DOI: 10.1002/ejoc.200800683

Synthesis of α-Amino Acids by Umpolung of Weinreb Amide Enolates

Sebastian Hirner,[a] Donata K. Kirchner,[a] and Peter Somfai*[a,b]

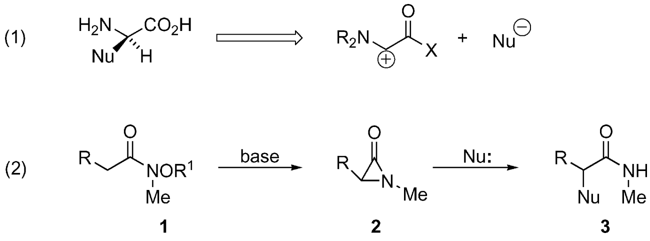
Keywords: Amino acids / Umpolung / Arylglycines / Grignard reaction / Weinreb amides

An efficient and diastereoselective synthesis of α-amino acids from readily available starting materials has been developed. The key feature of this reaction is an umpolung of a glycine-derived enolate, providing an alternative approach for the synthesis of α-amino acids.

Introduction

α-Amino acids and their derivatives serve a central role in chemistry and biology, being the fundamental constituents of peptides and proteins. Moreover, they are important templates in asymmetric catalysis, versatile building blocks in total synthesis and common subunits in many bioactive compounds and natural products.[1] Arylglycines, for example, are prevalent in widely used drugs, such as β-lactam and glycopeptide antibiotics (e.g. vancomycin)[2] and the cardiovascular agent Plavix.[3] As a consequence, much effort has been dedicated to the development of novel synthetic methods, especially for the synthesis of enantiomerically pure α-amino acids.[4] During the last decades, a wide range of asymmetric, often catalytic syntheses has been developed, such as catalytic asymmetric hydrogenations of dehydro-α-amino acids,[4a] asymmetric modifications of the Strecker reaction,[5] enantioselective alkylations of glycine derivatives under phase-transfer conditions[4b,4c] and catalytic asymmetric addition of nucleophiles to α-imino esters.[4d] Despite the great variety of well-tried methods and new asymmetric methodologies for the synthesis of α-amino acids, there is still need for efficient and technically feasible methods. For example, the synthesis of arylglycines remains a challenging task in organic synthesis[4e] and is still a very active field of research. Recent developments in that area include the transition-metal-catalyzed addition of arylboronic acids to imino esters[6] and the asymmetric insertion of α-diazocarbonyl compounds into the N–H bonds of carbamates.[7]

One of the most common strategies towards the synthesis of arylglycines and other α-amino acids is the reaction of glycine α-cation equivalents with nucleophiles [Scheme 1, Equation (1)].[8] Typically, imines, iminium ions and α-substituted glycine derivatives are used as electrophilic glycine surrogates. An alternative entry to glycine α-cation equivalents would be by umpolung of enolates derived from α-amino Weinreb amides. In this respect, it has previously been shown that subjecting compound **1** to base leads to the formation of α-lactam **2** [Scheme 1, Equation (2)].[9,10] When this material was treated with weak nucleophiles, such as hindered amines, chloride[9b] or azide,[9c] the lactam was regioselectively opened to give α-substituted amides **3**, the reaction most likely proceeding through an oxa-aza-allyl cation intermediate. We became interested in the possibility of generating lactam **2** from a suitable precursor and investigating its reaction with Grignard reagents as a novel entry to non-proteogenic α-amino acids. Recently, we communicated the initial results,[11] and herein we give a full account of this study.



Scheme 1.

Results and Discussion

Initial focus was directed towards identifying the optimal base and reaction conditions for generating the desired α-lactam and to study its reaction with Grignard reagents. Deprotonation of Weinreb amide **4a**[12] at room tempera-

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[a] Organic Chemistry, KTH Chemical Science and Engineering,
Royal Institute of Technology,
10044 Stockholm, Sweden,
Fax: +46-8-791-2333
[b] Institute of Technology, University of Tartu,
Nooruse 1, 50411 Tartu, Estonia
E-mail: somfai@kth.se

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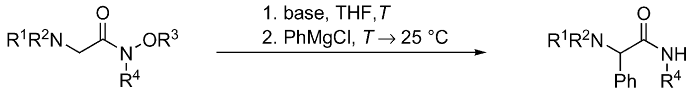
ture with NaH, followed by addition of PhMgCl yielded only small amounts of the desired α-arylated product **5a** (Table 1, Entry 1), the main product being ketone **6a** (Figure 1).[13] A similar result was obtained when the Grignard reagent itself was used as base and added at 0 °C to the reaction mixture (Entry 2). It was speculated that the sterically demanding NBn_2 moiety in **4a** prevented a facile deprotonation at the α-carbon atom, and to test this, compounds **4b**,**c**, having smaller *N*-protecting groups, were prepared and subjected to the reaction conditions (Entries 3 and 4). Indeed, this resulted in an improved yield of the desired α-arylated products **5b**,**c** and lower amounts of the corresponding ketones **6b**,**c**. Although these results were encouraging, there is obviously room for improvement. To suppress the formation of ketone **6**, it is necessary that amide **4** is completely converted into the corresponding enolate prior to the addition of the nucleophile. However, deprotonation of **4b** with stronger bases such as LiHMDS and *n*BuLi at –78 °C, followed by the addition of PhMgCl gave only traces of the desired product (Entries 5, 6). When LDA was used as base, formation of the acylation product **6b** could be completely prevented, but the desired product **5b** was isolated in only 12% yield (Entry 7). Instead, the main product from this reaction was amide **8** (Figure 1), the result of an undesired E2 pathway, together with N,O-acetal **7a**.[14] In order to minimize the formation of the demethoxylated product **8**, the *N*-methoxy substituent in **4b** was replaced by an *N-tert*-butoxy moiety to give compound **4e**,[15] and when this material was subjected to the same reaction conditions, the desired arylation product **5b** could be isolated in 77% yield (Entry 8). Simply decreasing the amount of base used resulted in an increased yield, allowing for 86% of **5b** (Entry 9). Excellent yields were also obtained for diallyl derivative **4f** (Entry 10), while the use of amide **4d** (Entry 11) required that the LDA was added at 0 °C to the reaction mixture in order to obtain full conversion. For this case, however, considerable amounts of N,O-acetal **7b** was formed that could not be separated from the desired

Table 1. Optimization of α-arylation.[a]

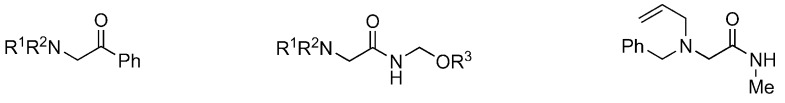


4a: $R^1 = R^2 = Bn$, $R^3 = R^4 = Me$
4b: $R^1 = Bn$, $R^2 = allyl$, $R^3 = R^4 = Me$
4c: $R^1 = R^2 = allyl$, $R^3 = R^4 = Me$
4d: $R^1 = R^2 = Bn$, $R^3 = tBu$, $R^4 = Me$
4e: $R^1 = Bn$, $R^2 = allyl$, $R^3 = tBu$, $R^4 = Me$
4f: $R^1 = R^2 = allyl$, $R^3 = tBu$, $R^4 = Me$
4g: $R^1 = Bn$, $R^2 = allyl$, $R^3 = tBu$, $R^4 = Ph$
4h: $R^1 = Bn$, $R^2 = Ts$, $R^3 = tBu$, $R^4 = Me$

5a: $R^1 = R^2 = Bn$, $R^4 = Me$
5b: $R^1 = Bn$, $R^2 = allyl$, $R^4 = Me$
5c: $R^1 = R^2 = allyl$, $R^4 = Me$
5d: $R^1 = Bn$, $R^2 = allyl$, $R^4 = Ph$

Entry	4	Base (equiv.)	T [°C]	Product	Product ratio[b]	Yield of **5** (%)[c]
1	**a**	NaH (1.2)	25	**5a** + **6a**	1:6	10
2	**a**	–	0	**5a** + **6a**	1:7	12[d]
3	**b**	–	0	**5b** + **6b**	1:1	44[d]
4	**c**	–	0	**5c** + **6c**	1:1	38[d]
5	**b**	LiHMDS (1.5)	–78	n. d.	n. d.	n. d.
6	**b**	BuLi (1.5)	–78	n. d.	n. d.	n. d.
7	**b**	LDA (1.5)	–78	**5b** + **7a** + **8**	n. d.	12
8	**e**	LDA (1.5)	–78	**5b** + **7b**	>20:1	77
9	**e**	LDA (1.0)	–78	**5b** + **7b**	>20:1	86
10	**f**	LDA (1.0)	–78	**5c** + **7d**	>20:1	87
11	**d**	LDA (1.0)	–78	**5a** + **7b**	7:1	72[e]
12	**g**	LDA (1.0)	–78	**5d**	n. d.	70
13	**h**	LDA (1.0)	–78	n. d.	n. d.	n. d.

[a] The reaction was carried out with amide **4** (1.0 equiv.), base and PhMgCl (2.0 equiv.) in THF. [b] Ratio determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yields. [d] No base and 3.0 equiv. PhMgCl were used. [e] LDA was added at 0 °C.



6a: $R^1 = R^2 = Bn$
6b: $R^1 = Bn$, $R^2 = allyl$
6c: $R^1 = R^2 = allyl$

7a: $R^1 = Bn$, $R^2 = allyl$, $R^3 = Me$
7b: $R^1 = R^2 = Bn$, $R^3 = tBu$
7c: $R^1 = Bn$, $R^2 = allyl$, $R^3 = tBu$
7d: $R^1 = R^2 = allyl$, $R^3 = tBu$

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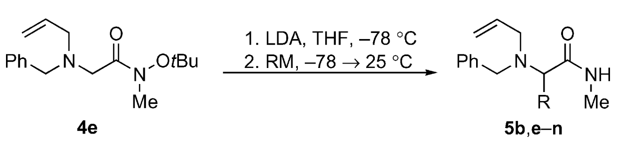
Figure 1. Byproducts formed during the α-arylation.

product. Thus, it seems that increased steric bulk at the α-amino moiety in **4** significantly slows down the enolization and, more importantly, allows for competing reaction pathways. In order to avoid the formation of **7**, the *N*-methyl substituent in **4b** was replaced by a phenyl group to give amide **4g**. However, this compound gave the desired arylated product only in moderate yields (Entry 12). Finally, use of *N*-Bn,*N*-Ts derivative **4h** gave a complex mixture of products, from which none of the desired product could be isolated (Entry 13).

With optimized conditions in hand, the reaction of **4e** with various nucleophiles was investigated (Table 2). Both PhLi and Ph_2CuLi gave complex reaction mixtures with only trace amounts of **5b** being formed (Entries 2, 3). Use of PhZnCl gave good yields of **5b**, provided that the base was added at 0 °C (Entry 4).[16] Both electron-poor and electron-rich aryl Grignard reagents proved compatible with the substrate and gave good to excellent yields of the corresponding adduct (Entries 5, 6). Similar yields were also obtained with biphenyl (Entry 7), heteroaromatic (Entries 8, 9) and functionalized heteroaromatic Grignard reagents (Entry 10). Alkyl and alkenyl Grignard reagents can also be successfully used in the addition to **4e** (Entries 11–13), whereas the use of the Grignard reagent derived from (trimethylsilyl)acetylene gave only trace amounts of the desired product after column chromatography (Entry 14). In most of the reactions it was necessary to add the LDA at 0 °C or to use an excess of the base in order to obtain full conversion. An explanation for this might be an incomplete enolization of the Weinreb amide, which is caused by side reactions of the LDA with the Grignard reagent. Further investigations on that topic are ongoing and will be reported in due course.

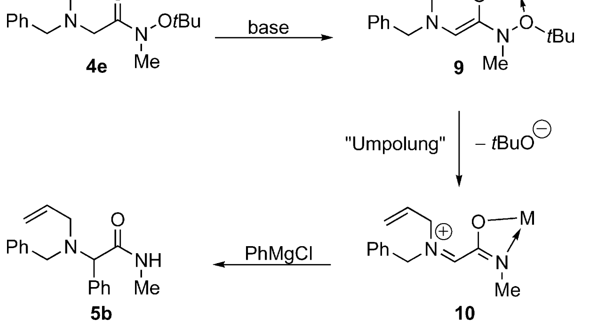
The proposed mechanism for the formation of compound **5b** from **4e** is depicted in Scheme 2. In the first step, Weinreb amide **4e** is deprotonated to afford enolate **9**. As seen in Table 1, it is important that the base is sufficiently strong to allow for a fast and complete enolization in order to avoid undesired ketone formation. Similarly, if the α-carbon atom in **4** is sterically hindered, the base will preferentially deprotonate the amide *N*-Me moiety. Lithium enolates derived from amides are known to have (*Z*) geometry, due to $A^{1,3}$ interactions between the α-carbon substituent and the *N*-substituent,[17] although recent studies suggests that similar enolates derived from Weinreb amides favour (*E*) geometry.[18] In any respect, the enolate geometry is inconsequential for the present investigation. Subsequent elimination of $tBuO^-$ from **9** constitutes the key step and generates iminium ion **10**. Addition of PhMgCl to **10** then gives amide **5b**. For the base-promoted addition of amines and halides to *O*-sulfonylated hydroxamic acid derivatives it has been shown that both α-CH deprotonation and loss of the *N*-OR moiety are occurring at the transition state of the rate-determining step.[9d] Application of this scenario to the present reaction suggests the direct formation of iminium ion **10** from enolate **9**, or conversion of **9** into the corresponding α-lactam (cf. structure **2**, Scheme 1) followed by ring opening to give **10** (compounds **2** and **10** are valence tautomers). Although the exact course of events cannot be deduced from the data available, the formation of compound **5b** as the sole regioisomer strongly suggests the involvement of iminium ion **10**. The overall result of this elimination is an unusual dipole reversal (umpolung) of the α-carbon atom in **4e**,[19] converting the nucleophilic character of the enolate into an electrophilic one (Scheme 2). Despite the synthetic potential of such transformation, only relatively few examples of umpolung of enolates have been reported. Typical examples involve the use of dithioketene acetals,[20] SET oxidation of enolates[21] and the anodic oxidation of silyl enol ethers.[22]

Table 2. Reaction of Weinreb amide **4e** with various nucleophiles.[a]



Entry	RM	Product (R)	Yield (%)[b]
1	PhMgCl	**5b** (Ph)	86
2	PhLi	**5b** (Ph)	n. d.
3	Ph_2CuLi	**5b** (Ph)	n. d.
4	PhZnCl	**5b** (Ph)	75
5	$4\text{-}FC_6H_4MgBr$	**5e** ($4\text{-}FC_6H_4$)	77[c]
6	$4\text{-}MeOC_6H_4MgBr$	**5f** ($4\text{-}MeOC_6H_4$)	92
7	$3\text{-}PhC_6H_4MgBr$	**5g** ($3\text{-}PhC_6H_4$)	81[d]
8	(2-thiophenyl)MgBr	**5h** (2-thiophenyl)	91[c]
9	(3-pyridinyl)MgCl·LiCl	**5i** (3-pyridinyl)	77[d]
10	5-Br(3-pyridinyl)MgCl·LiCl	**5j** [5-Br(3-pyridinyl)]	76[d]
11	MeMgBr	**5k** (Me)	82[d]
12	*i*PrMgCl	**5l** (*i*Pr)	79[d]
13	$CH_2{=}CHMgBr$	**5m** ($CH_2{=}CH$)	82
14	TMSC≡CMgBr	**5n** (TMSC≡C)	n. d.

[a] The reaction was carried out with amide **4e** (1.0 equiv.), LDA (1.0 equiv.) and RM (2.0 equiv.) in THF. [b] Yield of isolated product. [c] LDA (1.5 equiv.) was used. [d] LDA was added at 0 °C.



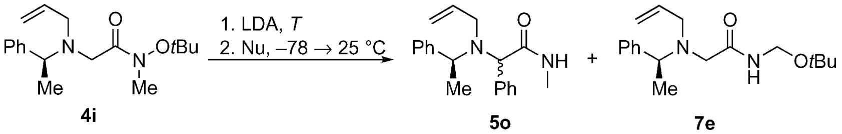
Scheme 2. Suggested mechanism for the α-arylation of Weinreb amide **5b**.

With an operationally simple and high-yielding procedure at hand, we next set out to develop an auxiliary controlled synthesis of enantiomerically enriched α-amino acids, and amide **4i**, synthesized in 2 steps from (–)-α-methylbenzylamine, was selected for initial screening. Under standard reaction conditions with PhMgCl, the desired product **5o** was formed as a 2:1 mixture of diastereomers together with considerable amounts of compound **7e** (Table 3, Entry 1). Apparently, the increased steric bulk imposed by the α-methylbenzyl moiety retards the desired enolization, making rearrangement to the N,O-acetal **7e** competitive. Screening of less basic nucleophiles showed that zinc reagents gave both higher diastereoselectivities and less rearranged product (Entries 3–5). By optimizing the solvent and amount of base, high selectivities were achieved when the reaction was performed in Et_2O with PhZnCl (Entries 6–8). These optimized conditions afforded the desired α-arylated product in good yield and selectivity (Scheme 3, 74%, *dr* = 7:1).

The diastereomers could be separated by flash chromatography, and the absolute configuration of the newly formed stereocenter in **5o** was determined to be (*S*) by transformation into phenylglycine methyl ester hydrochloride **14** (Scheme 3). It has been noted previously that a secondary amide functionality, as in compound **5**, constitutes an advantageous protective group for the carboxyl group, especially in racemization-prone arylglycines (phenylglycine is 60 times more prone toward reacemization than alanine).[23] For example, an *N*-methyl-amide protection strategy has been used for the synthesis of vancomycin antibiotics to circumvent epimerization of the terminal arylglycine residue.[24] Not surprisingly, however, all attempts to directly convert the *N*-methyl-amide moiety into the corresponding acid or ester were unsuccessful, and it was instead decided to use a 2-step procedure to accomplish this transformation.[25] *N*-Nitrosation of **5o** under standard conditions gave complete conversion to nitrosoamide **11**, which was directly subjected to MeOH and saturated $NaHCO_3$ to give ester **12** in 84% yield. Interestingly, attempts to hydrolyse **11** to give the corresponding acid [LiOOH, THF/H_2O (3:1), 0 °C] proved unsuccessful. Subsequent deallylation[26] and catalytic hydrogenolysis with $Pd(OH)_2$ gave enantiomerically pure **14**[27] in good overall yield and without epimerization.[28] For *ee* determination, **14** was converted into the free amine by treatment with $NaHCO_3$ in H_2O, and the *ee* was shown to be >96% by chiral HPLC.[29] It is notable that the hydrogenolysis was not regioselective when the reaction was performed with catalytic amounts of Pd/C; in this case, 20% of the product derived from cleavage at the α-carbon atom was obtained.

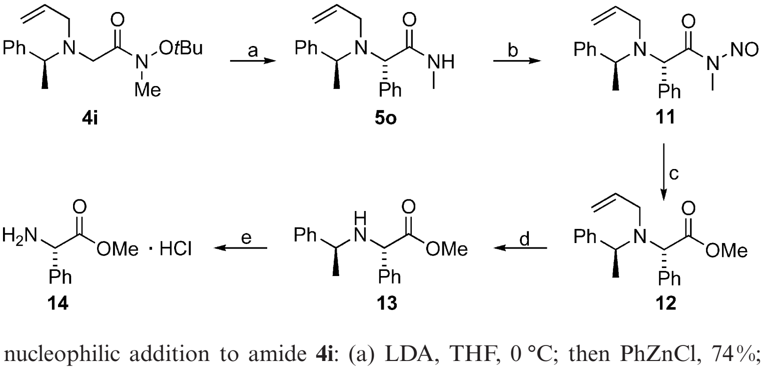
α-Amino acids having a quaternary α-stereocenter are an important class of compounds that has been used to impose restricted conformations onto a peptide chain,[30] and it was decided to briefly investigate if the current methodology could be used for preparing such compounds. Thus, subjecting the alanine-derived amide **15** to the standard conditions gave none of the desired product, and only recovered starting material and N,O-acetal **16** were isolated (Scheme 4). Apparently, the additional steric hindrance at

Table 3. Optimization of α-arylation by using chiral amide **4i**.[a]



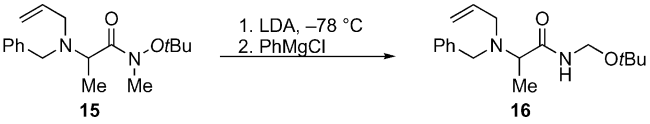
Entry	Nu	Solvent	LDA [equiv.]	*T* [°C]	**5o**/**7e**[b]	*dr* of **5o**[b]
1	PhMgCl	THF	1.4	–78	1.9:1	2.0:1
2	PhMgBr	THF	1.4	–78	2.5:1	1.4:1
3	$PhCeCl_2$	THF	1.4	–78	1.3:1	1.9:1
4	Ph_2Zn	THF	1.4	0	2.2:1	4.7:1
5	PhZnCl	THF	1.4	0	2.5:1	6.3:1
6	PhZnCl	toluene	1.4	0	1.8:1	5.7:1
7	PhZnCl	Et_2O	1.4	0	4.0:1	5.5:1
8	PhZnCl	Et_2O	1.05	0	4.4:1	6.9:1[c]

[a] The reaction was carried out with amide **4i** (1.0 equiv.) and Nu (2.0 equiv.). [b] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] PhZnCl (1.2 equiv.) was used.



Scheme 3. Diastereoselective nucleophilic addition to amide **4i**: (a) LDA, THF, 0 °C; then PhZnCl, 74%; (b) $NaNO_2$, CH_2Cl_2, Ac_2O, AcOH; (c) MeOH, $NaHCO_3$, reflux, 84% (over 2 steps); (d) [$Pd(PPh_3)_4$], *N*,*N′*-dimethylbarbituric acid, CH_2Cl_2, reflux, 92%; (e) $Pd(OH)_2$, MeOH, HCl, 100%.

the α-carbon atom in **15** prevents an efficient enolization, making the formation of N,O-acetal **16** a more favoured process.



Scheme 4.

Conclusions

An efficient and diastereoselective synthesis of α-amino acids from readily available starting materials has been developed. The key feature of this reaction is an umpolung of a glycine-derived enolate, providing an alternative approach for the synthesis of α-amino acids. Further studies of this reaction and its application in total synthesis are in progress and will be reported in due course.

Experimental Section

General Procedure A. 2-[(Allyl)(benzyl)amino]-*N*-methyl-2-phenylacetamide (5b): LDA (1.40 M, 71 µL, 0.10 mmol) was added to a solution of amide **4e** (29.0 mg, 0.10 mmol) in THF (2 mL) at –78 °C. The solution was stirred for 1 min, and PhMgCl (2.0 M in THF, 100 µL, 0.20 mmol) was added. The mixture was allowed to reach room temperature and the reaction quenched with satd. NH_4Cl (1 mL) and brine (1 mL). The aqueous phase was extracted twice with Et_2O, and the combined organic extracts were dried (K_2CO_3) and concentrated under reduced pressure. Flash chromatography [pentane (+ 1% *i*$PrNH_2$)/EtOAc, 95:5 → 60:40] of the residue gave **5b** (25.2 mg, 86%) as a colourless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 10 H), 7.20 (br., 1 H), 5.84 (m, 1 H), 5.18 (m, 2 H), 4.2 (s, 1 H), 3.82 (d, J = 14.0 Hz, 1 H), 3.33 (d, J = 14.0 Hz, 1 H), 3.25 (m, 1 H), 2.88 (d, J = 4.9 Hz, 3 H), 2.85 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 138.5, 134.7, 129.8, 128.5, 128.4, 128.1, 127.8, 127.2, 118.4, 68.9, 54.5, 53.2, 26.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 3308, 1657, 1521, 1453 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{19}H_{23}N_2O_3$ [M + H]$^+$ 295.1805; found 295.1801.

General Procedure B. 2-[(Allyl)(benzyl)amino]-2-(biphenyl-3-yl)-*N*-methylacetamide (5g): The Grignard reagent was prepared from 3-bromobiphenyl (333 µL, 2.0 mmol) and magnesium powder (73 mg, 3.0 mmol) in THF (5 mL). To a solution of amide **4e** (29.0 mg, 0.10 mmol) in THF (2 mL) was added LDA (1.40 M, 71 µL, 0.10 mmol) at 0 °C. The solution was stirred for 1 min, cooled to –78 °C and the freshly prepared Grignard solution (0.27 M in THF, 0.74 mL, 0.20 mmol) was added. The mixture was allowed to reach room temperature and the reaction quenched with satd. NH_4Cl (1 mL) and brine (1 mL). The aqueous phase was extracted twice with Et_2O, and the combined organic extracts were dried (K_2CO_3) and concentrated under reduced pressure. Flash chromatography [pentane (+ 1% *i*$PrNH_2$)/EtOAc, 95:5 → 65:35] of the residue gave **5g** (29.9 mg, 81%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.52–711 (m, 15 H), 5.79 (m, 1 H), 5.12 (m, 2 H), 4.42 (s, 1 H), 3.79 (d, J = 14.0 Hz, 1 H), 3.31 (d, J = 14.0 Hz, 1 H), 3.21 (dd, J = 14.6, 4.9 Hz), 2.85 (m, 1 H), 2.83 (d, J = 4.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 141.2, 141.1, 138.6, 135.3, 135.2, 134.8, 128.8, 128.8, 128.7, 128.6, 128.6, 127.3, 127.3, 126.8, 118.6, 69.2, 54.8, 53.4, 26.2 ppm. IR (film): $\tilde{\nu}_{max}$ = 3310, 2928, 1660, 1521, 1411 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{25}H_{27}N_2O$ [M + H]$^+$ 371.2118; found 371.2114.

2-(Dibenzylamino)-*N*-methyl-2-phenylacetamide (5a): General Procedure A was applied by using amide **4d** and PhMgCl (2.0 M in THF, 0.10 mL, 0.20 mmol). Flash chromatography [pentane (+ 1% *i*$PrNH_2$)/EtOAc, 95:5 → 60:40] of the residue gave **5a** (20.8 mg, 72%) as a colourless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.13 (m, 15 H), 6.95 (br., 1 H), 4.32 (s, 1 H), 3.77 (d, J = 13.9 Hz, 2 H), 3.28 (d, J = 13.9 Hz, 2 H), 2.81 (d, J = 5.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1, 138.6, 134.4, 130.2, 128.6, 128.6, 128.2, 127.8, 127.3, 67.9, 54.6, 26.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 3313, 3028, 1660, 1522, 1240 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{23}H_{25}N_2O$ [M + H]$^+$ 345.1961; found 345.1690.

2-(Diallylamino)-*N*-methyl-2-phenylacetamide (5c): General Procedure A was applied by using amide **4f** and PhMgCl (2.0 M in THF, 0.10 mL, 0.20 mmol). Flash chromatography [pentane (+ 1% *i*$PrNH_2$)/EtOAc, 95:5 → 60:40] of the residue gave **5c** (20.8 mg, 87%) as a colourless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.12 (m, 5 H), 5.73 (m, 2 H), 5.10 (m, 4 H), 4.33 (s, 1 H), 3.17 (m, 2 H), 2.80 (d, J = 4.9 Hz, 3 H), 2.77 (m, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.5, 135.0, 134.9, 129.7, 128.2, 127.8, 118.2, 69.6, 53.3, 26.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 3304, 3073, 1659, 1524, 1157 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{15}H_{21}N_2O$ [M + H]$^+$ 245.1648; found 245.1649.

2-[(Allyl)(benzyl)amino]-*N*,2-diphenylacetamide (5d): General Procedure A was applied by using amide **4g** and PhMgCl (2.0 M in THF, 0.10 mL, 0.20 mmol). Flash chromatography [pentane (+ 1% *i*$PrNH_2$)/EtOAc, 100:0 → 88:12] of the residue gave **5d** (24.9 mg, 70%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, 1 H), 7.68–7.06 (m, 15 H), 5.92 (m, 1 H), 5.31–5.23 (m, 2 H), 4.58 (s, 1 H), 3.94 (d, J = 16.0 Hz, 1 H), 3.37 (m, 2 H), 2.90 (dd, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 169.8, 138.2, 137.8, 134.5, 133.7, 130.3, 129.1, 128.8, 128.6, 128.4, 128.1, 127.5, 124.1, 119.3, 118.9, 69.4, 54.8, 53.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 3312, 3028, 1682, 1516, 1443 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{24}H_{25}N_2O$ [M + H]$^+$ 357.1961; found 357.1963.

2-[(Allyl)(benzyl)amino]-2-(4-fluorophenyl)-*N*-methylacetamide (5e): General Procedure A was applied by using LDA (1.5 equiv., 1.40 M, 107 µL, 0.15 mmol) and 4-FC_6H_4MgBr (1.0 M in THF, 0.20 mL, 0.20 mmol). Flash chromatography [pentane (+ 1% *i*$PrNH_2$)/EtOAc, 95:5 → 60:40] of the residue gave **5e** as a colourless oil (24.1 mg, 77%). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.12 (m, 8 H), 6.95 (m, 2 H), 5.74 (m, 1 H), 5.10 (m, 2 H), 4.32 (s, 1 H), 3.72 (d, J = 14.0 Hz, 1 H), 3.20 (d, J = 14.0 Hz, 1 H), 3.15 (m, 1 H), 2.78 (d, J = 4.8 Hz, 3 H), 2.73 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0, 163.3, 161.3, 138.3, 134.7, 131.5, 131.5, 130.3, 130.3, 128.5, 128.4, 127.3, 118.5, 115.1, 114.9, 67.9, 54.5, 53.2, 26.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 3309, 1660, 1508, 1224 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{19}H_{22}FN_2O$ [M + H]$^+$ 313.1711; found 313.1711.

2-[(Allyl)(benzyl)amino]-2-(4-methoxyphenyl)-*N*-methylacetamide (5f): General Procedure A was applied by using 4-$MeOC_6H_4MgBr$ (1.0 M in THF, 0.20 mL, 0.20 mmol). Flash chromatography [pentane (+ 1% *i*$PrNH_2$)/EtOAc, 95:5 → 60:40] of the residue gave **5f** (29.8 mg, 92%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.10 (m, 8 H), 6.81 (m, 2 H), 5.76 (m, 1 H), 5.10 (m, 2 H), 4.29 (s, 1 H), 3.72 (m, 4 H), 3.23 (d, J = 14.0 Hz, 1 H), 3.15 (m, 1 H), 2.79 (d, J = 4.1 Hz, 3 H), 2.76 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 159.1, 138.6, 134.8, 130.9, 128.47, 128.42, 127.1, 126.8, 118.3, 113.6, 68.3, 55.1, 54.5, 53.1, 26.0 ppm.

IR (film): $\tilde{\nu}_{max}$ = 3309, 2934, 1659, 1511, 1248 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{20}H_{25}N_2O_2$ [M + H]$^+$ 325.1911; found 325.1911.

2-[(Allyl)(benzyl)amino]-*N*-methyl-2-(thiophen-2-yl)acetamide (5h): General Procedure A was applied by using LDA (1.5 equiv., 1.40 M, 107 µL, 0.15 mmol) and (2-thiophenyl)MgBr (1.0 M in THF, 0.20 mL, 0.20 mmol). Flash chromatography [pentane (+ 1% *i*PrNH$_2$)/EtOAc, 95:5 → 65:35] of the residue gave **5h** (27.3 mg, 91%) as a colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.37–7.25 (m, 6 H), 7.16 (br., 1 H), 7.02 (m, 1 H), 6.98 (m, 1 H), 5.86 (m, 1 H), 5.23 (m, 2 H), 4.71 (s, 1 H), 3.83 (d, *J* = 13.8 Hz, 1 H), 3.39 (d, *J* = 13.8 Hz, 1 H), 3.25 (m, 1 H), 2.93 (m, 1 H), 2.87 (d, *J* = 5.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 171.1, 138.4, 136.4,135.0, 128.6, 128.5, 128.4, 127.3, 126.3, 125.6, 118.4, 63.3, 54.6, 53.5, 26.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 3307, 1661, 1522, 1409 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{17}H_{21}N_2OS$ [M + H]$^+$ 301.1369; found 301.1366.

2-[(Allyl)(benzyl)amino]-*N*-methyl-2-(pyridin-3-yl)acetamide (5i): General Procedure B was applied by using (3-pyridinyl)MgBr·LiCl, which was freshly prepared from 3-bromopyridine (19.3 µL, 0.20 mmol) and *i*PrMgCl·LiCl (1.0 M in THF, 200 µL, 0.20 mmol).[31] Flash chromatography [pentane (+ 1% *i*PrNH$_2$)/EtOAc, 95:5 → 50:50] of the residue gave **5i** (22.7 mg, 77%) as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.48 (m, 1 H), 8.41 (s, 1 H), 7.54 (m, 1 H), 7.33–7.12 (m, 7 H), 5.76 (m, 1 H), 5.15 (m, 2 H), 4.40 (s, 1 H), 3.77 (d, *J* = 13.9 Hz, 1 H), 3.19 (m, 1 H), 3.15 (d, *J* = 13.9 Hz, 1 H), 2.82 (d, *J* = 4.9 Hz, 3 H), 2.69 (m, 1 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 171.2, 151.1, 149.1, 138.0, 137.5, 134.6, 127.5, 123.0, 118.8, 65.9, 54.7, 53.4, 26.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 3293, 2930, 1664, 1524, 1424 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{18}H_{21}N_3O$ [M + H] 296.1757; found 296.1758.

2-[(Allyl)(benzyl)amino]-2-(5-bromopyridin-3-yl)-*N*-methylacetamide (5j): General Procedure B was applied by using [5-Br(3-pyridinyl)]-MgBr·LiCl, which was freshly prepared from 3,5-dibromopyridine (47.4 mg, 0.20 mmol) and *i*PrMgCl·LiCl (1.0 M in THF, 200 µL, 0.20 mmol).[31] Flash chromatography [pentane (+ 1% *i*PrNH$_2$)/EtOAc, 95:5 → 50:50] of the residue gave **5j** (28.4 mg, 76%) as a yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.56 (s, 1 H), 8.32 (s, 1 H), 7.68 (s, 1 H), 7.33–7.19 (m, 6 H), 5.76 (m, 1 H), 5.18 (m, 2 H), 4.38 (s, 1 H), 3.78 (d, *J* = 13.8 Hz, 1 H), 3.20 (m, 1 H), 3.14 (d, *J* = 13.8 Hz, 1 H), 2.83 (d, *J* = 5.3 Hz, 3 H), 2.68 (m, 1 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 170.6, 150.2, 149.2, 140.1, 137.7, 134.5, 131.4, 128.8, 128.4, 127.7, 120.4, 119.1, 65.3, 54.8, 53.5, 26.2 ppm. IR (film): $\tilde{\nu}_{max}$ = 3321, 3065, 2929, 1667, 1523, 1420 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{18}H_{21}BrN_3O$ [M + H]$^+$ 374.0863; found 374.0861.

2-[(Allyl)(benzyl)amino]-*N*-methylpropanamide (5k): General Procedure B was applied by using MeMgBr (3.0 M in THF, 67 µL, 0.20 mmol). Flash chromatography [pentane (+ 1% *i*PrNH$_2$)/EtOAc, 95:5 → 60:40] of the residue gave **5k** (22.3 mg, 96%) as a colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.30–7.15 (m, 6 H), 5.81–5.71 (m, 1 H), 5.20–5.08 (m, 2 H), 3.71 (d, *J* = 13.7 Hz, 1 H), 3.37–3.29 (m, 2 H), 3.09 (m, 1 H), 2.90 (m, 1 H), 2.73 (d, *J* = 5.0 Hz, 3 H), 1.18 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$): δ = 174.5, 138.9, 135.6, 128.6, 128.5, 127.3, 117.8, 58.1, 54.6, 53.2, 26.0, 8.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 2933, 1663, 1522, 1158 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{14}H_{21}N_2O$ [M + H]$^+$ 233.1648; found 233.1646.

2-[(Allyl)(benzyl)amino]-*N*,3-dimethylbutanamide (5l): General Procedure A was applied by using *i*PrMgCl·LiCl (1.0 M in THF, 0.20 mL, 0.20 mmol). Flash chromatography [pentane (+ 1% *i*PrNH$_2$)/EtOAc, 95:5 → 70:30] of the residue gave **5l** (20.6 mg, 79%) as a colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.32–7.13 (m, 5 H), 5.76 (m, 1 H), 5.44 (br., 1 H), 5.09 (m, 2 H), 3.99 (d, *J* = 14.6 Hz, 1 H), 3.44–3.37 (m, 1 H), 3.30 (d, *J* = 14.6 Hz, 1 H), 2.86 (m, 1 H), 2.77 (d, *J* = 4.9 Hz, 3 H), 2.53 (d, *J* = 9.7 Hz, 1 H), 2.14 (m, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.76 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$): δ = 171.9, 140.0, 137.2, 128.3, 128.2, 126.8, 116.8, 70.0, 54.3, 53.3, 27.0, 25.5, 19.9, 19.8 ppm. IR (film): $\tilde{\nu}_{max}$ = 3305, 2933, 1659, 1524, 920 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{16}H_{25}N_2O$ [M + H]$^+$ 261.1961; found 261.1962.

2-[(Allyl)(benzyl)amino]-*N*-methylbut-3-enamide (5m): General Procedure A was applied by using vinylmagnesium bromide (0.7 M in THF, 0.29 mL, 0.20 mmol). Flash chromatography [pentane (+ 1% *i*PrNH$_2$)/EtOAc, 95:5 → 60:40] of the residue gave **5m** (20.3 mg, 83%) as a colourless oil: ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.40–7.25 (m, 5 H), 7.19 (br., 1 H), 5.96–5.80 (m, 2 H), 5.51 (m, 1 H), 5.29–5.19 (m, 3 H), 3.85 (d, *J* = 13.7 Hz, 1 H), 3.74 (d, *J* = 9.3 Hz, 1 H), 3.39 (d, *J* = 13.7 Hz, 1 H), 3.25 (m, 1 H), 2.99 (m, 1 H), 2.86 (d, *J* = 5.0 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 172.6, 138.6, 135.2, 130.6, 128.6, 128.5, 127.3, 122.1, 118.2, 66.8, 54.7, 53.4, 26.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 3073, 2928, 1663, 1524, 1412 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{15}H_{21}N_2O$ [M + H]$^+$ 245.1648; found 233.1649.

(*S*)-2-{(Allyl)[(*S*)-1-phenylethyl]amino}-*N*-methyl-2-phenylacetamide (5o): PhMgCl (2.0 M in THF, 1.20 mL, 2.40 mmol) was added to a solution of dry ZnCl$_2$ (327 mg, 2.40 mmol) in THF (5 mL), and the resultant mixture was stirred at room temperature for 30 min. LDA (1.39 M, 1.52 Ml, 2.10 mmol) was added to a solution of amide **4i** (609 mg, 2.0 mmol) in Et$_2$O (20 mL) at 0 °C, and the resultant yellow solution was stirred for 1 min. The mixture was cooled to –78 °C, and the freshly prepared solution of PhZnCl was added. The reaction was quenched with satd. NH$_4$Cl (5 mL) and brine (10 mL), and the phases were separated. The aqueous layer was extracted twice with Et$_2$O, and the combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure (diastereomeric ratio 87:13, ^{1}H NMR analysis on the crude product). Flash chromatography (hexane/THF, 98:2 → 82:18) of the residue gave **5o** as a diasteromeric mixture (458 mg, 74%). The diastereomers could be separated by flash chromatography (pentane/Et$_2$O, 95:5 → 80:20) to yield pure **5o** as a colourless oil. $[\alpha]_D^{20}$ = +9.2 (*c* = 0.85, CH$_2$Cl$_2$). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.41–7.24 (m, 10 H), 6.94 (br., 1 H), 5.65 (m, 1 H), 5.03 (m, 2 H), 4.47 (s, 1 H), 4.12 (q, *J* = 6.9 Hz, 1 H), 3.31 (m, 1 H), 3.15 (m, 1 H), 2.75 (d, *J* = 5.0 Hz, 3 H), 1.17 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 172.9, 143.6, 137.2, 129.6, 128.4, 128.4, 127.8, 127.5, 127.0, 116.8, 69.1, 57.5, 51.1, 25.8, 15.3 ppm. IR (film): $\tilde{\nu}_{max}$ = 2970, 2931, 1658, 1523, 1452 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{20}H_{25}N_2O$ [M + H]$^+$ 309.1961; found 309.1958.

(*S*)-2-{(Allyl)[(*S*)-1-phenylethyl]amino}-*N*-methyl-*N*-nitroso-2-phenylacetamide (11): Sodium nitrite (263 mg, 3.8 mmol) was added to a solution of amide **5o** in CH$_2$Cl$_2$ (6 mL), Ac$_2$O (2 mL) and acetic acid (0.2 mL), and the mixture was stirred at room temp. for 6 h. The mixture was diluted with toluene (20 mL), filtered and concentrated under reduced pressure to give crude nitroso-amide **11** as a deep yellow oil, which was directly used in the next step.

Methyl (*S*)-2-{(Allyl)[(*S*)-1-phenylethyl]amino}-2-phenylacetate (12): Satd. NaHCO$_3$ (5 mL) was added to a solution of the crude nitroso-amide **11** in MeOH (10 mL). The mixture was slowly heated to reflux, diluted with brine and extracted three times with Et$_2$O. The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure. Flash chromatography (pentane/Et$_2$O, 98:2 → 80:20) gave **12** as a colourless oil. $[\alpha]_D^{20}$ = +(*c* = 0.85, CH$_2$Cl$_2$). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.36–7.14 (m, 10 H), 5.63 (m, 1 H), 4.98 (m, 1 H), 4.85 (m, 1 H), 4.57 (s, 1 H), 4.01 (q, J = 6.9 Hz, 1 H), 3.50 (s, 3 H), 3.31 (m, 2 H), 1.29 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 143.9, 139.1, 137.9, 128.6, 128.3, 128.2, 127.7, 127.6, 126.9, 115.0, 66.3, 59.1, 56.2, 50.5, 19.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 3029, 2975, 1738, 1453, 1157 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{20}H_{24}NO_2$ [M + H]$^+$ 310,1802; found 310,1802.

Methyl (*S*)-2-[(*S*)-1-Phenylethylamino]-2-phenylacetate (13): A solution of ester **12** (60.0 mg, 0.194 mmol), $Pd(PPh_3)_4$ (11.2 mg, 0.010 mmol) and *N*,*N*-dimethylbarbituric acid (151.4 mg, 0.97 mmol) in CH_2Cl_2 (1 mL) was refluxed for 3 h. The mixture was diluted with Et_2O, filtered and concentrated under reduced pressure. Flash chromatography [heptane (+ 1% *i*$PrNH_2$)/Et_2O, 97:3 → 80:20) of the residue gave **13** as a colourless oil (48.7 mg, 93%): $[\alpha]_D^{20}$ = +26.3 (c = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.17 (m, 10 H), 4.15 (s, 1 H), 3.73 (q, J = 6.5 Hz, 1 H), 3.64 (s, 1 H), 2.25 (br., 1 H), 1.31 (d, J = 6.5 Hz) ppm. ^{13}C NMR (125 MHz, CDCl3): δ = 174.2, 144.7, 138.4,128.7, 128.5, 127.9, 127.2, 127.1, 126.9, 62.9, 56.5, 52.1, 24.6 ppm. IR (film): $\tilde{\nu}_{max}$ = 2954, 1736, 1688, 1453, 1170 cm^{-1}. HRMS (ESI$^+$): calcd. for $C_{20}H_{25}N_2O$ [M + H]$^+$ 270,1489; found 270,1487.

Methyl (*S*)-2-Amino-2-phenylacetate Hydrochloride (14): A catalytic amount of $Pd(OH)_2$ (20% on C) was added to a solution of **13** (5.7 mg, 0.021 mmol) in MeOH (5 mL) and concd. HCl (0.25 mL). The resultant mixture was stirred under H_2 (1 atm) for 15 h, filtered through a pad of Celite and concentrated under reduced pressure to give **14** as a white solid (4.3 mg, 100%) with spectroscopic data characterizations in accordance with those previously reported in the literature.[27]

Supporting Information (see footnote on the first page of this article): General experimental procedure, preparation and analytical data for compounds **4a**,**c**,**d**,**f**–**h** and **15** and NMR spectra for all new compounds.

Acknowledgments

This work was financially supported by the Swedish Research Council and the Knut and Alice Wallenberg Foundation.

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Received: July 10, 2008
Published Online: October 13, 2008