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# The design, synthesis, and application of a chiral coupling reagent derived from strychnine for the enantioselective activation of a carboxylic group

Beata Kolesińska [a,*], Katarzyna Kasperowicz [a], Marek Sochacki [b], Adam Mazur [a], Stefan Jankowski [a], Zbigniew J. Kamiński [a]

[a] Institute of Organic Chemistry, Technical University of Lodz, Zeromskiego 116, 90-924 Lodz, Poland
[b] Centre of Molecular and Macromolecular Studies, PAS, Sienkiewicza 112, 90-363 Lodz, Poland

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ABSTRACT

The concept of a chiral coupling reagent for the enantioselective synthesis of peptides with a predictable configuration and enantiomeric purity from racemic substrates is presented. The reagent was prepared by treatment of strychninium tetrafluoroborate with 2-chloro-4,6-dimethoxy-1,3,5-triazine in the presence of sodium bicarbonate yielding *N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)strychninium tetrafluoroborate in high yield, which is stable at room temperature, and in a broad range of solvents gave enriched Z-Ala-Phe-OMe (dr from 95/5 to 60/40) in high yield with D-configuration on the alanine residue starting from *rac*-Z-Ala-OH.



The structural diversity of chiral N-protected amino acid building blocks is severely limited due to the laborious procedures leading to their enantiomerically homogeneous forms. Isolation from natural products and biotechnological methodology often lead to a single enantiomer only, the opposite remaining unavailable. Even asymmetric synthesis is of limited value because of complex or tedious synthetic procedures and often restricted access to pools of chiral auxiliaries with both configurations. The most general approach based on the resolution of racemates usually leads to successful results, although in most cases, time-consuming experimental work is necessary followed by additional efforts to appropriately protect functional groups in the resolved substrates. Therefore, an alternative approach based on chiral kinetic resolution of easily available racemic forms would be advantageous.[1] Optically active *N*-hydroxysuccinimide[2] and diacylamine[3] derivatives were evaluated by several research groups as enantioselective reagents for condensation involving racemic amino components as well as carboxylic components, but none were found to be acceptable. More promising results were obtained using chiral DMAP analogues,[4,5] *N*-methylimidazole,[6] tertiary amines,[7] phosphines,[8] and others[9] as chiral auxiliaries. So far, however, all are unacceptable for peptide synthesis and combinatorial chemistry because of the unpredictable configuration, enantiomeric enrichment, and the unoptimized reaction conditions, scope, and limitations of these methods. In all the cases, predicting the synthetic results requires studies on sterically complex relations involving at least three stereogenic centers. The consequence is that in the case of known approaches to enantioselective coupling, n modifications of the chiral reagent generate a collection of 2n diversified, diastereomeric intermediates, and detailed synthetic studies are necessary in order to predict their properties, reactivity, configuration, ee, and favorable coupling conditions.

Hence it is necessary to design an efficient enantioselective coupling reagent that overcomes the problems of the predictability of synthetic results, optimal coupling conditions, high overall yield, configuration, and the enantiomeric composition of the final product. We present herein a novel general approach toward designing a chiral reagent for the selective activation of preferred enantiomers from a racemic mixture of N-protected amino acids. To achieve this goal, a chiral auxiliary has been incorporated into the leaving group fragment which departs from the reacting system during the activation stage.

According to the concept, an enantioselective coupling reagent is a binary system consisting of a chiral auxiliary (L*) which is active during the enantio-discriminating activation of the carboxylic component and subsequently departs after completion of the process. Thus, the structure, reactivity, and properties of the activated carboxylic component should be exactly the same as those in reactions involving classic achiral reagents. Moreover, due to the departure of the chiral auxiliary after activation, all further stages of the coupling procedure should remain free from problems caused by the presence of the additional chiral center of the auxiliary, and therefore the configuration and enantiomeric purity, once established during the activation, should remain essentially intact in all the syntheses involving this carboxylic component and reagent.

Taking advantage of the modular structure of triazine coupling reagents, we attempted to prepare chiral *N*-triazinylammonium

* Corresponding author. Tel.: +48 426313221.
*E-mail address:* beata.kolesinska@p.lodz.pl (B. Kolesińska).

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salts as promising candidates for implementing this idea. In our preliminary studies, we observed the kinetic resolution of racemic carboxylic acids on activation by 2-chloro-4,6-dimethoxy-1,3,5-triazine in the presence of chiral amines such as strychnine, quinine, and sparteine. Under favorable circumstances, couplings using the above-mentioned reagents yielded excellent selectivity[10] with the Kagan coefficient exceeding s>100. However, due to the multistage formation of the enantioselective coupling reagent, relatively dispersed values of enantiomeric enrichment were observed in less experienced hands. Therefore, efforts were made to eliminate this disadvantage and to prepare a stable chiral coupling reagent for expedient enantioselective syntheses.

Treatment of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) with chiral tertiary amines **2a–e** possessing a stereogenic center at the nitrogen atom gave *N*-triazinylammonium chlorides **3a–e/Cl⁻** (Fig. 1) which were isolated and their structures were confirmed by $^1$H NMR and MS spectroscopy (see Table 1).

In the positive ion FAB mass spectra of *N*-triazinylammonium chlorides **3a-f**, peaks corresponding to *N*-triazinylammonium cations $[M-Cl^-]^+$ were observed at relative intensities from 20% to 100%. The base peaks corresponded to protonated tertiary amines, which are formed easily due to the high proton affinity of the amines. However, it was observed that in the anhydrous state **3a–f** were unstable and spontaneously decomposed even at low temperature, probably by dealkylation caused by the presence of a nucleophilic chloride anion.[11]

It is already well known that the addition of a protic solvent stabilizes quaternary ammonium salts, but in these cases, addition of protic solvents strongly decreased the enantioselectivity and therefore this approach was abandoned. We found it more promising to replace the relatively nucleophilic chloride anion with a much less nucleophilic tetrafluoroborate counterion.[12] On treatment of strychninium tetrafluoroborate with **1** in the presence of sodium bicarbonate, stable *N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)strychninium tetrafluoroborate (**4**) was obtained in 82% yield. The structure of **4** was confirmed by NMR studies. The presence of three bond [$^3J$(C,H)] correlations in the HMBC spectrum between the triazine carbon and the methylene protons in the strychnine residue unambiguously supports the formation of a new carbon-nitrogen bond. Analysis of the $^{13}$C NMR spectrum showed that quaternization of the nitrogen atom in **4** causes a strong downfield shift of adjacent carbon resonances in comparison to the $^{13}$C NMR spectrum of unsubstituted strychnine.[13]

In accordance with our assumption, **4** was found to be stable enough at room temperature in a broad range of aprotic solvents to accomplish systematic studies on the activation of a range of carboxylic acids. It has been shown that reaction of **4** with 4-methoxybenzoic acid yielded the 'superactive' ester 4,6-dimethoxy-1,3,5-triazin-2-yl 4-methoxybenzoate (**5a**) being identical with a product formed in the reaction involving the classic achiral reagent 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate (**6**) (see Table 2, entry 1).

The relatively slow activation was substantially accelerated by the treatment with additional or catalytic amounts of base (Table 2; entries 3–5). Under optimal conditions, in the presence of 10% equiv of the base, activation proceeded efficiently in 2.5 h.

For studies on the enantioselectivity of activation, *rac*-Z-Ala-OH was used as a carboxylic component yielding, with H-Phe-OMe, a mixture of diastereomers easily distinguished by the presence of methyl doublets in the $^1$H NMR spectrum. As expected, it was found that chiral coupling reagent **4** activated the enantiomers of *rac*-Z-Ala-OH at a different rate (Scheme 1). Experiments with

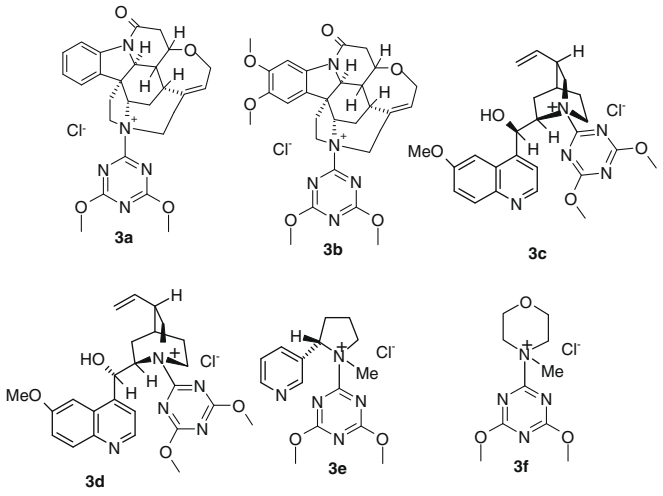



**Figure 1.** Structures of *N*-triazinylammonium chlorides **3a–f**.

**Table 1**
*N*-Triazinylammonium chlorides **3a–f** prepared by treatment of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) with tertiary amines **2a–f**

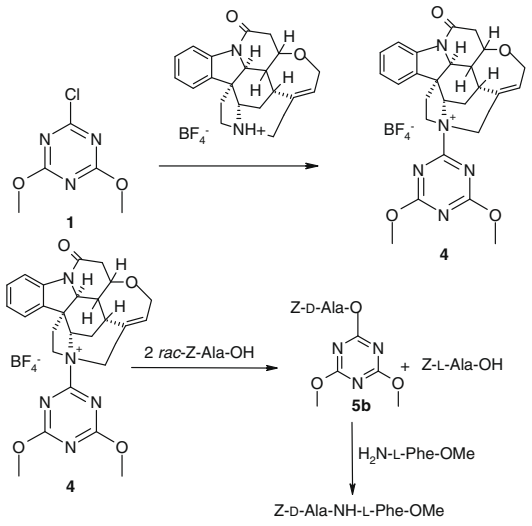
| Entry | Amine **2** | **3a–f** $[M\text{-}Cl^-]^+$ | **2a–f** $M+H^+$ |
|---|---|---|---|
| 1 | Strychnine (**2a**) | 474.4 | 335.2 |
| 2 | Brucine (**2b**) | 534.3 | 395.4 |
| 3 | Quinine (**2c**) | 464.3 | 325.3 |
| 4 | Quinidine (**2d**) | 464.3 | 325.3 |
| 5 | Nicotine (**2e**) | 441.3[a] | — |
| 6 | NMM[b] (**2f**) | 241.2 | — |

[a] 441.3 (**2e**+2CDMT+$H^+$).
[b] Achiral, model compound.

**Table 2**
Synthesis of 4,6-dimethoxy-1,3,5-triazin-2-yl 4-methoxybenzoate (**5a**) using **4**

| Entry | Time of activation (h) | Amount of tertiary amine | Yield (%) |
|---|---|---|---|
| 1[a] | 1.5 | 100% (**2f**) | 86 |
| 2 | 24 | — | 88 |
| 3 | 2 | 100% (**2g**)[b] | 85 |
| 4 | 2.5 | 10% (**2g**) | 86 |
| 5 | 2.5 | 10% strychnine (**2a**) | 85 |

[a] Synthesis of **5a** using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate (**6**).
[b] DIPEA (**2g**).




**Scheme 1.** Enantioselective peptide synthesis from a racemic substrate and chiral coupling reagent **4**.

**Table 3**
Enantioselective coupling of 2 equiv of *rac*-Z-Ala-OH with $NH_2$-L-Phe-OMe using **4** in different solvents in the presence of 10% of amine as additive (activation time 30 min)

| Entry | Additive | Solvent | Yield (%) | DL/LL |
|---|---|---|---|---|
| 1 | 10% Strychnine | THF | 68 | 80/20 |
| 2 | 10% Strychnine | DMF | 93 | 60/40 |
| 3 | 10% Strychnine | 1,2-Diethoxyethane | 78 | 84/16 |
| 4 | 10% Strychnine | EtOAc | 89 | 78/22 |
| 5 | 10% Strychnine | THF–*t*-BuOH (1:1) | 89 | 60/40 |
| 6 | 10% Strychnine | $CHCl_3$ | 96 | 83/17 |
| 7 | 10% Strychnine | $CH_3CN$ | 87 | 95/5 |
| 8 | 10% Strychnine | $CH_2Cl_2$ | 90 | 88/12 |
| 9 | 10% DIPEA | $CH_2Cl_2$ | 93 | 85/15 |
| 10 | 10% DIPEA | $CH_3CN$ | 89 | 90/10 |

two equivalents of the racemic carboxylic component gave a mixture of diastereomeric Z-Ala-Phe-OMe with the DL/LL ratio ranging from 60/40 to 95/5. Thus, in all the experiments, the D enantiomer **5b** was preferred in activation by **4**. The enantiomeric enrichment strongly depended on the solvent used.

The best results (dr 95/5, Table 3, entry 7) were obtained in acetonitrile in the presence of a catalytic amount of strychnine as additive. The least satisfying dr 60/40 was obtained in polar DMF as solvent (entry 2) and a THF–*t*-BuOH (1:1) mixture (entry 5). The control experiment involving coupling *rac*-Z-Ala-OH with *rac*-$NH_2$-Phe-OMe using achiral **6** demonstrated a relatively small, but opposite, effect on the diastereoselectivity of coupling by means of triazine superactive esters, diminishing the final enantioselectivity. Considering the extremely reduced excess of racemic components (2 equiv of racemate to 1 equiv of coupling reagent), the enantioselectivity of the presented procedure can be evaluated as very promising with the calculated Kagan coefficient reaching $s = 40$, which is in the range of the best results reached in the enantioselective process based on kinetic resolution.[14]

Therefore, studies on the scope and limitations of this approach are ongoing.

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## Supplementary data

Supplementary data (representative experimental details for the synthesis and characterization data for all the new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.105.

## References and notes

1. Wyatt, P.; Warren, S. *Workbook for Organic Synthesis: Strategy and Control*; J. Wiley & Sons: Chichester, 2008.
2. (a) Takeda, K.; Tsuboyama, K.; Suzuki, A.; Ogura, H. T. *Chem. Pharm. Bull.* **1985**, *33*, 2545; (b) Teramoto, T.; Deguchi, M.; Kurosaki, T. *Tetrahedron Lett.* **1981**, *22*, 1109; (c) Markowicz, S. W.; Karolak-Wojciechowska, J. *Pol. J. Chem.* **1994**, *68*, 1973.
3. (a) Murakami, Y.; Kondo, K.; Miki, K.; Akiyama, Y.; Watanabe, T.; Yokoyama, Y. *Tetrahedron Lett.* **1997**, *38*, 3751; (b) Kondo, K.; Kurosaki, T.; Murakami, Y. *Synlett* **1998**, 725; (c) Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J.; Russel, D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4413; (d) Evans, D. A.; Andersen, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, *34*, 5563; (e) Maezaki, N.; Furusawa, A.; Uchida, S.; Tanaka, T. *Tetrahedron* **2001**, *57*, 9309.
4. (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412; (b) Fu, G. C.; Yutaka, I. *Chem. Commun.* **2000**, 119; (c) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234; (d) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925; (e) Mermerian, A. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 949.
5. (a) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154; (b) Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, *68*, 7379; (c) Kawabata, T.; Stragies, R.; Fukaya, T.; Nagaoka, Y.; Schedel, H.; Fuji, K. *Tetrahedron Lett.* **2003**, *44*, 1545; (d) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844; (e) Dalaigh, C. O.; Hynes, S. J.; O'Brien, J. E.; McCabe, T.; Maher, D. J.; Watson, G. W.; Connon, S. J. *Org. Biomol. Chem.* **2006**, *4*, 2785; (l) Anstiss, M.; Nelson, A. *Org. Biomol. Chem.* **2006**, *4*, 4135.
6. (a) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481; (b) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496; (c) Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2824; (d) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226.
7. Terakado, D.; Koutaka, H.; Oriyama, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1157.
8. For a review, see: Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.
9. (a) Arseniyadis, S.; Valleix, A.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3314; (b) Pelotier, B.; Priem, G.; Macdonald, S. J. F.; Anson, M. S.; Upton, R. J.; Campbell, I. B. *Tetrahedron Lett.* **2005**, *46*, 9005; (c) Lewis, C. A.; Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3021; (d) Birman, V. B.; Jiang, H.; Li, X. *Org. Lett.* **2007**, *9*, 3237; (e) Kosugi, Y.; Akakura, M.; Ishihara, K. *Tetrahedron* **2007**, *63*, 6191; (f) Stamatov, S. D.; Stawinski, J. *Org. Biomol. Chem.* **2007**, *5*, 3787; (g) Karnik, A. V.; Kamath, S. S. *J. Org. Chem.* **2007**, *72*, 7435; (h) Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2006**, *62*, 285; (i) Terakado, D.; Oriyama, T. *Org. Synth.* **2006**, *83*, 70; (j) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536; (k) Moretto, A.; Peggion, C.; Formaggio, F.; Crisma, M.; Kaptein, B.; Broxterman, Q. B.; Toniolo, C. *Chirality* **2005**, *17*, 481.
10. Kamiński, Z. J.; Kolesińska, B.; Kamińska, J. E.; Góra, J. *J. Org. Chem.* **2001**, *66*, 6276.
11. (a) Sabatino, G.; Mulinacci, B.; Alcaro, M. C.; Chelli, M.; Rovero, P.; Papini, A. M. *Lett. Pept. Sci.* **2002**, *9*, 119; (b) Kolesińska, B.; Kamiński, Z. J. *Pol. J. Chem.* **2008**, *82*, 2115; (c) Kolesinska, B.; Kaminski, Z. J. *Tetrahedron* **2009**, *65*, 3573.
12. Kamiński, Z. J.; Kolesińska, B.; Kolesińska, J.; Sabatino, G.; Chelli, M.; Rovero, P.; Błaszczyk, M.; Główka, M. L.; Papini, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 16912–16920.
13. (a) Martin, G. E.; Hadden, C. E.; Crouch, R. C.; Krishnamurthy, V. V. *Magn. Reson. Chem.* **1999**, *37*, 517; (b) Thiele, C. M. *J. Org. Chem.* **2004**, *69*, 7403.
14. Kolesińska, B.; Kamiński, Z. J. *Org. Lett.* **2009**, *11*, 765–768.