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# A Straightforward Three-Component Synthesis of α-Amino Esters Containing a Phenylalanine or a Phenylglycine Scaffold

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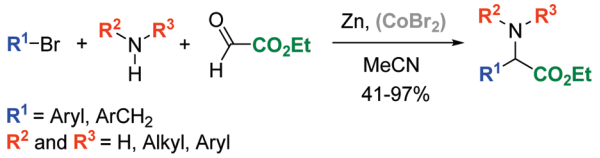


A range of α-amino esters has been synthesized in good to high yields using a straightforward three-component reaction among preformed or in situ generated aromatic or benzylic organozinc reagents, primary or secondary amines, and ethyl glyoxylate. The procedure, which is characterized by its simplicity, allows the concise synthesis of esters bearing a phenylglycine or a phenylalanine scaffold.

## Introduction

α-Amino acids constitute one of the most important families of natural products that play central roles both as structural units of proteins and as intermediates in metabolism. They are continuously employed in the elaboration of peptides and as chiral pools in multistep synthesis but also represent valuable chiral organocatalysts or attractive building blocks in drug discovery.[1] Consequently, the development of efficient methods for the synthesis of novel nonproteinogenic or unnatural α-amino acids has been a field of extensive research over the past few years.[2]

Although numerous methods allow the efficient preparation of a large range of α-amino acids derivatives, only a limited set of processes employing multicomponent procedures have been disclosed to date.[3] For instance, the Petasis three-component reaction[4] among boronic acids, amines, and glyoxylic acid has been employed for the diastereoselective synthesis of pyrrolidine-derived arylglycines[5] or a

(1) For some selected examples, see: (a) Sardina, J. F.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1872. (b) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4197–4212. (c) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495. (d) Kaiser, J.; Kinderman, S. S.; van Esseveldt, B. C. J.; van Delft, F. L.; Schoemaker, H. E.; Blaauw, R. H.; Rutjes, F. P. J. T. *Org. Biomol. Chem.* **2005**, *3*, 3435–3467. (e) Kazmaier, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 2186–2188. (f) List, B. *Tetrahedron* **2002**, *58*, 5573–5590. (g) Hicks, R. P.; Bhonsle, J. B.; Venugopal, D.; Koser, B. W.; Magill, A. J. *J. Med. Chem.* **2007**, *50*, 3026–3036. (h) Wang, J. Y.; Xie, J. M.; Schultz, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 8738–8739. (i) Jain, R.; Chawrai, S. *Mini-Rev. Med. Chem.* **2005**, *5*, 469–477.

(2) (a) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press, Oxford University Press: New York, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650. (c) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528–3529. (d) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem.—Eur. J.* **2002**, *8*, 3646–3652. (e) Park, H.; Jeong, B.; Yoo, M. S.; Lee, J.; Park, M.; Lee, Y. J.; Kim, M.; Jew, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036–3038. (f) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. (g) Perdih, A.; Dolenc, M. S. *Curr. Org. Chem.* **2007**, *11*, 801–832. (h) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517. (i) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525. (j) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028. (k) Katritzky, A. R.; Urogdi, L.; Mayence, A. *Synthesis* **1989**, 323–327. (l) Lee, E. C.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 12066–12067. (m) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 6360–6362. (n) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889–917. (o) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867. (p) Sakai, N.; Asano, J.; Kawada, Y.; Konakahara, T. *Eur. J. Org. Chem.* **2009**, 917–922. (q) Hirner, S.; Somfai, P. *J. Org. Chem.* **2009**, *74*, 7798–7803. (r) Lee, E. C.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 12066–12067. (s) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 6360–6362.

(3) Besides the Petasis or the Ugi reaction, the Strecker reaction might be relevant for the synthesis of α-amino acids through preliminary preparation of α-aminonitriles. For some exemples, see: (a) Strecker, A. *Justus Liebigs Ann. Chem.* **1850**, *75*, 27–51. (b) Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 8471–8474. (c) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762–766. (d) Baeza, A.; Nájera, C.; Sansano, J. M. *Synthesis* **2007**, 1230–1234. (e) Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Srinivas, M. *Tetrahedron* **2004**, *60*, 1767–1771. (f) Prakash, G. K. S.; Mathew, T.; Panja, C.; Alconcel, S.; Vaghoo, H.; Do, C.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *104*, 3703–3706.

(4) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583–586. (b) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *48*, 16463–16470. (c) Petasis, N. A.; Zavialov, A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446. (d) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799. (e) Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539–542. (f) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718–3723.

(5) Nanda, K. K.; Trotter, B. W. *Tetrahedron Lett.* **2005**, *46*, 2025–2028.

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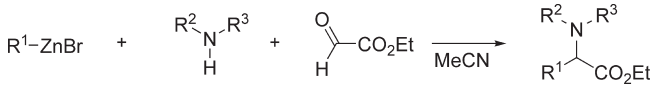
one-pot sequential α-amino ester formation and palladium-catalyzed cyclization process.[6] Isocyanide-based reactions like the Ugi 3-CR[7] have also been employed as an efficient tool for the synthesis of leading drugs like the antiplatelet agent clopidogrel.[8] However, while these methods afford a very convenient access to a variety of α-amino acids, none of them allows a fast and direct entry to α-amino esters and particularly those derived from phenylalanine.[9]

Over the past few years, our group has developed a multicomponent procedure allowing the efficient formation of α-branched amines starting from amines, aldehydes, and preformed or in situ generated organozinc reagents.[10] In a very recent paper, we also disclosed preliminary results regarding the use of ethyl glyoxylate as the carbonyl derivative to afford an instant access to α-amino esters.[11] Herein, we both confirm the possible use of ethyl glyoxylate as a convenient building block of α-amino esters and further broaden the scope of the procedure by showing its relevance for the formation of a larger range of α-amino esters bearing a phenylalanine or a phenylglycine moiety.

## Results and Discussion

As a starting point of the study, we envisaged to extend the procedure described in our previous works devoted to the multicomponent coupling of organozinc reagents with aromatic aldehydes and secondary amines to the synthesis of α-amino esters. In this purpose, it was simply proposed to replace the aldehyde by a non acidic glyoxylic acid equivalent[12] under its ethyl ester form (Scheme 1).

**SCHEME 1. Principle of the Three-Component Reaction**

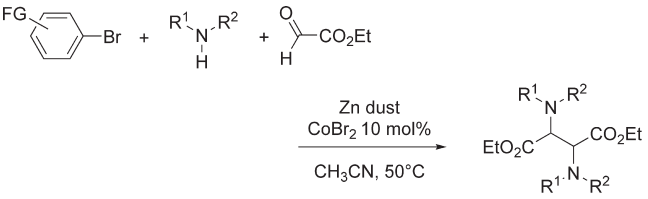



In a first set of experiments, we turned our attention to the synthesis of arylalanines. To this end, we envisaged to explore the reactivity of benzyl bromides in three-component couplings with amines and ethyl glyoxylate. Preliminary results indicated that these halides can be easily in situ metalated using zinc dust to afford coupling products in excellent yields. Consequently, we chose to simplify the process by operating under these Barbier-like conditions. Most general and efficient reaction conditions were defined as follows: acetonitrile is used as the solvent, zinc dust is used as the reductive metal, and the organic bromide (2.5 equiv[13]), the amine (1 equiv), and ethyl glyoxylate (1.3 equiv) are allowed to react at room temperature.[14] Under these conditions, reactions generally seemed to go to completion in less than 1 h. The results are presented in Table 1.

It appears that most benzyl bromides react quickly and efficiently with ethyl glyoxylate and a variety of amines, whatever the position of the functionality of the phenyl ring, and it is noteworthy that hindered benzyl bromides can also undergo the coupling (Table 1, entry 11). Another interesting result concerns the opportunity of operating with p-anisidine as the amine thus providing a potential access to proteinogenic phenylalanine derivatives by further oxidative deprotection of the p-methoxyphenyl (PMP) group (Table 1, entry 15).[15] It can also be mentioned that the reaction involving a *N*-substituted piperazine as the amine provides a slightly lower yield of the coupling product (Table 1, entry 3).[16]

In a second part of the study, we focused our research on the synthesis of arylglycines by using aromatic bromides in the process. Unfortunately, reactions with these halides were at once much more complicated to achieve because a cobalt catalyst is required during the arylzinc synthesis step, and Barbier-like conditions are not applicable. Indeed, under these latter conditions, it could be observed the major formation of a bis-amino ester resulting from the C−C reductive coupling of a formal iminium ion, in situ generated upon reaction between the amine and the aldehyde (Scheme 2).

**SCHEME 2. Attempted Three-Component Coupling Involving an Aryl Bromide under Barbier-like Conditions**




The formation of such compounds was also noticed, in some limited cases, when starting from benzyl bromides. However, only limited amounts could be detected in the reaction medium. This accounts for a competitive formation of the bis-amino ester and the three-component coupling product, and we assume that such a competition occurs in each case. Following this postulate, the fate of the reaction might clearly depend on the ease of formation of the organozinc reagent. Consequently, if the metalation of the organic halide is too slow, the reaction might lead to the major

(6) Grigg, R.; Sridharan, V.; Thayaparan, A. *Tetrahedron Lett*. **2003**, *44*, 9017–9019.

(7) (a) Ugi, I.; Meyer, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386–388. (b) Ugi, I. *Angew. Chem., Int. Ed. Engl*. **1962**, *1*, 8–21. (c) Dömling, A.; Ugi, I. *Angew. Chem*. **2000**, *112*, 3300–3344. (d) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed*. **2000**, *39*, 3168–3210.

(8) Kalinski, C.; Lemoine, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. *Synthesis* **2008**, 4007–4011.

(9) The Petasis reaction leads to α-amino acids with high yields. However, reaction times are generally important, and the reaction does not tolerate the presence of some electron-withdrawing groups connected to phenyl moieties. The Ugi reaction requires the use of cleavable isocyanides and a further hydrolysis step.

(10) (a) Le Gall, E.; Troupel, M.; Nédélec, J.-Y. *Tetrahedron Lett*. **2006**, *47*, 2497–2500. (b) Le Gall, E.; Troupel, M.; Nedelec, J.-Y. *Tetrahedron* **2006**, *62*, 9953–9965. (c) Sengmany, S.; Le Gall, E.; Le Jean, C.; Troupel, M.; Nédélec, J.-Y. *Tetrahedron* **2007**, *63*, 3672–3681. (d) Sengmany, S.; Le Gall, E.; Troupel, M. *Synlett* **2008**, 1031–1035. (e) Le Gall, E.; Haurena, C.; Sengmany, S.; Martens, T.; Troupel, M. *J. Org. Chem*. **2009**, *74*, 7970–7973.

(11) Haurena, C.; Sengmany, S.; Huguen, P.; Le Gall, E.; Martens, T.; Troupel, M. *Tetrahedron Lett*. **2008**, *49*, 7121–7123.

(12) Organozinc reagents are alkaline compounds.

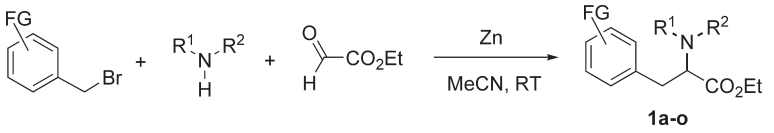
(13) It was mentioned in previous works that at least 2 equiv of the organozinc compound are required for the reaction to proceed efficiently.

(14) Although an exothermic reaction tends to develop, the temperature of the medium was not controlled. As a consequence, this rise of the medium temperature is sufficient to avoid a preliminary heating of ethyl glyoxylate (which is generally known to require a depolymerization step prior to use).

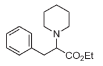
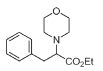
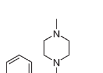
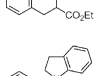
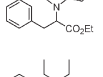
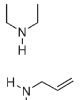
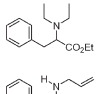
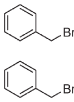
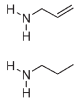
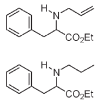
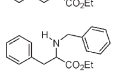
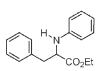
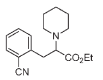
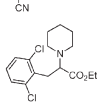
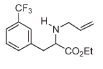
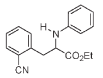
(15) (a) De Lamo Marin, S.; Martens, T.; Mioskowski, C.; Royer, J. *J. Org. Chem*. **2005**, *70*, 10592–10595. (b) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron Lett*. **2006**, *47*, 8109–8113.

(16) Piperazine derivatives generally furnish coupling products in lower yields. This behavior has already been observed in other studies conducted in our laboratory.

**TABLE 1. Three-Component Coupling between Benzyl Bromides, Amines, and Ethyl Glyoxylate[a]**




**1a-o**

| entry | benzyl bromide | amine | time (h) | product | | isolated yield (%) |
|---|---|---|---|---|---|---|
| 1 |  |  | 0.5 |  | **1a** | 95 |
| 2 |  |  | 1 |  | **1b** | 83 |
| 3 |  |  | 0.5 |  | **1c** | 41 |
| 4 |  |  | 0.5 |  | **1d** | 89 |
| 5 |  |  | 0.5 |  | **1e** | 93 |
| 6 |  |  | 0.33 |  | **1f** | 80 |
| 7 |  |  | 0.33 |  | **1g** | 83 |
| 8 |  |  | 0.5 |  | **1h** | 74 |
| 9 |  |  | 0.5 |  | **1i** | 65 |
| 10 |  |  | 1 |  | **1j** | 78 |
| 11 |  |  | 1 |  | **1k** | 87 |
| 12 |  |  | 1 |  | **1l** | 80 |
| 13 |  |  | 1 |  | **1m** | 55 |
| 14 |  |  | 1 |  | **1n** | 77 |
| 15 |  |  | 1 |  | **1o** | 67 |

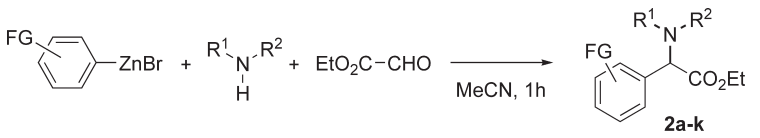
[a]Experiments were typically conducted with 40 mL of acetonitrile, 25 mmol of the benzyl bromide, 2.6 mL (13 mmol) of ethyl glyoxylate in toluene, 10 mmol of the amine, and 2 g (30 mmol) of zinc dust.

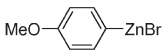
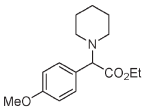
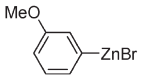
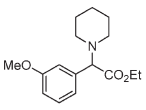
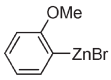
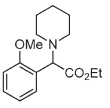
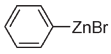
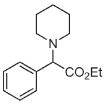
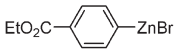
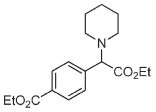
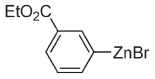
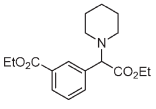
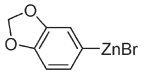
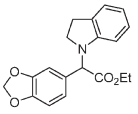
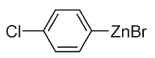
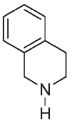
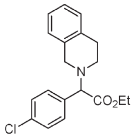
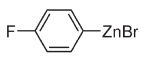
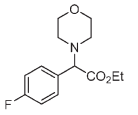
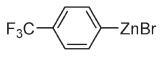
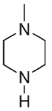
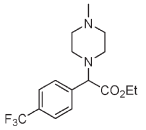
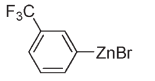
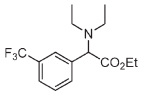
formation of the reductive coupling product. Considering that benzyl halides form organozinc reagents much more easily than aromatic bromides, they lead to the major formation of the three-component coupling product whereas aryl bromides do not.

With this limitation of the procedure in mind, we decided to realize some other preliminary experiments starting from preformed aromatic organozinc reagents. Thus, arylzinc reagents ( > 2 equiv) were generated in acetonitrile from aryl bromides using zinc dust and cobalt catalysis[17] and allowed to react with secondary amines (1 equiv) and ethyl glyoxylate (1.3 equiv). Results were generally unsatisfactory with only moderate conversion of the substrates into the expected α-amino esters, even after several hours at room temperature. We then envisaged optimizing the procedure and examined the influence of a set of parameters like the temperature of the medium, the amounts of reagents or the presence, during the coupling step, of additional salts like $ZnCl_2$, $CeCl_3$, CuI,

(17) (a) Fillon, H.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc.* **2003**, *125*, 3867–3870. (b) Kazmierski, I.; Gosmini, C.; Paris, J. −M.; Périchon, J. *Tetrahedron Lett.* **2003**, *44*, 6417–6420. (c) Gosmini, C.; Amatore, M.; Claudel, S.; Périchon, J. *Synlett* **2005**, 2171–2174.

**TABLE 2. Three-Component Coupling between Arylzinc Reagents, Secondary Amines, and Ethyl Glyoxylate**[a]




| entry | arylzinc reagent | amine | temp. (°C) | product | | isolated yield (%) |
|---|---|---|---|---|---|---|
| 1 |  |  | 25 |  | **2a** | 62 |
| 2 |  |  | 25 |  | **2b** | 60 |
| 3 |  |  | 25 |  | **2c** | 57 |
| 4 |  |  | 25 |  | **2d** | 88 |
| 5 |  |  | 50 |  | **2e** | 97[b] |
| 6 |  |  | 50 |  | **2f** | 54[b] |
| 7 |  |  | 25 |  | **2g** | 67[c] |
| 8 |  |  | 25 |  | **2h** | 66 |
| 9 |  |  | 25 |  | **2i** | 78 |
| 10 |  |  | 50 |  | **2j** | 37 |
| 11 |  |  | 50 |  | **2k** | 84 |

[a]Experiments were typically conducted with 25 mL of acetonitrile, ~15 mmol of the arylzinc bromide (preformed from 20 mmol of the corresponding aryl bromide), 2.6 mL (13 mmol) of ethyl glyoxylate in toluene, and 5 mmol of the amine. [b]Cobalt bromide 0.55 g (2.5 mmol) was added before coupling. [c]To the filtered organozinc solution was added the amine and ethyl glyoxylate.

$AlCl_3$, etc. over the reaction efficiency. These experiments, which were carried out using piperidine as a model amine, indicated that the temperature and the amount of ethyl glyoxylate are the most important reaction parameters. Thus, we could observe that the rise of the amount of ethyl glyoxylate has a general positive influence on the reaction efficiency, whatever the nature of the function connected to the phenyl moiety. The rise in temperature generally favors the three-component coupling except in the case of electron-rich arylzinc compounds for which the direct addition onto ethyl glyoxylate furnishing an alcohol rises upon heating, in particular when the glyoxylate is used in large excess. This is likely the consequence of a probable increased nucleophilicity compared to electron-deficient arylzinc reagents. For these latter compounds, it should be noted that the presence of an additional amount of cobalt bromide during the coupling step can promote the three-component reaction. This effect was observed in the particular case of an electron-deficient arylzinc reagent like 4-ethoxycarbonylphenylzinc bromide, which gave rise to the formation of the corresponding α-amino ester in almost quantitative yield (see below, Table 2, entry 5). This is not the case with electron-rich arylzinc reagents for which a further cobalt bromide addition tends again to afford mainly the benzhydryl alcohol. This unusual role of cobalt bromide was not explained so far.

In the following part of the study, we endeavored to take these indications into account to carry out three-component reactions between secondary amines, ethyl glyoxylate, and a range of preformed arylzinc reagents. A general procedure could be defined as follows: acetonitrile is used as the solvent, and the preformed arylzinc bromide ( > 2 equiv), the amine (1 equiv), and ethyl glyoxylate (2.6 equiv) are allowed to react for 1 h at room temperature or under moderate heating. The results are reported in Table 2.

These results indicate that an important range of functionalized arylzinc compounds and secondary amines is usable in the three-component reaction, providing an instant access to a variety of α-amino esters derivatives. In most cases, heating was not necessary, and reactions were conducted at room temperature. However, in agreement with the preliminary experiments discussed above, very satisfactory yields could be obtained from electron-deficient organozinc reagents provided that moderate heat is applied to the reaction medium (Table 2, entries 5, 6, 10, and 11).

Although the results reported herein provide representative examples of straightforward amino esters synthesis, the procedure suffers another drawback. As reported in a previous paper,[11] a limitation concerns the absence of three-component coupling when primary amines are used in the presence of aldehydes and aromatic organozinc reagents. This is likely due to the formation of imines whose limited reactivity toward nucleophiles is a well-known issue which might be overcome, for instance, by activation of the C=N bond under an acyliminium ion form.[18]

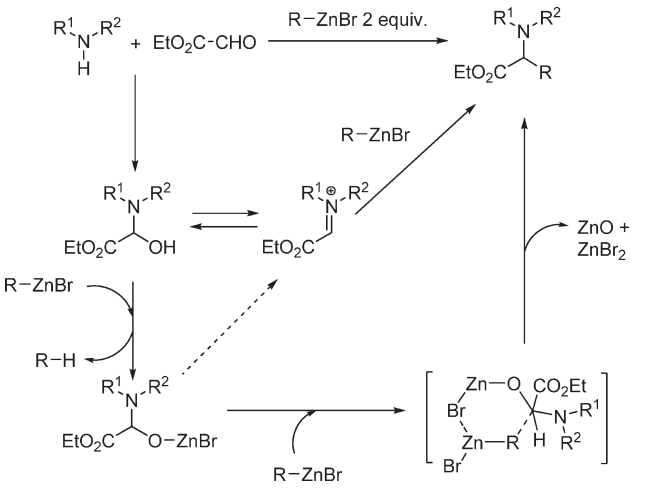



**FIGURE 1.** Plausible reaction pathways.

## Reaction Mechanism

The reaction mechanism remains unclear. Some works indicate that Bruylants-type reactions of α-aminonitriles are achievable using organozinc reagents as nucleophiles.[19] This suggests that these compounds constitute very convenient nucleophiles for addition onto iminium salts. Another possible mechanism is proposed by Fan and co-workers in a recent study dealing with the multicomponent reaction of allyl and benzylzinc halides, aldehydes, and primary amines.[20] It is mentioned that the imine, which is formed upon reaction between the amine and the aldehyde, is not the reactive electrophile of the process. It is suggested that the hemiaminal which is formed during the course of the reaction is deprotonated by the organozinc compound and that the resulting zinc alcoholate is subsequently engaged in a putative six-membered transition-state with a second equivalent of the organozinc to finally give rise to the formation of the three-component coupling product.

Both plausible reaction pathways are depicted in Figure 1.

Actually, we assume that the reaction pathway might not be univocal. Indeed, it was noticed that in close relationship with the aromatic or the benzylic nature of the organometallic, different amounts of ethyl glyoxylate are required for the reaction to proceed efficiently. We could also make the experimental observation that in situ metalations can be carried out only starting from benzyl bromides. These latter compounds are also able to react with aldehydes and primary amines whereas arylzinc compounds can not. Taken together, these results could simply indicate a significant difference of nucleophilicity between both organozinc species. However, this could also account for different reaction pathways, depending on the nature of the organic halide. Some further investigations dedicated to the comprehension of the reaction mechanism are currently in progress in the laboratory.

(18) For a review of additions to *N*-acyliminium ions, see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. For recent examples, see: (a) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497–1499. (b) Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2005**, *70*, 5133–5138. (c) Wei, C.; Li, C. -J. *Lett. Org. Chem.* **2005**, *2*, 410–414. (d) Black, D. A.; Arndtsen, B. A. *Tetrahedron* **2005**, *61*, 11317–11321. (e) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 1991–1993. (f) Zhang; Malinakova *C. J. Org. Chem.* **2007**, *72*, 1484–1487.

(19) (a) Le Gall, E.; Gosmini, C.; Troupel, M. *Tetrahedron Lett.* **2006**, *47*, 455–458. (b) Moumne, R.; Lavielle, S.; Karoyan, P. *J. Org. Chem.* **2006**, *71*, 3332–3334. (c) Bernardi, L.; Bonini, B. F.; Capito, E.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Ricci, A. *Synlett* **2003**, 1778–1782.

(20) Fan, R.; Pu, L.; Qin, L.; Wen, F.; Yao, G.; Wu, J. *J. Org. Chem.* **2007**, *72*, 3149–3151.

## Conclusion

In conclusion, we have demonstrated that non-natural α-aminoesters derived from phenylalanine and phenylglycine can be successfully obtained through a simple and efficient three-component reaction between ethyl glyoxylate, amines, and organozinc reagents. We could show that, while the formation of arylglycines has to be undergone starting from preformed arylzinc reagents, the synthesis of arylalanines can be realized in a single experimental step involving the in situ metalation of benzyl bromides and their subsequent three-component reaction with an amine and ethyl glyoxylate. Consequently, we found a reliable reaction system, able to provide an important variety of α-amino ester backbones in very useful reaction conditions, further making this strategy relevant for parallel synthesis. The extension of the process to cleavable amines, used as chiral auxiliaries, as well as the development of a chiral catalytic version of the reaction are currently under progress and will be reported in due course.

## Experimental Section

**Typical Procedure from Benzyl Bromides (A).** A dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (40 mL). Zinc dust (2 g, 30 mmol) and trifluoroacetic acid (0.2 mL) were added under vigorous stirring. After 5 min, the amine (10 mmol), ethyl glyoxylate (∼50% solution in toluene, 2.6 mL, ∼13 mmol), and the benzyl bromide (25 mmol) were added to the solution and allowed to react for 1 h at room temperature. The reaction was quenched with a saturated ammonium chloride solution (150 mL), and the organic products were extracted with dichloromethane (2 × 100 mL). After removal of the solvent, a chromatographic purification on neutral alumina using a pentane/diethyl ether mixture as an eluant (90/10→10/90) afforded the pure product. Alternatively, the pure α-amino ester could be obtained from the crude oil using an acid−base workup, as detailed in ref 10b.

**Typical Procedure from Aryl Bromides (B).** A dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (25 mL). Zinc dust (4 g, 61 mmol), trifluoroacetic acid (0.2 mL), and 1,2-dibromoethane (0.3 mL) were added, and the solution was heated under vigorous stirring until gas was evolved. Heating was stopped and the solution allowed to cool for 15 min. The aryl bromide (20 mmol) and cobalt bromide (0.44 g, 2 mmol) were added to the mixture, and after 30 min at room temperature, stirring was stopped and the surrounding solution was taken up using a syringe and transferred into another flask containing the amine (5 mmol) and ethyl glyoxylate (∼50% solution in toluene, 2.6 mL, ∼13 mmol, depolymerized prior to use by 30 min heating at 60 °C) in 10 mL of acetonitrile. After 1 h at room temperature, the reaction was quenched with a saturated ammonium chloride solution (100 mL), and the organic products were extracted with dichloromethane (2 × 100 mL). After removal of the solvent, a chromatographic purification on neutral alumina using a pentane/diethyl ether mixture as an eluant (90/10 → 10/90) afforded the pure product. Alternatively, the pure α-amino ester could be obtained from the crude oil using an acid−base workup, as detailed in ref 10b.

**Characterization Data for Compound 1a.** Obtained through typical procedure A as a colorless oil. $m$ = 2.48 g (95%). ATR-FTIR (neat, $cm^{-1}$): 2933, 1726, 1184, 1148, 1115, 1053, 747, 698. $^1H$ NMR (400 MHz): $\delta$ 7.29−7.18 (m, 5H), 4.11−4.03 (m, 2H), 3.41 (dd, $J$ = 9.8, $J$ = 5.5 Hz, 1H), 3.11−2.94 (m, 2H), 2.77−2.49 (m, 4H), 1.68−1.42 (m, 6H), 1.15 (t, $J$ = 7.1 Hz, 3H). $^{13}C$ NMR (100 MHz): $\delta$ 171.4, 138.4, 129.3, 128.2, 126.3, 70.4, 59.9, 51.1, 35.9, 26.5, 24.6, 14.4. MS $m/z$ (relative intensity): 188 ($[M - CO_2Et]^+$,79), 170 ($[M - PhCH_2]^+$,100), 142 (37), 124 (5), 105 (15), 96 (6). HRMS: calcd for $C_{16}H_{24}NO_2$ $[M + H]^+$ 262.1807, found 262.1815.

**Characterization Data for Compound 2a.** Obtained through typical procedure (B) as a yellow oil. $m$ = 0.86 g (62%). ATR-FTIR (neat, $cm^{-1}$): 2633, 1731, 1610, 1510, 1245, 1151, 1067, 835. $^1H$ NMR (400 MHz): $\delta$ 7.28 (d, $J$ = 8.7 Hz, 2H), 6.79 (d, $J$ = 8.7 Hz, 2H), 4.16−4.00 (m, 2H), 3.81 (s, 1H), 3.73 (s, 3H), 2.45−2.20 (m, 4H), 1.55−1.47 (m, 4H), 1.38−1.32 (m, 2H), 1.13 (t, $J$ = 7.1 Hz, 3H). $^{13}C$ NMR (100 MHz): $\delta$ 172.1, 159.5, 130.0, 128.3, 113.8, 74.4, 60.7, 55.3, 52.4, 25.8, 24.4, 14.2. MS $m/z$ (relative intensity): 204 ($[M - CO_2Et]^+$, 100), 136 (5), 121 (59). HRMS: calcd for $C_{16}H_{24}NO_3$ $[M + H]^+$ 278.1756, found 278.1745.

**Supporting Information Available:** Full experimental procedures, characterization data, and copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.