

Bi(OTf)₃-catalyzed three-component synthesis of α-amino acid derivatives†

Angelika E. Schneider, Tamara Beisel, Andrej Shemet and Georg Manolikakes*

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 2356

Received 5th February 2014,
Accepted 18th February 2014

DOI: 10.1039/c4ob00265b

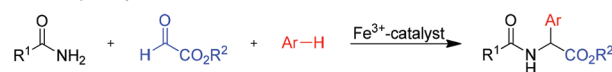
www.rsc.org/obc

A highly efficient Bi(OTf)₃-catalyzed multicomponent synthesis of arylglycines from readily available starting materials is described. The reaction proceeds under mild conditions and provides a general route to various N-protected arylglycines.

α-Arylglycines are interesting and important non-proteinogenic amino acids. The α-arylglycine motif is found in many significant drugs and natural products including glycopeptide antibiotics (e.g. vancomycin and teicoplanins) and the widely used β-lactam antibiotics (e.g. norcardicins, amoxicillins and cephalosporins) (Fig. 1).¹ Arylglycines have been shown to selectively modulate the activity of metabotropic glutamate receptors, a promising new approach for the treatment of neurodegenerative disorders such as Parkinson's disease.²

Due to this impressive range of biological activities, various methods for the synthesis of arylglycine derivatives have been developed during the last few decades.^{3,4} Reactions based on the addition of a carbon nucleophile to a reactive imine- or iminium-species,^{5,6} such as the Strecker reaction,⁷ the Mannich reaction⁸ or the Petasis reaction,⁹ are widely used in industry and academia. Recently, we have developed an

(1) Previous work: Fe³⁺-catalyzed reaction limited to primary amides and reactive arenes.



(2) This work: Bi³⁺-catalyzed reaction

primary and unhindered secondary amides, sulfonamides, less reactive arenes.



Scheme 1 Three-component synthesis of arylglycines.

efficient iron-catalyzed three-component synthesis of arylglycines from simple starting materials (Scheme 1).¹⁰ Although this method provides an atom-economic and cost-effective route to arylglycines, it has some limitations. Sulfonamides or unhindered secondary amides do not react in the presence of an iron-catalyst and only reactions with at least moderately electron-rich aromatic components, such as *m*-xylene, provide the desired products in reasonable yields. The observed modest catalytic activity of the employed iron(III) salts can be rationalized by their moderate Lewis acidity.¹¹ We anticipated that substitution of the iron-catalyst with a stronger Lewis acid should lead to a more general three-component reaction. In previous studies, we had already identified Bi(OTf)₃ as a very effective catalyst for three-component amidoalkylation reactions.¹² Since Bi(OTf)₃ is commercially available for a reasonable price,¹³ nontoxic, air- and moisture-stable, it is a very attractive catalyst.^{14–17}

Indeed, Bi(OTf)₃ could catalyze the reaction between benzamide, ethyl glyoxalate and *m*-xylene very efficiently even at low catalyst loadings (Table 1, entries 1–4). Other Bi³⁺ salts or HOTf, a possible byproduct from the hydrolysis of Bi(OTf)₃, displayed reduced catalytic activity. To exclude a possible

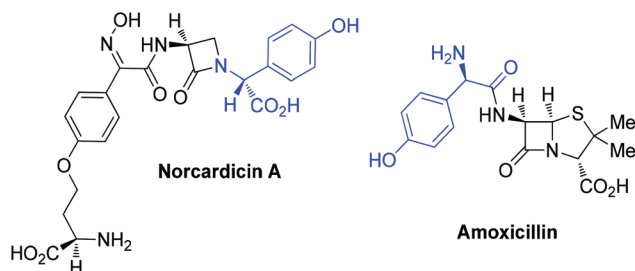


Fig. 1 Arylglycine moieties in biologically active molecules.

Department of Organic Chemistry and Chemical Biology, Goethe University Frankfurt, Frankfurt am Main, Germany.

E-mail: g.manolikakes@chemie.uni-frankfurt.de

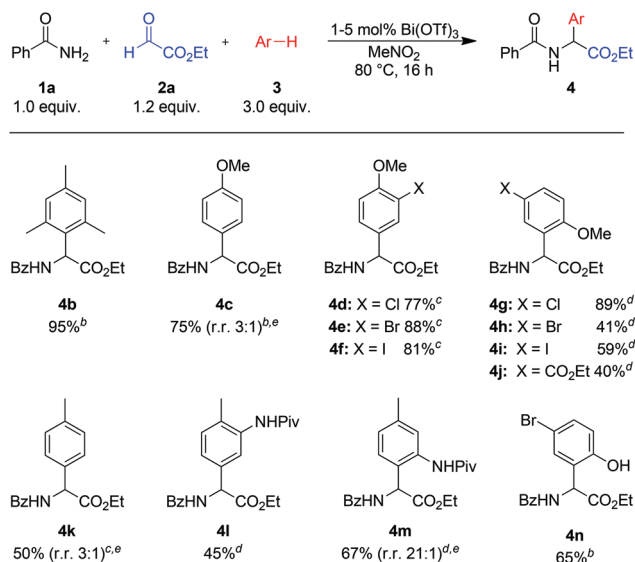
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob00265b



Table 1 Survey of catalysts^a

Entry	Catalyst (mol%)	Yield ^b (%)
1	Bi(OTf) ₃ (5)	84
2	Bi(OTf) ₃ (2)	89
3	Bi(OTf) ₃ (1)	88
4	Bi(OTf) ₃ (0.5)	77
5	BiCl ₃ (5)	72
6	BiBr ₃ (5)	69
7	HOTf (5)	49
8	Bi(OTf) ₃ (5) + dbpy (10)	84
9	Bi(OTf) ₃ (5) ^c	52

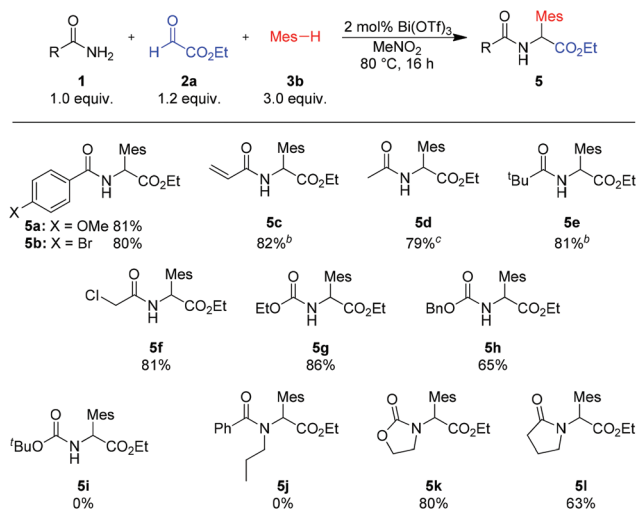
^a General reaction conditions: benzamide (1.0 equiv.), ethyl glyoxalate (1.2 equiv.), *m*-xylene (3.0 equiv.), catalyst (*x* mol%), 80 °C, 18 h.
^b Isolated yield of the analytically pure product. ^c Reaction in DCE.



Scheme 2 Variation of arenes^a. ^a Isolated yield of analytically pure product. ^b Reaction with 1 mol% Bi(OTf)₃. ^c Reaction with 2 mol% Bi(OTf)₃. ^d Reaction with 5 mol% Bi(OTf)₃. ^e Obtained as a mixture of regioisomers; the ratio of regioisomers is given in parentheses.

“hidden” catalysis¹⁸ by *in situ* generated Brønsted acids, we performed the reaction in the presence of 2,6-di-*tert*-butylpyridine (dbpy), a selective proton scavenger.¹⁹ Since no decrease in catalytic activity was observed, we assume that a Bi³⁺-species is the active catalyst. In general, best yields were obtained in nitromethane as a solvent (entries 1–4 and 9).

With the optimized conditions established, the scope of the method was explored. As shown in Scheme 2, reactions with electron rich arenes such as mesitylene (3b), 4-bromophenol (3n)²⁰ or anisole (3c) and its derivatives (3d–j) furnished the desired products in good to excellent yields (4b–i, 4n). The



Scheme 3 Variation of amides^a. ^a Isolated yields of analytically pure products. ^b Reaction with 1 mol% Bi(OTf)₃. ^c Reaction with 5 mol% Bi(OTf)₃. Mes = mesityl (2,4,6-trimethylphenyl).

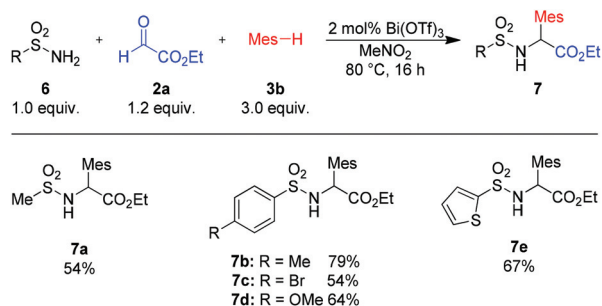
high catalytic activity of Bi(OTf)₃ allows reactions with less nucleophilic arenes, such as toluene or *N*-protected aniline derivatives (products 4k–m).²¹ In most cases the regioselectivity of the reaction is good to excellent. Only in a few cases, for example with anisole (3c) or toluene (3k), a mixture of regioisomers was obtained.

The reaction of various primary aryl or alkyl amides with ethyl glyoxalate and mesitylene provided the desired products in good to excellent yields (see Scheme 3, 5a–f). Even acid sensitive functionalities such as an acrylamide (product 5c) were well tolerated. Using carbamates as the amide component, the corresponding *N*-protected arylglycines, useful building blocks for further transformations, were obtained in 86% and 65% yield (5g and 5h). Also, in the case of the amide component, the high catalytic activity of Bi(OTf)₃ leads to a broader substrate scope and facilitates reactions with unhindered cyclic secondary amides or carbamates (products 5i–j). Sterically more demanding acyclic secondary amides, such as 1j, or *tert*-butyl carbamate (1i) did not react under the standard conditions.†

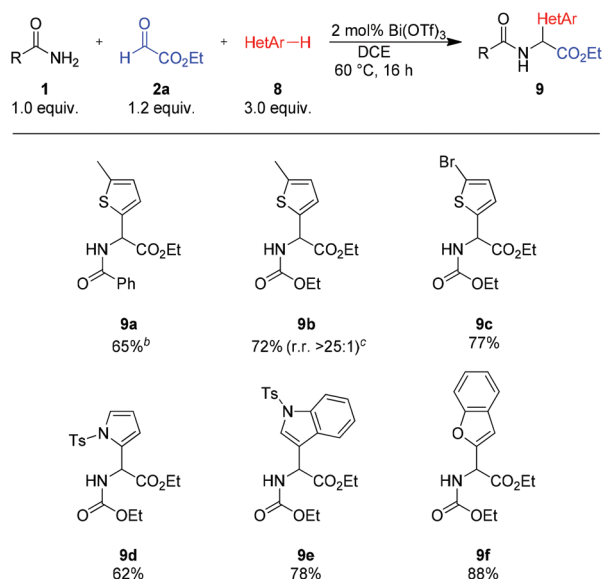
To our delight, also sulfonamides are suitable amide components (Scheme 4). Reactions with alkyl- as well as aryl-sulfonamides furnished the desired products in good to excellent yields (7a–e).

With heteroarenes as nucleophilic compounds, lower reaction temperatures were necessary to avoid direct addition of the heteroarene to the aldehyde (Scheme 5). In general, better results were obtained with urethane as the amide component and DCE as a solvent. Under these modified conditions, several heterocycles such as thiophenes (8a–c), *N*-tosylpyrrole (8d), *N*-tosylindole (8e) and benzofuran (8f) could be utilized as the nucleophilic component.

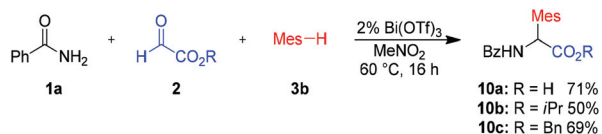
This method is not limited to ethyl glyoxalate as the aldehyde component. Reaction with different glyoxalates, such as isopropyl or benzyl glyoxalate, furnished the desired amino



Scheme 4 Variation of sulfonamides. Isolated yields of analytically pure products. Mes = mesityl (2,4,6-trimethyl-phenyl).



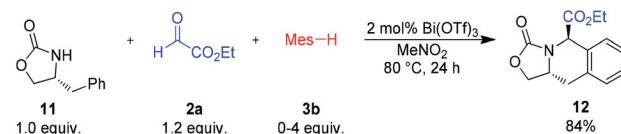
Scheme 5 Variation of heteroarenes^a. ^a Isolated yields of analytically pure products. ^b Reaction in nitromethane. ^c Obtained as a mixture of regioisomers; the ratio of regioisomers is given in parentheses.



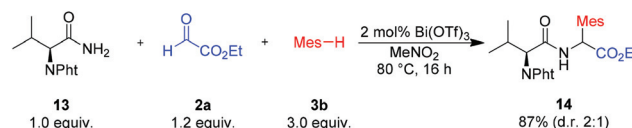
Scheme 6 Variation of alkyl glyoxalates. Isolated yields of analytically pure products. Mes = mesityl (2,4,6-trimethyl-phenyl).

acid derivatives in 50–69% yield (Scheme 6, products **10b–c**). This reaction is quite insensitive to air or moisture and therefore very simple to perform. Even an aqueous solution of glyoxylic acid could be used as an aldehyde source. In this case the free acid **10a** could be obtained in 71% yield.

In order to expand the utility of this method, we investigated possible diastereoselective reactions with chiral amide components. To our surprise, reaction with the chiral oxazolidione **11** yielded the cyclic amino acid **12** as a single product, even if an excess of the nucleophilic arene component **3b** was



Scheme 7 Reaction of (*R*)-4-methyloxazolidin-2-one (**11**). Isolated yield of the analytically pure product. Mes = mesityl (2,4,6-trimethyl-phenyl).



Scheme 8 Reaction of *N*-phthalyl-protected valinamide (**13**). Isolated yield of the analytically pure product. Mes = mesityl (2,4,6-trimethyl-phenyl). Pht = *N*-phthalyl.

used (Scheme 7). This reactivity can be rationalized by an intramolecular addition of the phenyl group to the formed acyliminium species. Unfortunately, other chiral oxazolidiones, derived from valine or norephedrine, did not react under the standard conditions.

Therefore we examined reactions with chiral primary amides derived from amino acids. The three-component reaction with *N*-phthalyl-protected valinamide **13** afforded the desired dipeptide **14** in high yield and moderate diastereoselectivity (Scheme 8).²² Since both diastereomers can be separated by simple chromatography, this reaction could be used for an unusual synthesis of dipeptides.

Conclusions

In summary, we have developed an efficient Bi(OTf)₃-catalyzed three-component synthesis of α-amino acid derivatives from readily available starting materials. This practical and operationally simple approach has a very broad scope and water is generated as the only by-product. In addition, we have demonstrated that reactions with chiral amide components proceed with moderate diastereoselectivity. The scope of these diastereoselective reactions and further asymmetric transformation are currently being investigated in our laboratory and will be reported in due course.

Acknowledgements

This work was financially supported by the Fonds der Chemischen Industrie (Liebig Fellowship to G. M. and A. E. S.), the Stiftung Polytechnische Gesellschaft Frankfurt am Main (Ph.D. Fellowship to T. B.), and the Goethe University (Nachwuchs im Fokus-Programm). We would like to thank Prof. Michael Göbel (Goethe University Frankfurt) for his support and Rockwood Lithium (Frankfurt), BASF



(Ludwigshafen) and Evonik Industries (Darmstadt) for the generous gift of chemicals.

Notes and references

‡ **General procedure for reactions with ethyl glyoxalate:** A 10 mL screw-cap vial was charged with Bi(OTf)₃ (1–5 mol%), amide (1.0 equiv.), and nitromethane (2 mL mmol^{−1} amide). Ethyl glyoxalate (1.2 equiv.) in nitromethane (2 mL mmol^{−1} amide) and the aromatic compound (3.0–4.0 equiv.) were added under vigorous stirring. The mixture was heated to 60–100 °C and stirred at this temperature for 16 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short plug of Celite. The plug was rinsed with additional EtOAc. The combined filtrates were concentrated under reduced pressure. Purification of the crude residue by column chromatography (hexane–EtOAc) afforded the analytically pure product.

- (a) E. Leemans, J. F. Fisher and S. Mobashery, *Antimicrobials*, 2014, 59; (b) G. L. Marcone and F. Marinelli, *Antimicrobials*, 2014, 85; (c) G. L. Plosker and K. A. Lyseng-Williamson, *Drugs*, 2007, 67, 613; (d) F. van Bambeke, Y. van Laethem, P. Courvalin and P. M. Tulkens, *Drugs*, 2004, 64, 913; (e) L. R. Wiseman and P. Benfield, *Drugs*, 1993, 45, 295; (f) D. M. Campoli-Richards, R. N. Brogden and D. Faulds, *Drugs*, 1990, 40, 449.
- A. Boto, R. Hernandez, A. Montoya and E. Suarez, *Tetrahedron Lett.*, 2002, 43, 8269.
- For reviews on asymmetric arylglycine synthesis see: (a) R. M. Williams and J. A. Hendrix, *Chem. Rev.*, 1992, 92, 889; (b) C. Nájera and J. M. Sansano, *Chem. Rev.*, 2007, 107, 4584.
- (a) P. Fang, M. R. Chaulagain and Z. D. Aron, *Org. Lett.*, 2012, 14, 2130; (b) Z. Xu, X. Yu, X. Feng and M. Bao, *Beilstein J. Org. Chem.*, 2012, 8, 1564; (c) X. Xiao, Y. Xie, C. Su, M. Liu and Y. Shi, *J. Am. Chem. Soc.*, 2011, 133, 12914; (d) Z.-Y. Xue, Q.-H. Li, H.-Y. Tao and C.-J. Wang, *J. Am. Chem. Soc.*, 2011, 133, 11757; (e) T. Mita, J. Chen, M. Sugawara and Y. Sato, *Angew. Chem., Int. Ed.*, 2011, 50, 1393; (f) T. Mita, Y. Higuchi and Y. Sato, *Org. Lett.*, 2011, 13, 2354; (g) S. Hirner, O. Panknin, M. Edefuhr and P. Somfai, *Angew. Chem., Int. Ed.*, 2008, 120, 1933; (h) E. C. Lee and G. C. Fu, *J. Am. Chem. Soc.*, 2007, 129, 2066; (i) G. Shang, Q. Yang and X. Zhang, *Angew. Chem., Int. Ed.*, 2006, 45, 6360; (j) S. Saaby, X. Fang, N. Gathergood and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2000, 39, 4114.
- For some reviews see: (a) A. Yazici and S. G. Pyne, *Synthesis*, 2009, 339; (b) M. Petrini and E. Torregiani, *Synthesis*, 2007, 159; (c) W. N. Speckamp and M. J. Moolenaar, *Tetrahedron*, 2000, 56, 3817; (d) H. Zaugg, *Synthesis*, 1984, 85.
- For examples of amidoalkylation reactions see: (a) T. A. Salama, *Synlett*, 2013, 713; (b) J. Jaratjaroonphong, S. Krajangsri and V. Reutrakul, *Tetrahedron Lett.*, 2012, 53, 2476; (c) G. C. Nandi, S. Samai, R. Kumar and M. S. Singh, *Tetrahedron Lett.*, 2009, 50, 7220; (d) P. Grundmann and W.-D. Fessner, *Adv. Synth. Catal.*, 2008, 350, 1729; (e) S. Shirakawa and S. Kobayashi, *Org. Lett.*, 2006, 8, 4939; (f) A. Schouteeten, Y. Christidis and G. Mattioda, *Bull. Soc. Chim. Fr. II*, 1978, 248; (g) D. Ben-Ishai, J. Altman, Z. Bernstein and N. Peled, *Tetrahedron*, 1977, 34, 467.
- A. Strecker, *Ann. Chem. Pharm.*, 1850, 75, 27; for a recent review see: J. Wang, X. Liu and X. Feng, *Chem. Rev.*, 2011, 111, 6947.
- C. Mannich and W. Krösche, *Arch. Pharm.*, 1912, 250, 647; for recent reviews see: (a) S. Kobayashi and M. Ueno in *Comprehensive Asymmetric Catalysis*, Springer, Berlin, 2004, vol. 1, (Supplement), p. 143; (b) A. Cordova, *Acc. Chem. Res.*, 2004, 37, 102.
- (a) N. R. Candeias, F. Montalbano, P. M. S. D. Cal and P. M. P. Gois, *Chem. Rev.*, 2010, 110, 6169; (b) N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1998, 120, 11798; (c) N. A. Petasis, A. Goodman and I. A. Zavialov, *Tetrahedron*, 1997, 53, 16463; (d) N. A. Petasis and I. Akritopoulou, *Tetrahedron Lett.*, 1993, 34, 583.
- J. Halli and G. Manolikakes, *Eur. J. Org. Chem.*, 2013, 7471.
- (a) W. B. Jensen, in *The Lewis Acid-Base Concepts: An Overview*, John Wiley & Sons Inc., Chichester, UK, 1980; (b) *Lewis Acid Reagents: A Practical Approach*, ed. H. Yamamoto, Oxford Univ. Press, New York, 1999.
- A. E. Schneider and G. Manolikakes, *Synlett*, 2013, 2057.
- 8.48 € g^{−1}, price obtained from Alfa Aesar on 03/02/2014.
- For reviews see: (a) J. M. Bothwell, S. W. Krabbe and R. S. Mohan, *Chem. Soc. Rev.*, 2011, 40, 4649; (b) H. Gaspard-Illoughmane and C. Le Roux, *Eur. J. Org. Chem.*, 2004, 2517.
- For selected recent applications see: (a) L. Zhang, Z. Li and R. Fan, *Org. Lett.*, 2013, 15, 2482; (b) Z. Li, B. Plancq and T. Ollevier, *Chem.-Eur. J.*, 2012, 18, 3144; (c) P. Rubenbauer, E. Herdtweck, T. Strassner and T. Bach, *Angew. Chem., Int. Ed.*, 2008, 47, 10106; (d) M. Rueping, B. J. Nachtsheim and A. Kuenkel, *Org. Lett.*, 2007, 9, 825; (e) H. Qin, N. Yamagiwa, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2007, 46, 409; (f) M. Rueping, B. J. Nachtsheim and T. Scheidt, *Org. Lett.*, 2006, 8, 3717.
- For Bi(OTf)₃-catalyzed Mannich-type amidoalkylation and Mannich-type reactions with reactive nucleophiles, see: (a) F. Pin, S. Comesse, B. Garrigues, S. Marchalin and A. J. Daïch, *Org. Chem.*, 2007, 72, 1181; (b) T. Ollevier and E. Nadeau, *Org. Biomol. Chem.*, 2007, 5, 3126; (c) T. Ollevier and E. J. Nadeau, *Org. Chem.*, 2004, 69, 9292; (d) T. Ollevier and T. Ba, *Tetrahedron Lett.*, 2003, 44, 9003.
- For the water content of Bi(OTf)₃ see ESI.†
- T. T. Dang, F. Boeck and L. Hintermann, *J. Org. Chem.*, 2011, 76, 9353.
- For the use of dbpy as a mechanistic probe to determine between Lewis and Brønsted acid catalysis see: T. C. Wabnitz, J.-Q. Yu and J. B. Spencer, *Chem.-Eur. J.*, 2004, 10, 484.
- Phenols cannot be employed in the Fe³⁺-catalyzed reaction due to competitive oxidative coupling reactions.
- Benzene did not react even under more forcing reaction conditions.
- No epimerization of both diastereomers is observed under the reaction conditions (2 mol% Bi(OTf)₃, 80 °C, 24 h).

