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Total Regioselective Transformation of Aromatic Aziridine 2-Carboxamides into 2-Aminoamides Promoted by Active Manganese

José M. Concellón,* Humberto Rodríguez-Solla, Vicente del Amo, and Pamela Díaz

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, 33071 Oviedo, Spain

jmcg@uniovi.es

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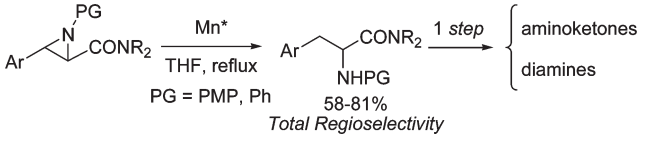


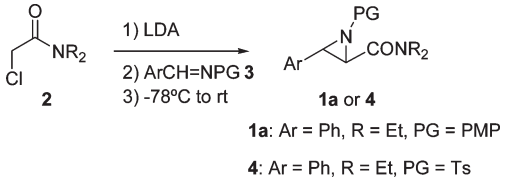
A novel, totally regioselective transformation of aromatic *N*-4-methoxyphenylaziridine 2-carboxamides into 2-aminoamides promoted by active manganese (Mn*) is reported. α-Amino ketones can be readily obtained by reaction of morpholine-derived 2-aminoamides with organolithium compounds.

Natural 2-amino acids and carbohydrates are the most abundant organic compounds in nature[1] and both are essential to life as parts of proteins and complex sugars. Also, some other non-natural 2-amino acids have shown biological activity.[1] In general, from a chemical point of view, 2-amino acids are versatile building blocks in organic synthesis and constitute one of the most important families of the chiral pool of natural products, which are often employed in the preparation of other enantiopure molecules.[2] According to the importance of amino acids, big efforts were made to develop novel laboratory methods to gain access to this family of compounds.[3]

Previous reports from the literature, due to Molander[4] and others,[5] have disclosed SmI_2-based ring-opening reactions of 2,3-epoxy esters or 2,3-epoxy ketones to afford the corresponding 3-hydroxy derivatives. Inspired by this seminal work, we reported the transformation of aromatic or aliphatic 2,3-epoxy amides into, more challenging, aliphatic and aromatic 2-hydroxyamides, by treating these compounds with samarium diiodide (in the presence of H_2O[6] or MeOH,[7] respectively), or with active manganese (Mn*).[8] Similarly, the totally regioselective opening of the aziridine ring of 2,3-imino acid derivatives to afford both regioisomers 2-amino[9] and 3-amino acid derivatives has been reported.[10] Concretely, the group of Molander has also pointed out that the treatment of 2-acylaziridines and 2,3-imino esters or amides with SmI_2 afford the corresponding 3-amino ketones, esters, or amides instead of the more desirable 2-aminocarbonylic compounds.[11] Taking into account these precedents, we focused our efforts on developing a novel synthetic method to transform aziridine 2-carboxamides into 2-amino amides, mediated by Mn*,[12] as we previously did for 2,3-epoxy amides.

Aziridine 2-carboxamides **1**, the starting materials for our study, were readily prepared through a Darzens reaction. Accordingly, the addition of the lithium enolate of chloroacetamides **2** to the corresponding imine **3** at −78 °C afforded the aziridine 2-carboxamide **1** after allowing the reaction mixture to reach room temperature (Scheme 1). To establish the most suitable protecting group for the nitrogen of the aziridines, *N*-(4-methoxyphenyl)phenylimine or *N*-tosylphenylimine[13] was used in the preparation of aziridines **1a** and **4**, respectively.

SCHEME 1. Synthesis of Aziridine 2-Carboxamides 1a or 4



Initially, both *N*-tosyl and *N*-PMP protected aziridines were treated with 2.4 equiv of Mn* in THF and the mixture was refluxed for 3 h. On the one hand, when the ring-opening reaction was performed on the *N*-tosyl-protected aziridine 2-carboxamide **4**, the corresponding (*E*)-cinnamamide was mainly observed amid a complex mixture of various byproducts. On the other hand, when the reaction was performed on the *N*-PMP-protected aziridine 2-carboxamide **1a**, the desired 2-amino amide **5a** was obtained in high yield (75%,

(1) Lindhorst, T. K. *Essentials of Carbohydrate Chemistry and Biochemistry*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2007.
(2) (a) Hudlický, T.; Reed, J. W. *The Way of Synthesis: Evolution of Design and Methods for Natural Products*, 1st ed.; Wiley-VCH: Weinheim, Germany, 2007. (b) Bhat, S. V.; Nagasampagi, B. A.; Sivakumar, M. *Chemistry of Natural Products*, 1st ed.; Springer: Berlin, Germany, 2005.
(3) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028.
(4) (a) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596–2599. (b) Molander, G. A.; La Belle, B. E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259.
(5) (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437–4440. (b) Reetz, M. T.; Lauterbach, E. H. *Tetrahedron Lett.* **1991**, *32*, 4477–4480.
(6) Concellón, J. M.; Bardales, E.; Gómez, C. *Tetrahedron Lett.* **2003**, *44*, 5323–5326.
(7) Concellón, J. M.; Bardales, E. *Org. Lett.* **2003**, *5*, 4783–4785.
(8) Concellón, J. M.; Bernad, P. L.; Rodríguez-Solla, H.; Díaz, P. *Adv. Synth. Catal.* **2009**, *351*, 2178–2184.
(9) Maguire, N. E.; McLaren, A. B.; Sweeney, J. B. *Synlett* **2003**, 1898–1900.
(10) (a) Pak, C. S.; Kim, T. H.; Ha, S. J. *J. Org. Chem.* **1998**, *63*, 10006–10010. (b) Lee, G. H.; Youn, I. K.; Choi, E. B.; Lee, H. K.; Yon, G. H.; Yang, H. C.; Pak, C. S. *Curr. Org. Chem.* **2004**, *8*, 1263–1287.
(11) (a) Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660–6661. (b) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887–8912.
(12) Kim, S.-H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *37*, 2197–2200.
(13) Wang, Y.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157.

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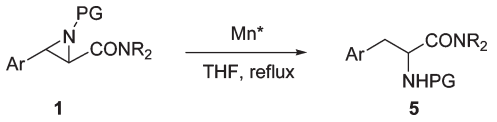
TABLE 1. Synthesis of 2-Amino Amides 5 from Aziridine 2-Carboxamides 1



1 5

entry	5	Ar	PG	NR_2	yield[a] (%)
1	**5a**	Ph	*p*-$MeOC_6H_4$	NEt_2	75
2	**5b**	Ph	*p*-$MeOC_6H_4$	$N(CH_2CH_2)_2O$[b]	80
3	**5c**	Ph	Ph	NEt_2	72
4	**5d**	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	NEt_2	81
5	**5e**	*m*-FC_6H_4	*p*-$MeOC_6H_4$	NEt_2	72
6	**5f**	*o*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	N-*i*-Pr_2	70
7	**5g**	*p*-CNC_6H_4	*p*-$MeOC_6H_4$	NEt_2[c]	58
8	**5h**	*m*-CH_2=CHC_6H_4	*p*-$MeOC_6H_4$	NEt_2[c]	67
9	**5i**	2-furyl	*p*-$MeOC_6H_4$	NEt_2[c]	64

[a]Isolated yield after flash chromatography based on compound **1**. [b]Morpholine. [c]Reaction carried out at 45 °C for 8 h.

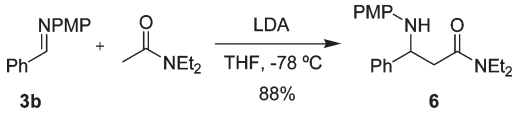
Table 1) and with total regioselectivity, as confirmed by ^{1}H NMR spectroscopy on the crude reaction mixture. To establish the generality of this transformation various *N*-PMP, or *N*-phenyl (Table 1 entry 3), aziridine 2-carboxamides were prepared and allowed to react under the established reaction conditions. The results summarized in Table 1 suggest that the reaction is general for aromatic aziridine 2-carboxamides bearing either electron-donor (Table 1, entry 6) or electron-withdrawing groups (Table 1, entry 7) at the aromatic ring. Moreover, the reaction also works successfully on heteroaromatic aziridines (Table 1, entry 9).

The regiochemistry of the ring-opening reaction was established by ^{1}H and ^{13}C NMR analysis and DEPT experiments of pure products **5**. For **5a** and **5e**, HMBC 2D-NMR experiments were also carried out. All these experiments confirmed that 2-amino amides were the regiosisomer obtained. To further corroborate the right structure of these compounds, a 3-amino amide **6** was prepared by reaction of the corresponding lithium enolate of *N*,*N*-diethylacetamide with *N*-(4-methoxyphenyl)phenylimine **3b** (Scheme 2). The spectroscopic data of **5a** were compared with the ^{1}H and ^{13}C NMR spectra of compound **6**, revealing obvious differences.

Aiming to broaden the scope of our Mn*-promoted ring-opening reaction we also prepared aliphatic aziridine 2-carboxamides. However, when these compounds were used as substrates, a mixture of products was obtained, even trying different reaction conditions, modifying temperature, or reaction times.

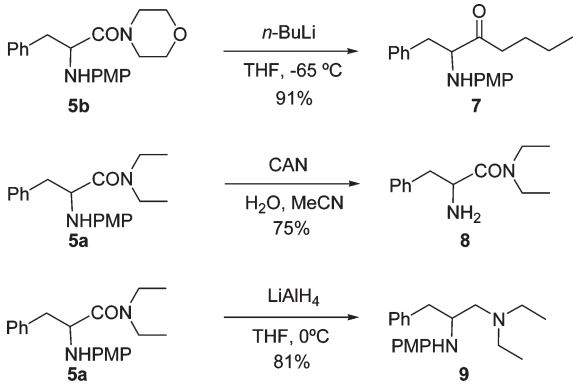
The 2-amino amides **5** obtained by our methodology could be versatile intermediates in organic synthesis. For instance, morpholine 2-amino amides could be readily transformed into amino ketones by reaction with organolithium compounds,[14] showing the value of these amino amide intermediates in the preparation of more complex 2-amino ketones. So, for example, the treatment of amino amide **5b** with *n*-butyllithium at −65 °C for 2 h gave the corresponding butyl ketone **7**, in 91% yield (Scheme 3). Nonetheless, compound **5a**, could be readily deprotected upon treatment

SCHEME 2. Synthesis of 3-Aminoamide 6



3b 6

SCHEME 3. Synthesis of 1-Amino-2-phenylethyl Butyl Ketone 7and Deprotection of 2-Amino Amide 5a and Preparation of 1,2-Diamine 9



with CAN,[15] rendering the corresponding amine-free compound **8**[16] in 75% isolated yield after purification. Finally, compound **5a** was also transformed into 1,2-diamine[17] **9** in 81% yield after purification (Scheme 3).

To explain the obtained results, we proposed that the reaction of both *N*-tosyl and *N*-PMP-protected aziridine 2-carboxamides with Mn* afforded the opening reaction of the aziridine ring. We assumed that the anion **10** is obtained with total regioselectivity due to the stabilization of this anion by conjugation with the aromatic ring. An indirect support for this proposed intermediate **10** was the absence of regioselectivity observed in the opening reaction of aliphatic aziridine 2-carboxamides.

The behavior of the generated anion **10** could be different, depending on whether *N*-tosyl or *N*-PMP aziridines were employed as starting substrates. The anion derived from *N*-tosyl derivatives **10a** undergoes a β-elimination process (path a, Scheme 4), favored by the coordination of the Mn(II) and the good leaving-group properties of the tosylamide. Thus the elimination reaction could take place through a cyclic transition state. We propose a chairlike transition state in which the Ar and amide groups are placed in a *pseudo*equatorial position. The elimination through this transition state affords the corresponding (*E*)-cinnamamides **11** which are observed in the reaction mixtures.

On the other hand, the intermediate anion **10b** from *N*-PMP protected (with a bad leaving group), the elimination reaction is not favored and the corresponding benzylic anion could be hydrolyzed to afford the corresponding 2-amino amides **5** (path b, Scheme 4).

In conclusion, we have reported the first regioselective Mn*-promoted ring-opening reaction of aromatic aziridine 2-carboxamides to give 2-amino amides with total regioselectivity

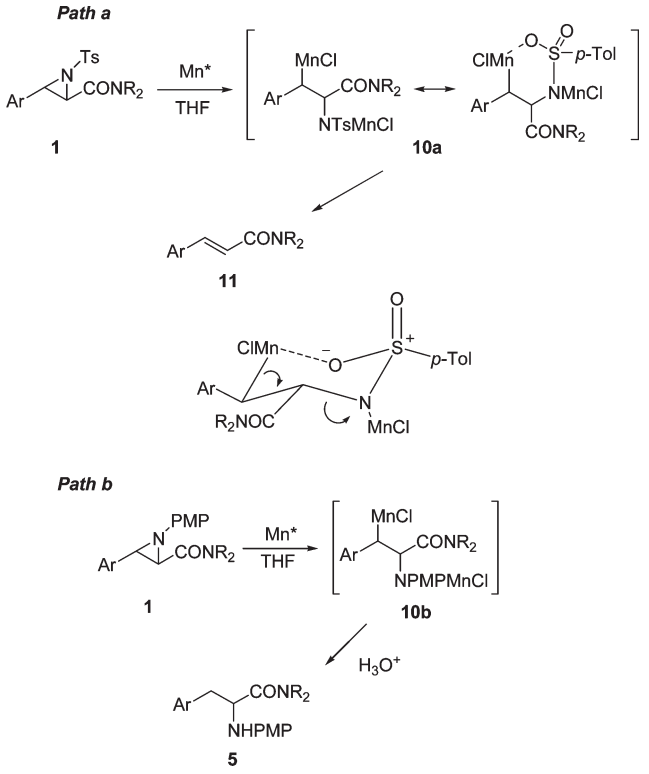
(14) Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414–1416.

(15) Berkowitz, D. B.; Wu, B.; Li, H. *Org. Lett.* **2006**, *8*, 971–974.

(16) Anderson, J. C.; Skerratt, S. *J. Chem. Soc., Perkin Trans. I* **2002**, 2871–2879.

(17) (a) Peruncheralathan, S.; Henze, M.; Schneider, C. *Synlett* **2007**, 2289–2291. (b) Yadav, J. S.; Reddy, B. V. S.; Vishweshwar Rao, K.; Saritha Raj, K.; Prasad, A. R. *Synthesis* **2002**, 1061–1064.

SCHEME 4. Mechanistic Proposal for the Conversion of 1 into 5 or 11



and in good to high yields. The outcome of the reaction is dependent on the *N*-substituent of the aziridine: *N*-PMP aziridines lead to the desired products, whereas *N*-tosyl aziridines afford complex reaction mixtures featuring the corresponding (*E*)-cinnamamides. Generalization of this transformation with aliphatic aziridine 2-carboxamides is currently under investigation in our laboratory.

Experimental Section

Preparation of Highly Active Manganese (Mn*). A mixture of lithium (26 mmol, 0.18 g) and 2-phenylpyridine (4 mmol, 0.98 mL) in THF (20 mL) was stirred for 3 h under nitrogen atmosphere. In a separate flask, a solution of the complex $MnCl_2 \cdot 2LiCl$ was prepared by stirring a suspension of anhydrous $MnCl_2$ (13 mmol, 1.62 g) and LiCl (26 mmol, 1.10 g) in THF (20 mL) for 30 min. This solution was added over the 2-phenylpyridine/lithium mixture previously prepared and the resulting mixture was stirred overnight under nitrogen atmosphere at room temperature to afford a black solution.

Synthesis of 2-amino amides (5): A slurry of Mn* (1.5 mmol, 4.5 mL) in THF was added to a stirred solution of the corresponding aziridine 2-carboxamide (0.5 mmol) in THF (2 mL) under inert atmosphere. The mixture was stirred at reflux for 3 h before it was quenched with 3 M HCl. The organic material was extracted with diethyl ether (3 × 20 mL), then the combined organic extracts were washed successively with 3 M HCl (2 × 10 mL), saturated $NaHCO_3$ (2 × 20 mL), and water (2 × 20 mL) and dried over Na_2SO_4. Solvents were removed under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc 3:1) provided pure compounds.

***N*,*N*-Diethyl-2-(4-methoxyphenylamino)-3-phenylpropanamide (5a):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.24 (m, 5 H), 6.82 (d, J = 9.2 Hz, 2 H), 6.68 (d, J = 9.2 Hz, 2 H), 4.39 (dd, J = 8.3, 5.3 Hz, 1 H), 3.79 (s, 3 H), 3.59−3.48 (m, 1 H), 3.20−2.84 (m, 5 H), 1.90−1.55 (br s, 1 H), 1.07 (t, J = 7.2 Hz, 3 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 152.8 (C), 140.8 (C), 137.6 (C), 129.4 (2 × CH), 128.4 (2 × CH), 126.6 (CH), 116.2 (2 × CH), 114.9 (2 × CH), 56.9 (CH), 55.7 (CH_3), 41.3 (CH_2), 40.4 (CH_2), 39.7 (CH_2), 14.1 (CH_3), 12.7 (CH_3); MS (70 eV, EI) m/z (%) 326 [$M^+ + H^+$, 37], 325 (24), 234 (90), 225 (100), 133 (50); HRMS (70 eV) calcd for $C_{20}H_{26}N_2O_2$ 326.1994, found 326.1995; IR (neat) 3329, 2983, 1634, 1265 cm^{-1}; R_f 0.63 (hexane:EtOAc 1:1).

4-{[1-(4-Methoxyphenylamino)-2-phenylpropyl]carbonyl}morpholine (5b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5 H), 6.80 (d, J = 8.8 Hz, 2 H), 6.68 (d, J = 8.5 Hz, 2 H), 4.49 (dd, J = 9.0, 5.0 Hz, 1 H), 3.77 (s, 3 H), 3.65−3.54 (m, 2 H), 3.48−3.33 (m, 3 H), 3.27−3.16 (m, 2 H), 2.99−2.80 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 (C), 153.2 (C), 139.9 (C), 136.9 (C), 129.4 (2 × CH), 128.6 (2 × CH), 127.0 (CH), 116.2 (2 × CH), 114.9 (2 × CH), 66.5 (CH_2), 65.9 (CH_2), 56.0 (CH_3), 55.6 (CH), 45.7 (CH_2), 42.2 (CH_2), 39.7 (CH_2); HRMS (ESI$^+$) calcd for [$C_{20}H_{24}N_2O_3 + H^+$] 341.1860, found 341.1860; IR (neat) 3054, 1650, 1266, 738 cm^{-1}; R_f 0.12 (hexane:EtOAc 3:1).

***N*,*N*-Diethyl-3-phenyl-2-(phenylamino)propanamide (5c):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.18 (m, 7 H), 6.79−6.72 (m, 1 H), 6.67 (apparent d, J = 8.2 Hz, 2 H), 4.60−4.45 (m, 1 H), 3.60−3.44 (m, 1 H), 3.16−2.85 (m, 5 H), 1.62 (s, 1 H), 1.07 (t, J = 6.9 Hz, 3 H), 0.93 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (C), 146.6 (C), 137.4 (C), 129.4 (CH), 129.3 (2 × CH), 128.4 (2 × CH), 126.7 (2 × CH), 118.0 (CH), 113.9 (2 × CH), 55.1 (CH), 41.3 (CH_2), 40.4 (CH_2), 39.5 (CH_2), 14.1 (CH_3), 12.7 (CH_3); MS (APCI) m/z (%) 297 [$M^+ + H^+$, 69], 196 (100), 100 (15); HRMS (ESI$^+$) calcd for [$C_{19}H_{24}N_2O + H^+$] 297.1961, found 297.1961; IR (neat) 3330, 1634, 1497, 749 cm^{-1}; R_f 0.66 (hexane:EtOAc 1:1).

3-(4-Chlorophenyl)-*N*,*N*-diethyl-2-(4-methoxyphenylamino)-propanamide (5d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.2 Hz, 2 H), 7.17 (d, J = 8.2 Hz, 2 H), 6.80 (d, J = 9.1 Hz, 2 H), 6.65 (d, J = 9.1 Hz, 2 H), 4.33 (dd, J = 7.6, 5.7 Hz, 1 H), 3.76 (s, 3 H), 3.48 (hp, J = 6.9 Hz, 1 H), 3.21−2.93 (m, 5 H), 1.90 (br s, 1 H), 1.05 (t, J = 6.9 Hz, 3 H), 0.94 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (C), 153.1 (C), 140.3 (C), 136.0 (C), 132.5 (C), 130.7 (2 × CH), 128.5 (2 × CH), 116.4 (2 × CH), 114.9 (2 × CH), 56.9 (CH), 55.6 (CH_3), 41.5 (CH_2), 40.5 (CH_2), 38.8 (CH_2), 14.2 (CH_3), 12.7 (CH_3); MS (APCI) m/z (%) 361 [$M^+ + H^+$, 100], 327 (10), 260 (97); HRMS (ESI$^+$) calcd for [$C_{20}H_{25}ClN_2O_2 + H^+$] 361.1677, found 361.1677; IR (neat) 3372, 2982, 1639, 739 cm^{-1}; R_f 0.57 (hexane:EtOAc 1:1).

***N*,*N*-Diethyl-3-(3-fluorophenyl)-2-(4-methoxyphenylamino)-propanamide (5e):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.22 (m, 1 H), 7.03−7.01 (apparent d, J = 6.8 Hz, 1 H), 6.97−6.90 (m, 2 H), 6.79 (d, J = 8.8 Hz, 2 H), 6.65 (d, J = 8.8 Hz, 2 H), 4.35 (dd, J = 8.8, 5.9 Hz, 1 H), 3.76 (s, 3 H), 3.58−3.45 (m, 1 H), 3.16−2.91 (m, 5 H), 1.05 (t, J = 6.8 Hz, 3 H), 0.92 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (C), 162.7 (d, J = 244.6 Hz, C), 152.9 (C), 140.5 (C), 140.1 (C), 129.8 (CH), 125.0 (CH), 116.3 (2 × CH), 116.0 (CH), 114.9 (2 × CH), 113.5 (d, J = 21.0 Hz, CH), 56.6 (CH), 55.6 (CH_3), 41.4 (CH_2), 40.4 (CH_2), 39.2 (CH_2), 14.1 (CH_3), 12.7 (CH_3); MS (ESI$^+$) m/z (%) 345 [$M^+ + H^+$, 100], 244 (12); HRMS (ESI$^+$) calcd for [$C_{20}H_{25}FN_2O_2 + H^+$] 345.1973, found 345.1972; IR (neat) 3376, 1638, 1513, 1266 cm^{-1}; R_f 0.57 (hexane:EtOAc 1:1)

***N*,*N*-Diisopropyl-3-(2-methoxyphenyl)-2-(4-methoxyphenylamino)propanamide (5f):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.15 (m, 3 H), 6.87 (d, J = 8.1 Hz, 1 H), 6.75 (d, J = 9.0 Hz, 2 H), 6.64 (d, J = 9.0 Hz, 2 H), 4.58 (dd, J = 7.8, 6.0 Hz, 1 H), 4.02−3.90 (m, 1 H), 3.93 (s, 3 H), 3.74 (s, 3 H), 3.40−3.25 (m, 1 H), 3.16 (dd, J = 13.2, 6.0 Hz, 1 H), 2.86 (dd, J = 13.2, 7.8 Hz, 1 H), 1.30 (br s, 1 H), 1.29 (d, J = 7.0 Hz, 3 H), 1.28 (d, J = 7.0 Hz, 3 H), 1.02 (d, J = 6.1 Hz, 3 H), 0.70 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 157.6 (C), 152.4 (C),

141.5 (C), 132.0 (CH), 127.9 (CH), 126.0 (C), 120.6 (CH), 116.0 (2 × CH), 114.6 (2 × CH), 110.0 (CH), 55.7 (CH_3), 55.3 (CH_3), 54.9 (CH), 48.1 (CH), 45.9 (CH), 35.3 (CH_2), 21.1 (CH_3), 20.6 (CH_3), 20.2 (CH_3), 20.1 (CH_3); MS (ESI^+) *m*/*z* (%) 385 [$M^+ + H^+$, 100], 383 (4), 256 (5); HRMS (ESI^+) calcd for [$C_{23}H_{32}N_2O_3 + H^+$] 385.2486, found 385.2485; IR (neat) 2970, 1630, 1265, 909 cm^{-1}; R_f 0.62 (hexane:EtOAc 1:1).

3-(4-Cyanophenyl)-*N*,*N*-diethyl-2-(4-methoxyphenylamino)-propanamide (5g): ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 8.2 Hz, 2 H), 6.79 (d, J = 8.8 Hz, 2 H), 6.64 (d, J = 8.8 Hz, 2 H), 4.36 (t, J = 6.3 Hz, 1 H), 3.84−3.73 (m, 1 H), 3.76 (s, 3 H), 3.53−3.43 (m, 1 H), 3.24−3.01 (m, 4 H), 1.05 (t, J = 7.2 Hz, 3 H), 0.95 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (C), 154.0 (C), 142.8 (C), 132.1 (2 × CH), 130.3 (2 × CH), 129.3 (C), 118.7 (C), 117.4 (2 × CH), 114.9 (2 × CH), 110.7 (C), 57.3 (CH), 55.6 (CH_3), 41.6 (CH_2), 40.6 (CH_2), 39.0 (CH_2), 14.2 (CH_3), 14.2 (CH_3); MS (ESI^+) *m*/*z* (%) 352 [$M^+ + H^+$, 100], 309 (4), 252 (3), 251 (37); HRMS (ESI^+) calcd for [$C_{21}H_{25}N_3O_2 + H^+$] 352.2020, found 352.2019; IR (neat) 3345, 2976, 1635, 1510 cm^{-1}; R_f 0.25 (hexane:EtOAc 1:1).

***N*,*N*-Diethyl-3-(3-vinylphenyl)-2-(4-methoxyphenylamino)-propanamide (5h):** ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.24 (m, 4 H), 6.81−6.78 (m, 2 H), 6.69−6.65 (m, 3 H), 5.74 (d, J = 17.9 Hz, 1 H), 5.25 (d, J = 10.7 Hz, 1 H), 4.37 (dd, J = 8.8, 5.9 Hz, 1 H), 3.77 (s, 3 H), 3.59−3.44 (m, 1 H), 3.13−3.06 (m, 2 H), 3.02−2.94 (m, 2 H), 2.90−2.82 (m, 1 H), 1.64 (br s, 1 H), 1.03 (t, J = 6.8 Hz, 3 H), 0.89 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (C), 152.8 (C), 140.7 (C), 137.7 (C), 137.6 (C), 136.6 (CH), 128.8 (CH), 128.6 (CH), 127.3 (CH), 124.5 (CH), 116.2 (2 × CH), 114.9 (2 × CH), 113.9 (CH_2), 56.7 (CH), 55.7 (CH_3), 41.3 (CH_2), 40.4 (CH_2), 39.6 (CH_2), 14.1 (CH_3), 12.8 (CH_3); MS (ESI^+) *m*/*z* (%) 353 [$M^+ + H^+$, 16], 352 (9), 351 (100), 250 (4); HRMS (ESI^+) calcd for [$C_{22}H_{28}N_2O_2 + H^+$] 353.2224, found 353.2223; IR (neat) 2254, 1633, 908, 734 cm^{-1}; R_f 0.77 (hexane:EtOAc 1:1).

***N*,*N*-Diethyl-3-(2-furyl)-2-(4-methoxyphenylamino)propanamide (5i):** ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 1.3 Hz, 1 H), 6.80 (d, J = 8.8 Hz, 2 H), 6.75 (d, J = 8.8 Hz, 2 H), 6.31−6.28 (m, 1 H), 6.12 (d, J = 3.2 Hz, 1 H), 4.50 (apparent t, J = 5.7 Hz, 1 H), 3.77 (s, 3 H), 3.61−3.39 (m, 2 H), 3.23−2.98 (m, 4 H), 1.06 (t, J = 7.6 Hz, 3 H), 1.01 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (C), 155.3 (C), 151.1 (C), 145.6 (C), 141.5 (CH), 117.2 (2 × CH), 114.8 (2 × CH), 110.6 (CH), 107.8 (CH), 55.6 (CH_3), 55.3 (CH), 41.2 (CH_2), 40.4 (CH_2), 31.7 (CH_2), 14.3 (CH_3), 12.6 (CH_3); MS (ESI^+) *m*/*z* (%) 317 [$M^+ + H^+$, 100], 235 (3), 216 (14); HRMS (ESI^+) calcd for [$C_{18}H_{24}N_2O_3 + H^+$] 317.1860, found 317.1859; IR (neat) 3310, 1630, 1513, 741 cm^{-1}; R_f 0.17 (hexane:EtOAc 1:1).

Synthesis of butyl [2-phenyl-α-(4-methoxyphenyl)eth-1-yl] ketone 7: *n*-Butyllithium (3.0 mmol) was added dropwise to the corresponding 2-amino amide **5b** (1.0 mmol) in THF (4 mL) at −78 °C. After being stirred for 3 h the reaction was quenched with an aqueous saturated solution of NH_4Cl (10 mL), followed by extraction with diethyl ether (3 × 10 mL). Usual workup provided crude product **7**, which was purified by flash column chromatography on silica gel (hexane:EtOAc 3:1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.16 (m, 5 H), 6.77 (d, J = 8.8 Hz, 2 H), 6.52 (d, J = 8.5 Hz, 2 H), 4.20 (t, J = 6.6 Hz, 1 H), 3.75 (s, 3 H), 3.11−2.96 (m, 2 H), 2.50−2.30 (m, 2 H), 1.55−1.43 (m, 2 H), 1.38−1.17 (m, 3 H), 0.85 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4 (C), 152.8 (C), 140.6 (C), 136.7 (C), 129.1 (2 × CH), 128.6 (2 × CH), 126.9 (CH), 114.9 (2 × CH), 114.8 (2 × CH), 64.7 (CH), 55.6 (CH_3), 39.9 (CH_2), 38.1 (CH_2), 25.2 (CH_2), 22.1 (CH_2), 13.7 (CH_3); MS (APCI) *m*/*z* (%) 312 [$M^+ + H^+$, 33], 297 (9), 294 (6); HRMS (ESI^+) calcd for [$C_{20}H_{25}NO_2 + H^+$] 312.1958, found 312.1958; IR (neat) 2957, 1711, 1513, 1240 cm^{-1}; R_f 0.72 (hexane:EtOAc 1:1).

***N*-(1-(Diethylamino)-3-(phenylpropan-2-yl)-4-methoxybenzenamine (9):** To the amide **5a** (0.4 mmol, 1 equiv) in anhydrous THF (4 mL) was added $LiAlH_4$ (2 mmol, 5 equiv) at 0 °C. The reaction was stirred for 2 h at 0 °C, then the reaction was quenched by the addition of a mixture of ice/water and extracted with diethyl ether (3 × 10 mL). The organic layers were washed with water (1 × 10 mL), and concentrated under vacuum. Purification by flash column chromatography on silica gel (hexane/EtOAc, 1:2) afforded the pure compound **9** as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.21 (m, 5 H), 6.82 (d, J = 8.7 Hz, 2 H), 6.68 (d, J = 8.7 Hz, 2 H), 3.78 (s, 3 H), 3.61−3.52 (m, 1 H), 3.04 (dd, J = 14.0, 4.4 Hz, 1 H), 2.78 (dd, J = 14.0, 7.9 Hz, 1 H), 2.63−2.41 (m, 6 H), 1.35 (br s, 1 H), 0.98 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0 (C), 142.3 (C), 138.7 (C), 129.4 (2 × CH), 128.2 (2 × CH), 126.0 (CH), 115.0 (2 × CH), 114.8 (2 × CH), 56.3 (CH_2), 55.7 (CH), 52.9 (CH_3), 46.7 (2 × CH_2), 39.3 (CH_2), 11.5 (2 × CH_3); MS (ESI^+) *m*/*z* (%) 312 [M^+, 100], 226 (63), 190 (50), 91 (100); HRMS (ESI^+) calcd for [$C_{20}H_{28}N_2O + H^+$] 313.2274, found 313.2275; IR (neat) 3335, 2968, 1510, 738 cm^{-1}; R_f 0.30 (EtOAc).

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **1**, **5**−**7**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.