05–7.39 (m, 2H). ^{13}C NMR (50 MHz): (major isomer: **3e**): δ 9.8 (CH_3), 21.9 (CH_3), 27.0 (CH_2), 49.6 (CH), 51.3 (CH_3), 55.1 (CH_3), 60.2 (CH), 110.3 (CH), 120.4 (CH), 127.2 (CH), 127.6 (CH), 139.9 (C), 157.1 (C), 176.3 (C═O); (minor isomer: **4e**): δ 10.2 (CH_3), 22.9 (CH_3), 26.2 (CH_2), 50.7 (CH), 51.2 (CH_3), 55.1 (CH_3), 60.4 (CH), 110.4 (CH), 120.5 (CH), 126.8 (CH), 127.4 (CH), 132.8 (C), 156.9 (C), 175.5 (C═O). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42. Found: C, 66.70; H, 8.31. Treating **1e** (100 mg, 0.45 mmol) according to method B, at −40°C, led to **3e** and **4e** (108 mg, 0.43 mmol, 95%) in a 42:58 ratio.

Methyl 3-methyl-2-(1-*o*-methoxyphenylethylamino)-butanoate (9e and 10e). Treating **1e** (100 mg, 0.45 mmol) according to method A, at −40°C, in the presence of isopropyl iodide led to a mixture of **9e** and **10e** (86 mg, 0.32 mmol, 72%), isolated as a colorless oil after purification by FC (5% EtOAc/pentane). The diastereomeric ratio (57:43) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (200 MHz): (major isomer: **9e**): δ 0.85 (d, 3H, *J*=6.8 Hz), 0.88 (d, 3H, *J*=6.8 Hz), 1.22 (d, 3H, *J*=6.6 Hz), 1.75 (oct, 1H, *J*=6.8 Hz), 1.87 (br s, 1H), 2.76 (d, 1H, *J*=6.6 Hz), 3.60 (s, 3H), 3.70 (s, 3H), 4.03 (q, 1H, *J*=6.6 Hz), 6.73–6.90 (m, 2H), 7.05–7.46 (m, 2H); (minor isomer: **10e**): δ 0.80 (d, 3H, *J*=6.8 Hz), 0.82 (d, 3H, *J*=6.8 Hz), 1.24 (d, 3H, *J*=6.6 Hz), 1.75 (oct, 1H, *J*=6.8 Hz), 1.87 (br s, 1H), 2.92 (d, 1H, *J*=6.6 Hz), 3.38 (s, 3H), 3.73 (s, 3H), 3.96 (q, 1H, *J*=6.6 Hz), 6.73–6.90 (m, 2H), 7.05–7.46 (m, 2H). ^{13}C NMR (50 MHz): (major isomer: **9e**): δ 18.9 (CH_3), 19.4 (CH_3), 23.2 (CH_3), 31.7 (CH), 51.0 (CH), 51.2 (CH_3), 55.2 (CH_3), 64.8 (CH), 110.3 (CH), 120.6 (CH), 127.1 (CH), 127.4 (CH), 132.9 (C), 157.3 (C), 176.3 (C═O); (minor isomer: **10e**): δ 18.6 (CH_3), 18.9 (CH_3), 21.7 (CH_3), 31.9 (CH), 49.5 (CH), 51.5 (CH_3), 55.2 (CH_3), 65.4 (CH), 110.4 (CH), 120.5 (CH), 127.3 (CH), 127.6 (CH), 133.5 (C), 156.8 (C), 175.6 (C═O). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74. Found: C, 67.85; H, 8.72. Treating **1e** (100 mg, 0.45 mmol) according to method B, at −40°C, in the presence of isopropyl iodide, led to **9e** and **10e** (98 mg, 0.37 mmol, 82%) in a 44:56 ratio.

Methyl 3,3-dimethyl-2-(1-*o*-methoxyphenylethylamino)-butanoate (7e and 8e). Treating **1e** (100 mg, 0.45 mmol) according to method A, at −40°C, in the presence of *t*-butyl iodide led to a mixture of **7e** and **8e** (106 mg, 0.38 mmol, 84%), isolated as a colorless oil after purification by FC (5% EtOAc/pentane). The diastereomeric ratio (62:38) was determined from ^{1}H NMR on the crude reaction mixture. ^{1}H NMR (200 MHz): (major isomer: **7e**): δ 0.84 (s, 9H),

1.19 (d, 3H, J=6.8 Hz), 1.92 (br s, 1H), 2.63 (s, 1H), 3.56 (s, 3H), 3.69 (s, 3H), 3.97 (q, 1H, J=6.8 Hz), 6.68–6.90 (m, 2H), 7.02–7.42 (m, 2H); (minor isomer: **8e**): δ 0.85 (s, 9H), 1.24 (d, 3H, J=6.6 Hz), 1.92 (br s, 1H), 2.82 (s, 1H), 3.30 (s, 3H), 3.72 (s, 3H), 3.88 (q, 1H, J=6.6 Hz), 6.68–6.90 (m, 2H), 7.02–7.42 (m, 2H). ^{13}C NMR (50 MHz): (major isomer: **7e**): δ 23.3 (CH_3), 26.7 (3×CH_3), 34.2 (C), 49.1 (CH), 50.7 (CH_3), 55.3 (CH_3), 67.7 (CH), 110.3 (CH), 120.5 (CH), 127.1 (CH), 127.3 (CH), 132.9 (C), 156.8 (C), 176.0 (C=O); (minor isomer: **8e**): δ 21.6 (CH_3), 26.4 (3×CH_3), 34.2 (C), 50.6 (CH), 52.5 (CH_3), 55.2 (CH_3), 68.5 (CH), 110.4 (CH), 120.3 (CH), 127.3 (CH), 127.5 (CH), 133.6 (C), 156.8 (C), 175.4 (C=O). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02. Found: C, 68.77; H, 8.97.Treating **1e** (100 mg, 0.45 mmol) according to method B, at −40°C, in the presence of *t*-butyl iodide, led to **7e** and **8e** (110 mg, 0.39 mmol, 87%) in a 30:70 ratio.

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15. A competitive experiment was carried out on an equimolar mixture of **1a** and **2b** under conditions (i) at −40°C in the presence of 6 equiv. of *t*-BuI. Approximately 50% of unreacted **1a** was recovered, together with **7a** and **8a**, and **2b** was completely transformed into a mixture of **12**, **13** and **16**, **17**.

16. For analogues of **1b** see: (a) Ukaji, Y.; Watai, T.; Sumi, T.; Fujisawa, T. *Chem. Lett.* **1991**, 1555–1558. (b) Higashiyama, K.; Fujikura, H.; Takahashi, H. *Chem. Pharm. Bull.* **1995**, *45*, 722. (c) Betz, J.; Heuschmann, M. *Tetrahedron Lett.* **1995**, *36*, 4043. (d) Pridgen, L. N.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237–1241. For analogues of **1c** see: (e) Miao, C. K.; Sorcek, R.; Jones, P. J. *Tetrahedron Lett.* **1993**, *34*, 2259–2264. (f) Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1542–1544. (g) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull.* **1983**, *31*, 2895–2898. For analogues of **1d** see: (h) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340–1344.

17. In the case of **1b**, the structure of which is very close to that of **1a**, the assignments were based on the relative shielding of the proton α to the amino group and to the carboxylate in the diastereomeric products. With regard to **1c** and **1d**, correlations can be established between the relative chemical shift of the proton α to nitrogen in the chiral auxiliary in the diastereomeric adducts and

their sterochemistry. Similar trends are observed in literature data, see Refs. 16f–h.

18. As the reactions are conducted on 0.5 mmol or 1 mmol, the injection of 5 mL of air corresponds to 10% or 5% molar O_2; the injection of 20 mL of air corresponds approximately to 35 or 20% molar quantities of oxygen.

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