Synthetic Methods

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Synthesis of Aryl Glycines by the α Arylation of Weinreb Amides

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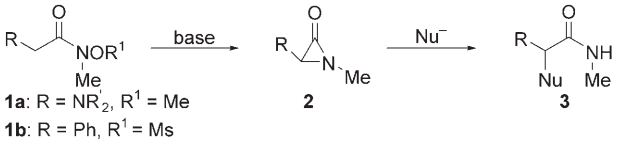
Aryl glycines are an important class of nonproteinogenic α-amino acids that are present in many drugs and natural products, such as glycopeptide antibiotics (e.g. vancomycin)[1] and many β-lactam antibiotics (e.g. penicillins, cephalosporins,[2] and nocardicins[3]). Despite their deceptively simple structure, the enantioselective synthesis of aryl glycines is complicated by the ease of base-catalyzed racemization of the α stereocenter. As a result, many aryl glycines are synthesized in racemic form, and the enantiomers are then separated by resolution.[4a] During the last few decades, a wide range of racemic and asymmetric syntheses of aryl glycines have been developed.[4,5] However, owing to the lack of generality and functional diversity of most of these methods, the generation of aryl glycines remains a challenge in organic chemistry.

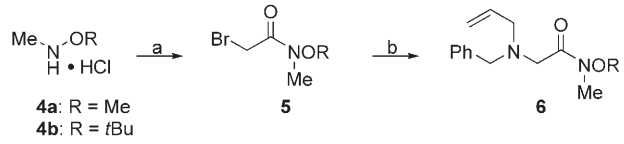
A straightforward approach to aryl glycines is the α arylation of electrophilic glycine equivalents with aryl nucleophiles.[5e,6] We envisaged that α-lactams **2**, derived from hydroxamic esters **1a**, could serve as electrophilic glycine equivalents in reactions with various nucleophiles (Scheme 1). A related intramolecular version of this reaction



Scheme 1. Proposed generation of electrophilic glycine equivalents. Ms = methanesulfonyl.

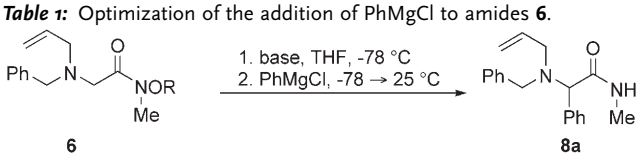
was reported recently by Mislin et al.,[7] and a similar strategy has also been used for the synthesis of α-heteroatom-substituted amides from *N*-mesyloxy amides **1b**.[8]

We commenced our investigation of this method with the Weinreb amide **6a**, which was synthesized in two steps from *N*,*O*-dimethylhydroxylamine hydrochloride (**4a**; Scheme 2).[9] We circumvented the direct formation of an aryl ketone from **6a** by generating the corresponding α-lactam at low temperature prior to the addition of the Grignard reagent.[10] After several attempts with different strong bases (Table 1), we



Scheme 2. Synthesis of amide **6**: a) bromoacetyl bromide, K_2CO_3, H_2O/Et_2O, **5a**: 80%, **5b**: 83%; b) *N*-allyl-*N*-benzylamine, K_2CO_3, MeCN, **6a**: 74%, **6b**: 80%.

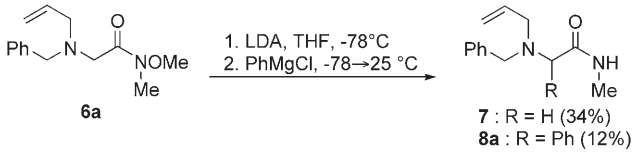
Table 1: Optimization of the addition of PhMgCl to amides **6**.



Entry	R	Base (equiv)	Yield [%][a]
1	Me	LiHMDS (1.5)	trace
2	Me	*n*BuLi (1.5)	trace
3	Me	LDA (1.5)	12
4	*t*Bu	LDA (1.5)	77
5	*t*Bu	LDA (1.0)	86

[a] Yield of the isolated product. HMDS = hexamethyldisilazide, LDA = lithium diisopropylamide.

found that the deprotonation of **6a** with LDA (1.5 equiv) at −78 °C and subsequent addition of PhMgCl (2.0 equiv) afforded the desired α-arylated product **8a**, albeit in low yield (Scheme 3, Table 1, entry 3). The main product isolated from the reaction mixture was the secondary amide **7**, which results from the demethoxylation of **6a** by an E2 elimination reaction.[11]



Scheme 3. Addition of PhMgCl to amide **6a**.

It has been shown previously that this type of elimination can be suppressed by using an *N*-*tert*-butoxy substituent.[11a] Thus, compound **6b** was selected as a suitable substrate and prepared in the same manner as amide **6a**, in this case from *N*-methyl-*O*-*tert*-butylhydroxylamine hydrochloride (**4b**; Scheme 2). When **6b** was treated with LDA and PhMgCl, the desired arylation product **8a** was isolated in good yield (Table 1, entry 4). The yield of **8a** was increased further to 86% simply by decreasing the amount of base used (Table 1, entry 5).

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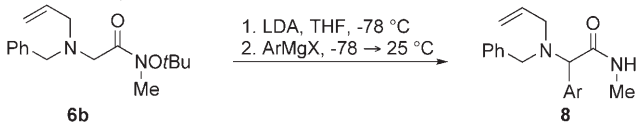
We investigated the reaction of **6b** with various aryl Grignard reagents under the optimized conditions (Table 2). The adduct **8** was formed in good to excellent yield when

Table 2: α Arylation of amide **6b**.[a]

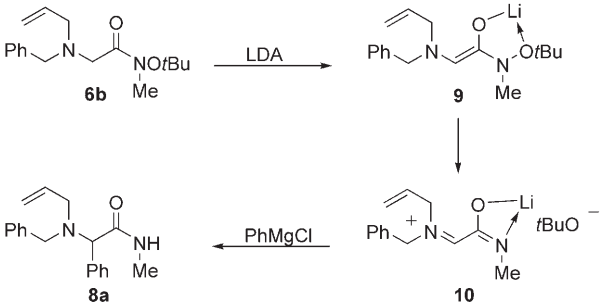


Entry	ArMgX	Product	Yield [%][b]
1	PhMgCl	**8a**	86
2[c]	4-FC_6H_4MgBr	**8b**	77
3	4-$MeOC_6H_4MgBr$	**8c**	92
4[d]	3-PhC_6H_4MgBr	**8d**	81
5[c]	(2-thienyl)MgBr	**8e**	91
6[d]	(3-pyridinyl)MgCl·LiCl	**8f**	77
7[d]	(5-bromo-3-pyridinyl)MgCl·LiCl	**8g**	76

[a] Molar ratio: **6b**/LDA/RMgX 1:1:2. [b] Yield of the isolated product. [c] 1.5 equivalents LDA. [d] LDA was added at 0 °C.

electron-donating or electron-withdrawing substituents were present on the aryl ring. Functionalized aryl Grignard reagents were synthesized in situ from the corresponding bromides by Br–Mg exchange with *i*PrMgCl·LiCl (Table 2, entries 6 and 7).[12] With most of the Grignard reagents screened, full conversion was only observed when the LDA was added at 0 °C (Table 2, entries 4, 6, 7) or 1.5 equivalents of LDA were used (entries 2 and 5).[13]

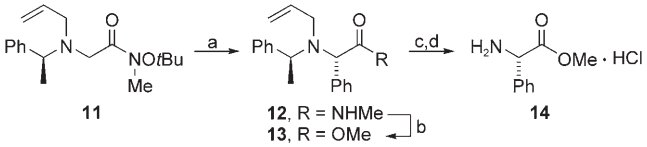
We propose the following mechanism for the formation of compound **8a** from **6b** (Scheme 4): The deprotonation of **6b** generates enolate **9**. Subsequent elimination of *t*BuO$^-$ from



Scheme 4. Proposed mechanism for the formation of **8a** from **6b**.

this intermediate constitutes the key step and generates iminium ion **10** with the overall result that the dipole of the α carbon center is reversed (umpolung). The addition of the Grignard reagent to **10** then gives amide **8a**. For the base-promoted addition of amines and halides to O-sulfonylated hydroxamic acid derivatives, it has been shown that both deprotonation of the α carbon atom and loss of the N–OR moiety are occurring at the transition state of the rate-determining step.[7,8] The application of this scenario to the present reaction suggests the direct formation of iminium ion **10** from enolate **9**, or the conversion of **9** into the corresponding α-lactam (see structure **2** in Scheme 1) followed by ring opening to give **10** (compounds **2** and **10** are valence tautomers). Although the exact course of events can not be deduced from the data present, the formation of compound **8a** as the sole regioisomer strongly suggests the involvement of iminium ion **10**.

With an operationally simple and high yielding procedure for the synthesis of racemic aryl glycines at hand, we next set out to develop an asymmetric protocol. Amide **11**, derived from (−)-α-methylbenzylamine, was selected for an initial study (Scheme 5). The treatment of **11** with LDA (1.05 equiv)



Scheme 5. Diastereoselective nucleophilic addition to amide **11**: a) LDA, THF, 0 °C; then PhMgCl, $ZnCl_2$, −78→25 °C, 74%, d.r. 7:1; b) 1. $NaNO_2$, CH_2Cl_2, Ac_2O, AcOH; 2. MeOH, $NaHCO_3$, reflux, 84% (2 steps); c) 1. $[Pd(PPh_3)_4]$, *N*,*N*′-dimethylbarbituric acid, CH_2Cl_2, reflux, 92%; 2. $Pd(OH)_2$, MeOH, HCl, 100%.

followed by PhZnCl (1.2 equiv), which was used instead of the more basic Grignard reagent to minimize potential epimerization, yielded the desired adduct **12** in high yield with high selectivity (d.r. 7:1). The configuration of the newly formed stereocenter was determined to be *S* by the transformation of **12** into the known methyl ester **14**.[14,15] After separation of the diastereomers by flash chromatography, amide **12** was converted into ester **13** without epimerization.[16,17] Subsequent deallylation[18] and hydrogenolysis gave enantiomerically pure **14** in good overall yield. As noted previously for related compounds, the *N*-methylamide functionality in **12** constitutes an advantageous protecting group for the carboxy terminus of aryl glycines.[16] By straightforward derivatization to the corresponding *N*-nitrosoamide, the amide can be hydrolyzed to the free amino acid[16b] or converted into the methyl ester.[19]

In summary, an efficient and diastereoselective synthesis of aryl glycines from readily available starting materials has been developed. We are presently exploring the scope and limitations of this reaction.

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[1] F. Wolter, S. Schoof, R. D. Süssmuth, *Top. Curr. Chem.* **2007**, *267*, 143–185.
[2] H. Schutt, G. Schmidt-Kastner, A. Arens, M. Preiss, *Biotechnol. Bioeng.* **1985**, *27*, 420–433.
[3] G. M. Salituro, C. A. Townsend, *J. Am. Chem. Soc.* **1990**, *112*, 760–770.

[4] For reviews on the asymmetric synthesis of aryl glycines, see: a) R. M. Williams, J. A. Hendrix, *Chem. Rev.* **1992**, *92*, 889 – 917; b) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584 – 4671.
[5] For leading references on aryl glycine syntheses, see: a) E. L. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 12066 – 12067; b) M. A. Beenen, D. J. Weix, J. A. Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 6304 – 6305; c) G. Shang, Q. Yang, X. Zhang, *Angew. Chem.* **2006**, *118*, 6508 – 6510; *Angew. Chem. Int. Ed.* **2006**, *45*, 6360 – 6362; d) R. Cannella, A. Clerici, W. Panzeri, N. Pastori, C. Punta, O. Porta, *J. Am. Chem. Soc.* **2006**, *128*, 5358 – 5359; e) P. Calí, M. Begtrup, *Synthesis* **2002**, 63 – 66; f) K. L. Reddy, K. B. Sharpless, *J. Am. Chem. Soc.* **1998**, *120*, 1207 – 1217.
[6] P. D. Bailey, A. N. Boa, J. Clayson, *Contemp. Org. Synth.* **1995**, *2*, 173 – 187.
[7] G. L. Mislin, A. Burger, M. A. Abdallah, *Tetrahedron* **2004**, *60*, 12139 – 12145.
[8] a) R. V. Hoffman, N. K. Nayyar, W. Chen, *J. Am. Chem. Soc.* **1993**, *115*, 5031 – 5034; b) R. V. Hoffman, N. K. Nayyar, W. Chen, *J. Org. Chem.* **1995**, *60*, 4121 – 4125; c) R. V. Hoffman, Z. Zhao, A. Costales, D. Clarke, *J. Org. Chem.* **2002**, *67*, 5284 – 5294.
[9] R. Tillyer, L. F. Frey, D. M. Tschaen, U.-H. Dolling, *Synlett* **1996**, 225 – 226.
[10] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815.
[11] a) O. Labeeuw, P. Phansavath, J.-P. Genêt, *Tetrahedron Lett.* **2004**, *45*, 7107 – 7110; b) S. L. Graham, T. H. Scholz, *Tetrahedron Lett.* **1990**, *31*, 6269 – 6272.
[12] A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396 – 3399; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333 – 3336.
[13] Use of the standard reaction conditions resulted in recovery of the starting material.
[14] $[\alpha]_D^{20} = +125.6$ ($c = 0.43$, MeOH); lit:[15] $[\alpha]_D^{24.1} = +136.0$ ($c = 2.17$, MeOH). For the determination of the *ee* value, the hydrochloride was converted into the free amine by treatment with $NaHCO_3$ in H_2O. The *ee* value was shown to be greater than 96% by HPLC on a chiral phase (chiralcel OD-RH, KPF_6 (50 mM)/MeCN, 85:15 → 70:30, 0.4 mL min^{-1}).
[15] G.-I. Li, G. Zhao, *Org. Lett.* **2006**, *8*, 633 – 636.
[16] a) D. A. Evans, J. C. Barrow, P. S. Watson, A. M. Ratz, C. J. Dinsmore, D. A. Evrard, K. M. DeVries, J. A. Ellman, S. D. Rychnovsky, J. Lacour, *J. Am. Chem. Soc.* **1997**, *119*, 3419 – 3420; b) D. A. Evans, P. H. Carter, C. J. Dinsmore, J. C. Barrow, J. L. Katz, D. W. Kung, *Tetrahedron Lett.* **1997**, *38*, 4535 – 4538.
[17] No epimerization of the α stereocenter was observed for the ester-formation and deallylation steps (Scheme 5, steps b and c) by ^{1}H NMR spectroscopic analysis of the crude products.
[18] F. Garro-Helion, A. Merzouk, F. Guibé, *J. Org. Chem.* **1993**, *58*, 6109 – 6113.
[19] D. M. Shendage, R. Fröhlich, G. Haufe, *Org. Lett.* **2004**, *6*, 3675 – 3678.

