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Synthesis of α-Amino Amides via *N*,*O*-Acetals Derived from Weinreb Amides

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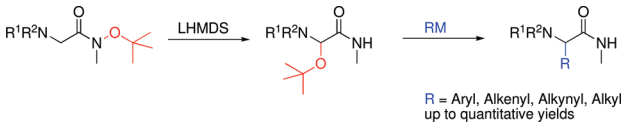

An easy and straightforward synthesis of α-amino amides via a base-mediated rearrangement of modified Weinreb amides into *N*,*O*-acetals is presented. Subsequent arylation, alkylation, alkenylation, or alkynylation of this intermediate affords the corresponding α-amino amides in excellent yields. Furthermore, a more generalized protocol for the α-arylation of Weinreb amides lacking an α-amino moiety is also discussed.

Introduction

The synthesis of nonproteinogenic and unnatural α-amino acids has attracted much attention as these compounds both provide access to new drug candidates and act as valuable biological probes.[1] As a result, the development of new methods for their synthesis has been a field of active research for many years and several versatile and excellent techniques have been developed.[2] However, for the synthesis of several important subsets of amino acids, standard methods, such as phase-transfer catalyzed alkylation of glycine derivatives,[2c−e] are not generally applicable. For example, the synthesis of arylglycines,[3] vinylglycines,[4] and alkynylglycines[5] is still a challenging task in organic synthesis, and the development of a general, environmentally friendly and economically reasonable protocol for their preparation remains elusive. Arylglycines, especially, are of broad interest in organic synthesis due to their prevalence in biologically significant targets. This includes commercial blockbusters like the antiplatelet agent clopidogrel (**6**)[6] as well as several drugs from the WHO list of essential medicines, such as the antibiotics amoxicillin and vancomycin.[7]

Recently, we developed a new method for the α-arylation of glycine equivalent **1** with Grignard reagents, affording α-amino amides **2** in high yields, which can easily be converted into the corresponding free amino acid (Scheme 1).[8,9]

During our studies on this reaction, we observed a remarkable enhancement of yield when the base was added at 0 °C instead of −78 °C for some substrates. Reinvestigation of the reaction revealed that this effect is caused by the intermediate formation of glyoxylic *N*,*O*-acetals. These reactive

(1) For examples, see: (a) Hicks, R. P.; Bhonsle, J. B.; Venugopal, D.; Koser, B. W.; Magill, A. J. *J. Med. Chem.* **2007**, *50*, 3026–3036. (b) Wang, J. Y.; Xie, J. M.; Schultz, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 8738–8739. (c) Jain, R.; Chawrai, S. *Mini-Rev. Med. Chem.* **2005**, *5*, 469–477.

(2) For recent reviews on the synthesis of α-amino acids, see: (a) Perdih, A.; Dolenc, M. S. *Curr. Org. Chem.* **2007**, *11*, 801–832. (b) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517. (d) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525. (e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028.

(3) For leading references on the synthesis of arylglycines, see: (a) Lee, E. C.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 12066–12067. (b) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 6360–6362. (c) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889–917.

(4) For a recent review, see: (a) Berkowitz, D. B.; Charette, B. D.; Karukurichi, K. R.; McFadden, J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 869-882. For recent examples on the synthesis of vinylglycines, see: (b) Armstrong, A.; Challinor, L.; Moir, J. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5369–5372. (c) Wolfer, J.; Bekele, T.; Abraham, C. J.; Dogo-Isonagie, C.; Lectka, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 7398–7400. (d) Alexander, P. A.; Marsden, S. P.; Subtil, D. M. M.; Reader, J. C. *Org. Lett.* **2005**, *7*, 5433–5436.

(5) For leading references on the synthesis of alkynylglycines, see: (a) Shao, Z. H.; Chan, A. S. C. *Synthesis* **2008**, 2868–2870. (b) Ji, J. X.; Au-Yeung, T. L.; Wu, J.; Yip, C. W.; Chan, A. S. C. *Adv. Synth Catal.* **2004**, *346*, 42–44. (c) Meffre, P.; LeGoffic, F. *Amino Acids* **1996**, *11*, 313–328.

(6) (a) Coukell, A. J.; Markham, A. *Drugs* **1997**, *54*, 745−750. For a recent synthesis of clopidogrel, see: (b) Wang, L. X.; Shen, J. F.; Tang, Y.; Chen, Y.; Wang, W.; Cai, Z. G.; Du, Z. J. *Org. Process Res. Dev.* **2007**, *11*, 487–489.

(7) *WHO model list of essential medicines*, 15th list; World Health Organization: Geneva, Switzerland, 2007. http://www.who.int/medicines/publications/EML15.pdf

(8) (a) Hirner, S.; Kirchner, D. K.; Somfai, P. *Eur. J. Org. Chem.* **2008**, 5583–5589. (b) Hirner, S.; Panknin, O.; Edefuhr, M.; Somfai, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1907–1909.

(9) For a recent review on Weinreb amides, see: Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707−3738.

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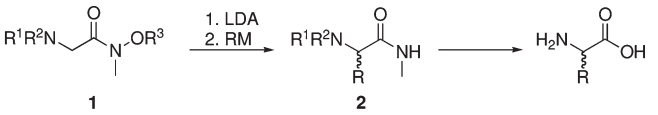
SCHEME 1. Synthesis of Arylglycines from Weinreb Amides



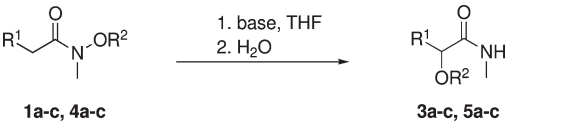
compounds represent valuable glycine cation equivalents and have previously been used for the synthesis of α-amino esters.[10,11] Herein, we describe an improved protocol for the synthesis of α-amino amides **2**, which is based on the quantitative generation of *N*,*O*-acetals from **1**. Moreover, we were intrigued to investigate if an analogous reaction could be developed for substrates lacking an α-amino moiety, and these initial results will be discussed.

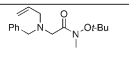
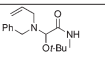
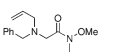
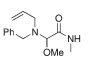
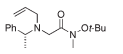
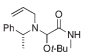
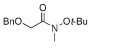
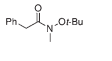
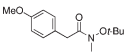
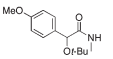
Results and Discussion

Our investigations commenced with quenching experiments, in which the reaction of Weinreb amide **1a** with LDA was terminated by the addition of water. When LDA was added at −78 °C, followed by quenching at the same temperature, only starting material was recovered (Table 1, entry 1). When the reaction was carried out at 0 °C and quenched after 60 min, the starting material was completely consumed, and *N*,*O*-acetal **3a** was formed as the main product (entry 2), presumably formed via a base-promoted N → C migration of the *tert*-butoxy group.[12,13] However, all attempts to purify **3a** by standard methods failed, probably due to the sensitive nature of the *N*,*O*-acetal moiety. To circumvent purification and to reduce the formation of byproducts, a significantly milder base was employed. Indeed, with LHMDS full conversion was achieved after only 30 min, and quantitative yields of **3a** could be isolated after simple filtration (entry 3). Also Weinreb amide **1b** (entry 4) and chiral substrate **1c** (entry 5) afforded quantitative yields of the corresponding *N*,*O*-acetals. Notably, for the more bulky substrate **1c** a prolonged reaction time (2 h) was necessary in order to achieve full conversion, and the product was obtained as a mixture of diastereomers (dr = 1:1.6). The same kind of rearrangement took place when the amino moiety was replaced by an α-hydroxy substituent. In this case, the corresponding *O*,*O*-acetal **5a** was formed in excellent yield (entry 6).

On the basis of these results, we were intrigued to determine if substrates lacking an α-heteroatom would show similar rearrangement upon treatment with a base, and substrate **4b** with an α-phenyl substituent was tested under

TABLE 1. Base-Promoted Rearrangement of Weinreb Amides[a]



entry	substrate		base	T (°C)	*t* (min)	product		yield (%)[b,c]
1		**1a**	LDA	-78	120		**3a**	0[d]
2			LDA	0	60			75[e]
3			LHMDS	0	30			quant
4		**1b**	LHMDS	0	30		**3b**	99
5		**1c**	LHMDS	0	120		**3c**	99[f]
6		**4a**	LHMDS	0	30		**5a**	92
7		**4b**	LHMDS	0	120		**5b**	0[d]
8			LDA	0	120			0[d]
9		**4c**	LHMDS	0	360		**5c**	9
10			LHMDS	25	360			14

[a]Reaction conditions: **1** (0.20 mmol), base (0.24 mmol), THF (2 mL). [b]Isolated yield. [c]"Quant" means: ^{1}H NMR purity of the crude product >95%; mass balance >99%. [d]Starting material recovered. [e]Yield determined by ^{1}H NMR of the crude product. [f]dr = 1:1.6, determined by ^{1}H NMR of the crude product.

the same reaction conditions. However, rearranged product **5b** was not obtained when employing either LHMDS (entry 7) or LDA (entry 8), and only starting material could be recovered. To increase the reactivity, we next exchanged the phenyl substituent for a 4-methoxyphenyl group, envisioning that any positive charge formed during the elimination of *t*-BuO$^-$ would be stabilized by a strong electron-donating substituent. Indeed, stirring Weinreb amide **4c** with LHMDS for 6 h at 0 °C afforded the desired product **5c**, albeit in poor yield along with unreacted starting material (entry 10). Increasing the reaction temperature resulted in full conversion, but the yield was only slightly improved, and many unidentified byproducts were formed (entry 11).

Synthesis of α-Amino Amides from *N*,*O*-Acetal 3. With an easy and high-yielding procedure for the synthesis of *N*,*O*-acetals in hand, their potential as versatile glycine cation equivalents was studied next. Due to the delicate nature of these substrates, it was planned to generate them in situ prior to the addition of a nucleophile. Thus, when **1a** was treated with LHMDS for 30 min at 0 °C, followed by addition of PhMgCl at −78 °C, complete conversion was achieved and amide **2a** could be isolated in 96% yield (Table 2, entry 1).

Somewhat surprisingly, when Weinreb amide **1b** was used instead, the desired product was only isolated in moderate yields (entry 2) together with unreacted *N*,*O*-acetal **3b**. The bis(allyl)-protected amide **1d** gave excellent yields whereas in the reaction of the bis(benzyl)-protected substrate **1e** some byproducts were formed (entries 3 and 4, respectively). Since the possibility to use orthogonal nitrogen protecting

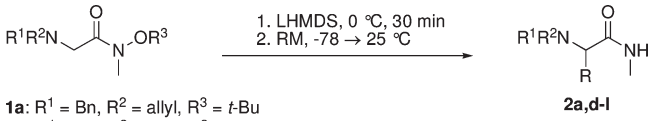
(10) (a) Sakai, N.; Asano, J.; Shimano, Y.; Onakahara, T. *Tetrahedron* **2008**, *64*, 9208–9215. (b) Bourhis, M.; Bosc, J. J.; Golse, R. *J. Organomet. Chem.* **1983**, *256*, 193–201. (c) Gloede, J.; Freiberg, J.; Bürger, W.; Ollmann, G.; Gross, H. *Arch. Pharm.* **1969**, *302*, 354. (d) Gross, H.; Gloede, J.; Freiberg, J. *Liebigs Ann. Chem.* **1967**, *702*, 68.

(11) For a review on glyoxylates as building blocks for the synthesis of α-amino acids, see: Meester, W. J. N.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. *Eur. J. Org. Chem.* **2003**, 2519−2529.

(12) The same type of rearrangement has been reported previously, see: Alberola, A.; Ortega, A. G.; Sadaba, M. L.; Sanudo, C. *Tetrahedron* **1999**, *55*, 6555−6566.

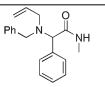
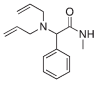
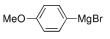
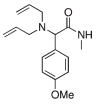
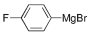
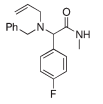
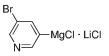
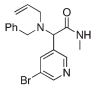
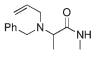
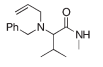
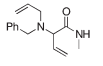
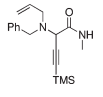
(13) For a related rearrangement of *N*-alkyl-*O*-acyl hydroxamic acids, see: (a) Clark, A. J.; Al-Faiyz, Y. S. S.; Patel, D.; Broadhurst, M. J. *Tetrahedron Lett.* **2001**, *42*, 2007–2009. (b) Clark, A. J.; Al-Faiyz, Y. S. S.; Broadhurst, M. J.; Patel, D.; Peacock, J. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, *7*, 1117–1127.

TABLE 2. Synthesis of α-Amino Amides 2[a]



1a: R^1 = Bn, R^2 = allyl, R^3 = *t*-Bu
1b: R^1 = Bn, R^2 = allyl, R^3 = Me
1d: R^1 = R^2 = allyl, R^3 = *t*-Bu
1e: R^1 = R^2 = Bn, R^3 = *t*-Bu

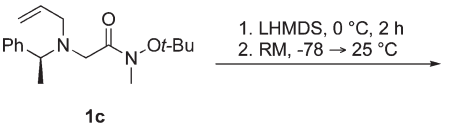
2a,d-l

entry	1	RM	product		yield[b,c]
1	**a**			**2a**	96
2	**b**				51
3	**d**			**2d**	97
4	**e**			**2e**	82
5	**d**			**2f**	95[d]
6	**a**			**2g**	quant[e]
7	**a**			**2h**	85
8	**a**			**2i**	96
9	**a**			**2j**	quant
10	**a**			**2k**	quant
11	**a**			**2l**	quant

[a]Reaction conditions: **1** (0.10 mmol), LHMDS (0.12 mmol), RM (0.20 mmol), THF (2 mL). [b]Isolated yields. [c]"Quant" means: ^{1}H NMR purity of the crude product >95%; mass balance >99%. [d]The reaction was performed on a 0.20 mmol scale. [e]The reaction was performed on a 2.5 mmol scale.

groups enhances the synthetic utility of this transformation significantly, we focused our efforts on substrate **1a**. Screening of different Grignard reagents showed that electron-rich (entry 5), electron-poor (entry 6), and functionalized heteroaromatic arylgrignards (entry 7) gave excellent yields under the selected reaction conditions. In addition, it was found that the use of alkyl- (entries 8 and 9), alkenyl- (entry 10), and alkynyl- (entry 11) Grignard reagents also afforded the corresponding α-amino amides in quantitative yields. For several products no purification by column chromatography was needed and quantitative amounts of the analytically pure material could be obtained by simple filtration through silica (entries 6 and 9−11).

TABLE 3. Asymmetric Synthesis of α-Amino Amides[a]



1c **2m-r**

entry	RM	product		yield (%)[b,c]	*dr*[d]
1			**2m**	91	2:1
2				93	8:1
3			**2n**	95	6:1
4			**2o**	90	4:1
5			**2p**	67	2:1
6			**2q**	quant	2:1
7			**2r**	84[e]	7:1

[a]Reaction conditions: **1c** (0.20 mmol), LHMDS (0.24 mmol), RM (0.3 mmol), THF (2 mL). [b]Combined isolated yield of diastereomers. [c]"Quant" means: ^{1}H NMR purity of the crude product >95%; mass balance >99%. [d]dr determined by ^{1}H NMR of the crude product. [e]The reaction was performed on a 8.15 mmol scale.

Diastereoselective Synthesis. With these results at hand, we decided to investigate the stereoselective synthesis of α-substituted glycine derivatives. Toward this end, subjecting **1c** to LHMDS for 2 h at 0 °C, followed by addition of PhMgCl at −78 °C, afforded compound **2m** in excellent yield, but in poor dr (Table 3, entry 1).

However, when PhZnCl was used instead, the selectivity was significantly enhanced, and amide **2m** was obtained in 93% yield as a 8:1 mixture of diastereomers (entry 2).[14] It should be noted that the dr obtained in these reactions does not correspond to the one obtained for the formation of **3c** (Table 1, entry 5), indicating that an iminium ion is formed upon the addition of the nucleophile. Similar yields and selectivities were also obtained for electron-rich (entry 3) and electron-poor arylzinc reagents (entry 4), whereas only moderate selectivity was obtained with alkenyl- and alkynylzinc reagents (entries 5 and 6). By using (2-ClC_6H_4)ZnCl as a nucleophile, amide **2r** could be synthesized in good yield and selectivity on gram scale (entry 7). On the basis of this intermediate, a total synthesis of clopidogrel (**6**) is currently under investigation and will be presented in due course (Figure 1).

α-Arylation of Weinreb Amides. As an extension of this methodology, we envisioned that Weinreb amides without an α-amino group would likewise represent suitable substrates for the α-arylation with Grignard reagents. The products formed in such a reaction, α-aryl carboxylic acid deri-

(14) All products were isolated as diasteromeric mixtures. The absolute configuration of **2m** was assigned previously (ref 8), and all other products were assigned by analogy to that compound.

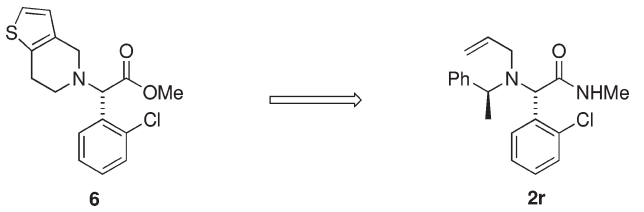
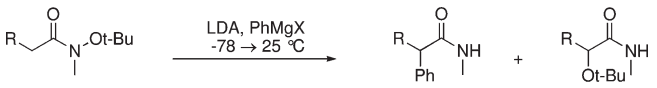


FIGURE 1. Intended use of amide **2p** for the synthesis of clopidogrel (**6**).

TABLE 4. α-Arylation of Weinreb Amides[a]



4 7 5

entry	4	R	solvent	PhMgX (equiv)	7:5[b] ratio	yield of 7,[c] %
1	**c**	4-MeOC$_6$H$_4$	THF	PhMgCl (2)	1:1	42
2	**c**	4-MeOC$_6$H$_4$	tol	PhMgBr (7.5)	4:1	67
3	**b**	Ph	tol	PhMgBr (7.5)	n.d.	40
4	**d**	Me	tol	PhMgBr (7.5)	n.d.	56
5	**a**	BnO	tol	PhMgBr (7.5)	1:2	34
6	**e**	PhS	tol	PhMgBr (7.5)	1:3	29

[a]Reaction conditions: **4** (0.20 mmol), LDA (0.24 mmol), solvent (2 mL). [b]Ratio determined by ^{1}H NMR of the crude product. [c]Isolated yield.

vatives, represent highly valuable building blocks in organic synthesis and are prevalent in important natural products and drugs, such as atropine, naproxen, and ibuprofen.

We started our investigations with amide **4c**, speculating that the electron-rich 4-methoxyphenyl substituent not only activates the substrate to migration of the *N*-alkoxy group, but also would facilitate α-arylation. To avoid the irreversible formation of **5c** prior to the addition of the Grignard reagent, the reaction was performed in analogy to our previously reported arylation method, using a strong base at low temperatures (Scheme 1). Thus, when **4c** was treated with LDA and PhMgCl at −78 °C and warmed to room temperature, full conversion was achieved within 30 min, and the desired product **7c** was isolated in 42% yield along with equimolar amounts of the migration product **5c**. Notably, the same reaction gives only traces of **5c** when no Grignard reagent is added. This indicates that PhMgCl not only acts as a nucleophile but also strongly enhances the reactivity of the Weinreb amide. The exact mechanism for this surprising activation has not been clarified yet and is currently under investigation. To suppress the undesired formation of **5c**, the reaction conditions were optimized: switching from THF to toluene and using an excess of concentrated PhMgBr (3 M in Et_2O) increased both the yield and selectivity, and **7c** could be isolated in 67% yield (Table 4, entry 2). Using these optimized conditions, a selection of Weinreb amides was next screened. Gratifyingly, both substrates bearing nonactivated aryl (entry 3) and alkyl (entry 4) groups gave the desired arylated product in moderate yield and without detectable migration of the *tert*-butoxy group. However, with α-heteroatom-substituted Weinreb amides **5d** and **5e**, only minor amounts of the arylated amides were formed, the main product being the corresponding *O*,*O*- and *S*,*O*-acetal, respectively (entries 5 and 6).

Conclusions

In summary, we have demonstrated that Weinreb amides easily can undergo a base-promoted rearrangement, effecting migration of the *N*-alkoxy group to the α-carbon. On the basis of this reaction we have developed a simple and high-yielding synthesis of α-amino amides from readily available starting materials. As an extension of this procedure, we have also shown that modified Weinreb amides without an α-amino group can undergo α-arylation with Grignard reagents.

Experimental Section

General Procedure A: Rearrangement of Weinreb Amides to *N*, *O*-Acetals. To a solution of Weinreb amide **1** (0.20 mmol) in 2 mL of dry THF was added LHMDS (1.0 M in THF, 0.24 mL, 0.24 mmol) at 0 °C and the resulting mixture was stirred for the indicated reaction time (Table 1). The reaction was quenched by addition of one drop of water, diluted with Et_2O (10 mL), and filtered over cotton. The solvent was removed under reduced pressure to give **3** as a colorless oil, which rapidly decomposes in the presence of moisture.

2-(*N*-Allyl-*N*-benzylamino)-2-*tert*-butoxy-*N*-methylacetamide (3a). Prepared according the general procedure A with Weinreb amide **1a** (58.1 mg, 0.20 mmol). Yield 58.0 mg (99%), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−6.92 (m, 6H), 6.54 (br s, 1H), 5.64 (m, 1H), 4.91 (m, 2H), 4.39 (s, 1H), 3.59 (s, 2H), 3.06 (m, 2H), 2.61 (d, J = 5.0 Hz, 3H), 0.97 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 139.5, 136.6, 129.0, 128.1, 126.7, 117.2, 83.5, 75.0, 53.2, 52.1, 28.6, 25.3 ppm.

2-(*N*-Allyl-*N*-benzylamino)-2-methoxy-*N*-methylacetamide (3b). Prepared according the general procedure A with Weinreb amide **1b** (49.7 mg, 0.20 mmol). Yield 49.3 mg (99%), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.14 (m, 5H), 6.57 (br s, 1H), 5.79 (m, 1H), 5.11 (m, 2H), 4.22 (s, 1H), 3.77 (m, 2H), 3.31 (s, 3H), 3.24 (m, 2H), 2.76 (d, J = 5.0 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 139.2, 136.1, 128.9, 128.1, 126.9, 117.5, 90.1, 55.7, 53.3, 52.3, 25.3 ppm.

2-(*N*-Allyl-*N*-((*S*)-1-phenylethyl)amino)-2-*tert*-butoxy-*N*-methylacetamide (3c). Prepared according the general procedure A with Weinreb amide **1c** (60.1 mg, 0.20 mmol). Yield 61.5 mg (quant), colorless oil. ^{1}H NMR (1.6:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 500 MHz, $CDCl_3$) δ 7.46−7.12 (m, 5H), 6.82 (br, 1H), 5.80 (m, 1H), 5.24−4.92 (m, 2H), 4.71* (s, 1H), 4.66 (s, 1H), 4.18 (m, 1H), 3.43* (m, 1H), 3.25 (m, 1H), 3.20−3.08 (m, 1H), 2.80* (d, J = 5.0 Hz, 3H), 2.78 (d, J = 5.0 Hz, 3H), 1.45 (d, J = 6.7 Hz, 3H), 1.39* (d, J = 6.8 Hz, 3H), 1.18 (s, 9H), 1.17* (s, 4H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7*, 172.2, 145.4*, 144.5, 137.6, 137.7*, 128.0*, 127.9, 127.7, 127.6*, 126.4, 116.3, 116.0*, 84.1, 82.5*, 74.*, 74.3, 57.3*, 56.0, 49.1*, 47.7, 28.6*, 28.6, 25.6, 25.5*, 19.8*, 18.2 ppm.

2-*tert*-Butoxy-2-(benzyloxy)-*N*-methylacetamide (5a). To a cooled (0 °C) solution of Weinreb amide **4a** (0.20 mmol, 50.3 mg) in 2 mL of dry THF was added LHMDS (1.0 M in THF, 0.24 mmol, 0.24 mL) and the resulting mixture was stirred for 30 min at 0 °C. The reaction was quenched by addition of water (2 mL), the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried (K_2CO_3) and concentrated under reduced pressure to give acetal **5a** (46.3 mg, 92%) as a white solid: mp 98−100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.26 (m, 5H), 6.65 (br, 1H), 5.13 (s, 1H), 4.63 (d, J = 11.1 Hz, 1H), 4.52 (d, J = 11.1 Hz, 1H), 2.86 (d, J = 4.9 Hz, 3H), 1.30 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ

169.4, 137.5, 128.2, 127.9, 127.5, 93.7, 76.2, 66.9, 28.5, 25.6 ppm; IR (film) ν_{max} 3375, 2981, 1670, 1527, 1041 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_{22}NO_3$ $[M + H]^+$ m/z 252.15942, found 252.15958.

2-*tert*-Butoxy-2-(4-methoxyphenyl)-*N*-methylacetamide (5c). To a cooled (0 °C) solution of Weinreb amide **4c** (0.2 mmol, 50.3 mg) in 2 mL of dry THF was added LHMDS (1.0 M in THF, 0.24 mmol, 0.24 mL) and the resulting mixture was stirred for 6 h at room temperature. The reaction was quenched by addition of water (10 mL) and EtOAc (10 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane, EtOAc 5→60%) to give **5c** (7.2 mg) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 2H), 6.85 (m, 2H), 6.81 (br s, 1H), 4.89 (s, 1H), 3.78 (s, 3H), 2.81 (d, J = 5.0 Hz, 3H), 1.22 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 159.1, 132.3, 127.5, 113.6, 76.0, 74.2, 55.2, 28.2, 25.8 ppm; IR (film) ν_{max} 3352, 2970, 1666, 1512, 1173 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_{22}NO_3$ $[M + H]^+$ m/z 252.15942, found 252.15932.

General Procedure B: Synthesis of α-Amino Amides with Grignard Reagents. To a solution of Weinreb amide **1** (0.10 mmol) in 2 mL of dry THF was added LHMDS (1.0 M in THF, 0.12 mL, 0.12 mmol) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C before it was cooled to −78 °C and the Grignard reagent (0.20 mmol) was added. The reaction was allowed to reach room temperature, quenched by the addition of water (0.10 mL), diluted with Et_2O (10 mL), and filtered. The solvent was removed under reduced pressure to give the crude product.

2-(Diallylamino)-2-(4-methoxyphenyl)-*N*-methylacetamide (2f). Prepared according the general procedure B with Weinreb amide **1d** (48.0 mg, 0.20 mmol), LHMDS (1.0 M in THF, 0.24 mL, 0.24 mmol), and 4-$MeOC_6H_4MgBr$ (0.5 M in THF, 0.40 mmol, 0.80 mL). Flash chromatography (pentane + 1% i-$PrNH_2$, EtOAc 5→40%) of the crude product gave **2f** as a colorless oil (51.9 mg, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.22 (m, 1H), 7.18 (m, 2H), 6.87 (m, 2H), 5.80 (m, 2H), 5.23−5.12 (m, 4H), 4.35 (s, 1H), 3.80 (s, 3H), 3.22 (m, 2H), 2.87 (d, J = 4.8 Hz, 3H), 2.85−2.80 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 159.0, 134.8, 130.6, 127.1, 117.9, 113.5, 68.8, 55.0, 53.1, 25.8 ppm; IR (film) ν_{max} 3309, 2935, 1658, 1510, 1250 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{23}N_2O_2$ $[M + H]^+$ m/z 275.17540, found 275.17523.

2-(*N*-Allyl-*N*-benzylamino)-*N*-methyl-4-(trimethylsilyl)but-3-ynamide (2l). Prepared according the general procedure B with Weinreb amide **1a** (29.0 mg, 0.10 mmol). The Grignard reagent was freshly prepared from ethynyltrimethylsilane (19.6 mg, 0.20 mmol) and i-PrMgCl·LiCl (1.0 M in THF, 0.20 mL, 0.20 mmol).[15] Yield 31.2 mg (quant), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5H), 6.90 (br, 1H), 5.79 (m, 1H), 5.24 (m, 1H), 5.15 (m, 1H), 4.12 (s, 1H), 3.77 (d, J = 13.5 Hz, 1H), 3.36 (d, J = 13.5 Hz, 1H), 3.16 (m, 1H), 2.96 (m, 1H), 2.73 (d, J = 5.0 Hz, 3H), 0.18 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 138.0, 135.0, 128.9, 128.5, 127.5, 118.4, 97.4, 92.7, 58.2, 55.7, 54.7, 26.2, 0.1 ppm; IR (film) ν_{max} 3552, 2958, 2168, 1974, 1520 cm^{-1}; HRMS (ESI+) calcd for $C_{18}H_{27}N_2OSi$ $[M + H]^+$ m/z 315.18872, found 315.18854.

General Procedure C: Stereoselective Synthesis of α-Amino Amides with Zinc Reagents. To a solution of Weinreb amide **1c** (60.9 mg, 0.20 mmol) in 2 mL of THF was added LHMDS (1.0 M in THF, 0.24 mL, 0.24 mmol) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C before it was cooled to −78 °C and the indicated zinc reagent (0.30 mmol) was added. The reaction was allowed to reach room temperature, quenched by the addition of water (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure to give the crude product.

Preparation of the zinc reagent: To the indicated Grignard reagent was added a solution of $ZnCl_2$ in THF at 0 °C, and the resulting mixture was stirred for 30 min at room temperature.

2-(*N*-Allyl-*N*-((*S*)-1-phenylethyl)amino)-2-(4-methoxyphenyl)-*N*-methylacetamide (2n). Prepared according the general procedure C. The zinc reagent was freshly prepared from 4-MeO-C_6H_4MgBr (0.5 M, 0.6 mL, 0.30 mmol) and $ZnCl_2$ (1.0 M in THF, 0.30 mL, 0.30 mmol). Flash chromatography (pentane + 1% i-$PrNH_2$, EtOAc 5→40%) of the crude product gave **2n** (64.3 mg, 95%) as a colorless oil: ^{1}H NMR (6:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 500 MHz, $CDCl_3$) δ 7.40−7.20 (m, 7H), 6.97 (m, 1H), 6.86 (m, 2H), 6.79* (m, 2H), 5.71−5.56 (m, 1H), 5.10−4.96 (m, 2H), 4.41 (s, 1H), 4.10 (q, J = 6.9 Hz, 1H), 4.03* (q, J = 6.9 Hz, 1H), 3.80 (s, 3H), 3.78* (s, 3H), 3.29 (m, 1H), 3.12 (m, 1H), 3.03* (m, 1H), 2.88* (d, J = 4.9 Hz, 3H), 2.75 (d, J = 4.9 Hz, 3H), 1.41* (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3*, 173.1, 159.1, 158.9*, 143.6, 143.2*, 138.0*, 137.2, 130.8*, 130.6, 129.2, 128.5*, 128.4*, 128.3, 127.5*, 127.5, 127.2*, 126.9, 116.6, 116.0*, 113.7, 113.5*, 68.4, 67.4*, 58.8*, 57.3, 55.15, 55.12*, 51.3*, 51.0, 25.9*, 25.7, 19.5*, 15.1 ppm; HRMS (ESI+) calcd for $C_{21}H_{27}N_2O_2$ $[M + H]^+$ m/z 339.20670, found 339.20676.

2-(*N*-Allyl-*N*-((*S*)-1-phenylethyl)amino)-2-(4-fluorophenyl)-*N*-methylacetamide (2o). Prepared according the general procedure C with Weinreb amide **1c** (60.9 mg, 0.20 mmol). The zinc reagent was freshly prepared from 4-FC_6H_4MgBr (1.0 M, 0.30 mL, 0.30 mmol) and $ZnCl_2$ (1.0 M in THF, 0.30 mL, 0.30 mmol). Flash chromatography (pentane + 1% i-$PrNH_2$, EtOAc 5→40%) of the crude product gave **2o** (58.5 mg, 90%) as a colorless oil: ^{1}H NMR (4:1 diastereomeric ratio, asterisk denotes minor diastereomer peaks, 500 MHz, $CDCl_3$) δ 7.33−7.11 (m, 7H), 6.97−6.81 (m, 3H), 5.63−5.49 (m, 1H), 5.03−4.90 (m, 2H), 4.35 (s, 1H), 4.00 (q, J = 6.9 Hz, 1H), 3.93* (q, J = 6.9 Hz, 1H), 3.25−3.16 (m, 1H), 3.10−3.01 (m, 1H), 2.95* (m, 1H), 2.79* (d, J = 5.0 Hz, 3H), 2.65 (d, J = 5.0 Hz, 3H), 1.32* (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9*, 172.6, 162.3 (d, J = 247 Hz), 162.1* (d, J = 247 Hz), 143.4, 143.0*, 137.6*, 137.0, 133.0 (d, J = 3.1 Hz), 132.1* (d, J = 3.2 Hz), 131.4* (d, J = 8.0 Hz), 131.2 (d, J = 8.0 Hz), 128.6*, 128.4, 127.5, 127.4*, 127.3, 127.1*, 116.9, 116.3*, 115.2 (d, J = 21 Hz), 114.9* (d, J = 21 Hz), 67.8, 66.9*, 58.8*, 57.5, 51.4*, 50.9, 26.0*, 25.8, 19.4*, 15.5 ppm; HRMS (ESI+) calcd for $C_{20}H_{24}FN_2O$ $[M + H]^+$ m/z 327.18672, found 327.18643.

General Procedure D: α-Arylation of Weinreb Amides. To a solution of Weinreb amide **5** (0.20 mmol) in 1 mL of dry toluene was added LHMDS (1.0 M in THF, 1.0 mL, 0.24 mmol) at −78 °C. Then, PhMgBr (3.0 M in Et_2O, 0.5 mL, 1.5 mmol) was added dropwise, and the resulting mixture was allowed to warm to room temperature. The reaction was quenched by the addition of water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product.

2-(Benzyloxy)-*N*-methyl-2-phenylacetamide (7a). Prepared according the general procedure D with Weinreb amide **4a** (50.3 mg, 0.20 mmol). To destroy the formed byproduct **5a**, which cannot be removed by flash chromatography, the crude product was dissolved in THF (3 mL) and HCl (1 M in H_2O, 3 mL) and stirred for 3 h at 60 °C. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (pentane, EtOAc 5→60%) to give **7a** as a colorless oil (17.2 mg, 34%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.28 (m, 10H), 6.81 (br s, 1H), 4.84 (s, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.44 (d, J = 11.5 Hz, 1H), 2.83 (d, J = 5.0 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 137.1, 137.0, 128.5, 128.4, 128.1, 128.0, 127.1, 81.3, 71.1, 25.7 ppm;

(15) Krasovskiy, A.; Tishkov, A.; del Amo, V.; Mayr, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5010–5014.

IR (film) ν_{max} 3317, 2931, 2873, 1666, 1531, 1095 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{18}NO_2$ $[M + H]^+$ m/z 256.13321, found 256.13315.

2-(4-Methoxyphenyl)-*N*-methyl-2-phenylacetamide (7c). Prepared according the general procedure D with Weinreb amide **4c** (50.3 mg, 0.20 mmol). Flash chromatography (pentane, EtOAc 5 → 60%) of the crude product gave an unseparable mixture of **5c** and **7c**. Recrystallization from hot toluene/heptane gave pure **7c** as a white solid (34.2 mg, 67%). Mp 156−158 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.22 (m, 7H), 7.16 (m, 2H), 6.86 (m, 2H), 5.56 (br, 1H), 4.89 (s, 1H), 3.79 (s, 3H), 2.84 (d, J = 4.8 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 158.7, 139.9, 131.6, 129.9, 128.8, 128.6, 127.1, 114.1, 58.2, 55.2, 26.6 ppm; IR (neat) ν_{max} 3305, 1647, 1512, 1250 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{18}NO_2$ $[M + H]^+$ m/z 256.13321, found 256.13303.

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Supporting Information Available: General experimental procedure, preparation, and analytical data for compounds **4a**−**e**, **2a**,**d**,**e**,**g**−**k**,**m**,**p**−**r**, and **7b**,**d**,**e** and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.