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$TiCl_4$-Promoted Multicomponent Reaction: A New Entry to Functionalized α-Amino Acids

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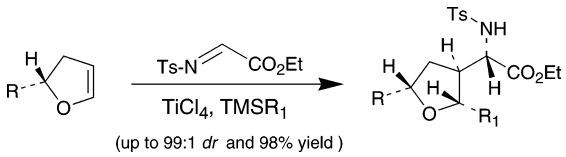
ABSTRACT



$TiCl_4$-promoted multicomponent reactions involving *N*-tosyl imino ester, cyclic enol ether, and silane reagents in a single one-pot operation provide functionalized α-amino acids with multiple stereogenic centers in good to excellent yields. Cis/trans selectivities with optically active substituted dihydrofurans have been investigated.

The biological relevance of unnatural α-amino acids continues to foster immense interest in their design and synthesis. As a consequence, a number of effective methodologies have been developed over the years.[1] In continuation of our interest in probing enzyme active sites with designed ligands, we required a range of α-amino acids with cyclic ether templates. The use of such amino acids, particularly those that contain a tetrahydrofuran or tetrahydropyran ring, has been limited by the lack of effective and practical methodologies for their synthesis.[2] Our interest in this area has now led us to devise a straightforward approach to these heterocyclic amino acids using multicomponent reactions.

Recently, we developed syntheses of a variety of substituted tetrahydrofurans and tetrahydropyrans by a novel multicomponent coupling reaction.[3] We now plan to develop this reaction further so as to provide functionalized, complex amino acids in a single one-pot operation. Herein, we report $TiCl_4$-promoted multicomponent reactions with an *N*-tosyl imino ester that provide rapid access to functionalized α-amino acids containing up to three contiguous chiral centers in good to excellent isolated yields. Asymmetric reactions with optically active substituted dihydrofurans are also reported; these proceed with excellent diastereoselectivities.

Our basic strategy for the synthesis of functionalized heterocyclic amino acids is depicted in Scheme 1. Since our previous multicomponent reactions with glyoxalates and pyruvates were remarkably efficient, we initially investigated the reaction of the *N*-benzyl imine of ethyl glyoxalate with dihydrofuran and triethylsilane. However, the desired condensation product could not be obtained under a variety of reaction conditions. Since *N*-tosyl imines of ethyl glyoxalate are much more stable and can be prepared readily, we examined subsequent multicomponent reactions with the *N*-sulfonyl imino ester **1**. Weinreb and co-workers were the first to show the utility of such imino esters in thermal ene reactions.[4] More recently, Lectka et al.[5] have shown the application of this imino ester in enantioselective alkylation reactions leading to α-amino acids.

(1) For recent reviews of amino acid synthesis: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergammon, New York, 1989. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (d) Hegadus, L. *Acc. Chem. Res.* **1995**, *28*, 299. (e) Boger, D. L.; Patane, M. A.; Zhou, J. J. *J. Am. Chem. Soc.* **1994**, *116*, 8544.

(2) Ghosh, A. K.; Thompson, W. J.; McKee, S. P.; Duong, T. T.; Lyle, T. A.; Chen, J. C.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 292.

(3) (a) Ghosh, A. K.; Kawahama, R.; Wink, D. *Tetrahedron Lett.* **2000**, *41*, 8425. (b) Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 1083. (c) Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 4751.

(4) (a) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058. (b) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131.

(5) Ferraris, D.; Young, B.; Cox, C.; Dudding, C.; Drury, W. J.; Ryzhkow, L.; Taggi, A.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67.

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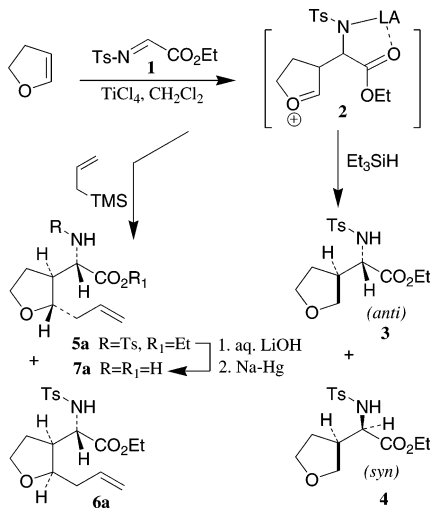
Scheme 1. Multicomponent Reactions with *N*-Tosyl Imino Ester and Dihydrofuran and Silanes



After surveying a number of Lewis acids, we found that the multicomponent reactions could be carried out effectively with $TiCl_4$. Accordingly, freshly distilled *N*-tosyl imino ester (**1**, 1 equiv) and 2,3-dihydrofuran (1.2 equiv) in CH_2Cl_2 were treated with $TiCl_4$ (1 M in CH_2Cl_2, 1.2 equiv) at −78 °C for 1 h. Triethylsilane (3 equiv) was added, and the resulting reaction mixture was allowed to stir at −78 °C for 2 h. After this period, the reaction was quenched with saturated aqueous $NaHCO_3$ solution at −78 °C and warmed to 23 °C. Standard workup and flash chromatography over silica gel provided a single condensation product **3** in 71% yield as a single diastereomer (by ^1H and ^{13}C NMR analysis).

When the presumed oxocarbenium ion derived from the reaction of *N*-tosyl imino ester (**1**) and 2,3-dihydrofuran was reacted with allyltrimethylsilane as a nucleophile, the reaction proceeded smoothly (−78 °C for 2 h). However, multicomponent products **5a** and **6a** were obtained as a 2.4:1 mixture, which were separable by silica gel chromatography. As depicted in Figure 1, the relative stereochemistry of the major diastereomer **5a** was determined by X-ray crystallography.[6] The major diastereomer **5a** was converted to amino acid **7a** by a two-step sequence involving saponification by aqueous LiOH followed by exposure of the resulting acid to Na−Hg in methanol at reflux. Functionalized amino acid **7a** was obtained in 98% for the two-step sequence.

(6) Crystal data for **5a**: $C_{18}H_{25}NO_5S$; MW = 367.45; colorless crystal; crystal system, block; space group, *P*21/*c*; cell parameters, a = 23.9477 Å, b = 9.0234 Å, c = 18.1405 Å, β = 104.100(2)°, V = 3801.9(5) Å^3, Z = 8; Mo Kα radiation (λ = 0.71073 Å, T = 173(2) K, R_1 = 0.0542, wR_2 = 0.1053 ($I > 2\sigma(I)$); R_1 = 0.1264, wR_2 = 0.1214 (all data). Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (deposition no. 252667). Crystal data for **13**: $C_{21}H_{25}NO_5S$; MW = 403.48; colorless crystal; crystal system, block; space group, *P*21/*c*; cell parameters, a = 17.9352 Å, b = 6.2661 Å, c = 18.4264 Å, β = 93.710(2)°, V = 2066.5-(3) Å^3, Z = 4; Mo Kα radiation (λ = 0.71073 Å, T = 298(2) K, R_1 = 0.0657, wR_2 = 0.1747 ($I > 2\sigma(I)$); R_1 = 0.1049, wR_2 = 0.1988 (all data). Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (deposition no. 252668). These data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif, by email to data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

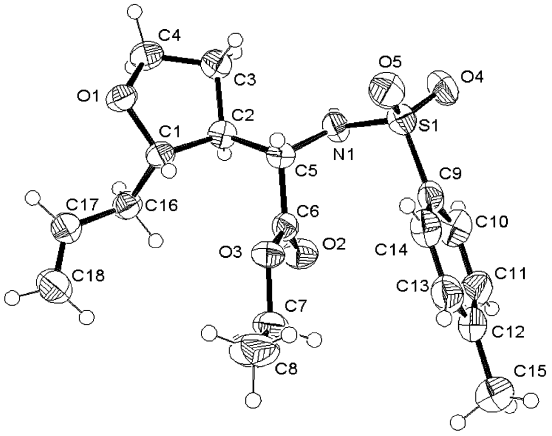


Figure 1. ORTEP drawing of X-ray structure of **5a**.

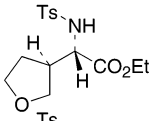
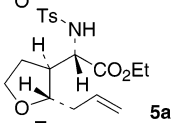
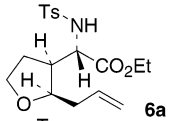
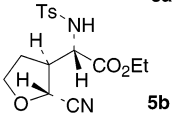
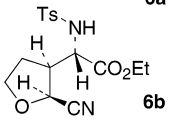
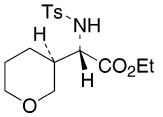
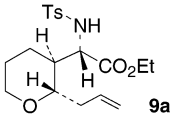
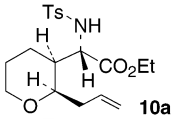
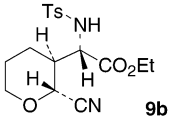
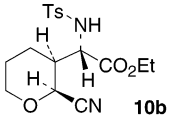
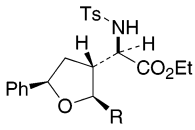
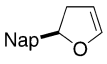
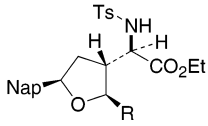
The feasibility of this multicomponent reaction was examined with dihydropyran and the substituted optically enriched dihydrofurans **11** and **12** in the presence of a number of nucleophiles. The results are summarized in Table 1. Reaction of dihydrofuran-derived oxocarbenium ion with trimethylsilyl cyanide provided the corresponding nitrile **5b** with excellent selectivity (99:1, entry 3). Reaction with 3,4-dihydro-2-*H*-pyran and triethylsilylsilane as the nucleophile proceeded with excellent diastereoselectivity (entry 4). The corresponding reactions with allyltrimethylsilane provided a 3:1 mixture of diastereomers in excellent yield (entry 5). Unlike dihydrofuran, reaction of the dihydropyran-derived oxocarbenium ion with trimethylsilyl cyanide provided significantly lower selectivity (4:1, entry 6).

We have investigated the stereochemical outcome of our multicomponent reaction with dihydrofurans having aryl substituents at the 5-position. Multicomponent reactions of *N*-tosyl imino ester with racemic phenyl dihydrofuran in the presence of triethylsilane as the nucleophile and CH_3CN as an additive provided a single diastereomer **13** in 71% yield (entry 7). The presence of CH_3CN prevented the formation of an unidentified byproduct. The scope of this additive effect is being investigated in detail. The assignment of the relative stereochemistry of the three chiral centers of **13** was made by X-ray crystallography.[6] As can be seen in Figure 2, the relative stereochemistry of the α-tosylamine and β-tetrahydrofuranyl chiral centers in **13** is the same as that in derivative **5a**. Encouraged by this stereochemical outcome, we subsequently prepared phenyl and naphthyl dihydrofurans in optically active form and investigated the issue of diastereoselection with a variety of nucleophiles. The phenyl and 2-naphthyl dihydrofurans **11** and **12** were prepared using asymmetric Heck reactions[7] in optically enriched form.[8] As shown, when the above reaction was carried out with optically active phenyl dihydrofuran in the presence of

(7) (a) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 1485. (b) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.

(8) Optical purities of 5-phenyl and 5-naphthyl dihydrofuran were 89 and 88% ee, respectively.

Table 1. $TiCl_4$-Promoted Multicomponent Reactions of *N*-Tosyl Imino Ester with Vinyl Ethers[a]

entry	vinyl ether	nucleophile	major Product(s)	ratio [b]	yield (%)[c]
1		Et_3SiH	 **3**	99 : 1	71
2	"	Me_3Si 	 **5a**  **6a**	2.4 : 1[d]	79
3	"	Me_3SiCN	 **5b**  **6b**	99 : 1	64
4		Et_3SiH	 **8**	99 : 1	98
5	"	Me_3Si 	 **9a**  **10a**	3 : 1[d]	94
6	"	Me_3SiCN	 **9b**  **10b**	4 : 1[d]	98
7	 **11**	Et_3SiH	 **13** (R = H)	99 : 1[e]	71
8		Me_3SiCN	**14** (R = CN)	95 : 5	88
9		Me_3Si 	**15** (R = $CH_2CH{=}CH_2$)	99 : 1[e]	84
10	 **12**	Et_3SiH	 **16** (R = H)	98 : 2[e]	65
11		Me_3SiCN	**17** (R = CN)	99 : 1	59
12		Me_3Si	**18** (R = $CH_2CH{=}CH_2$)	99 : 1[e]	84

[a] All reactions were carried out as described in the text. [b] Determined by ^1H NMR for entries 1−12 and by LCMS for entries 7−9. [c] Isolated yield. [d] Ring stereochemistry was assigned after NOESY experiment. [e] CH_3CN (5 equiv) was added as an additive; see Supporting Information for experimental details.

trimethylsilyl cyanide, it afforded diastereomer **14** as a major product (mixture ratio 95:5, entry 8). The corresponding reaction with allyltrimethylsilane as a nucleophile provided single product **15** in excellent yield (entry 9). Optical purities of compounds **14** and **15** were determined by reduction of these compounds with $LiAlH_4$ in ether at 0 °C followed by conversion of the respective alcohol to the Mosher ester.[9] The ^{19}F NMR analysis of the Mosher esters established optical purities of 84 and 86% ee for **14** and **15**, respectively. The depicted absolute and relative stereochemistry was assigned on the basis of the X-ray structure of **13** as well as extensive NOESY experiments on compounds **14** and **15** (Figure 3). We have also investigated stereoselection in the multicomponent reactions with naphthyl dihydrofuran (entries 10−12). These reactions also proceeded with excellent diastereoselectivities and isolated yields.

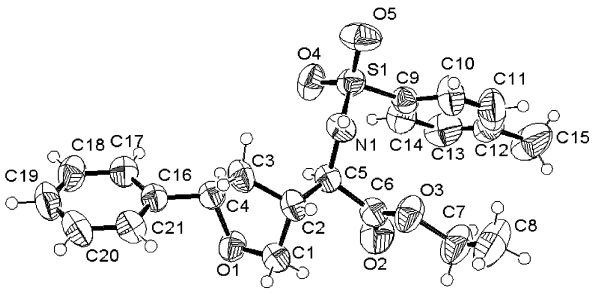


Figure 2. ORTEP drawing of X-ray structure of **13**.

To rationalize the stereoselectivities observed, we propose stereochemical models **A** and **B**. In these we postulate that one of the electron pairs of the ethoxy oxygen is donated to the oxo carbenium ion from the pseudoaxial side for stabilization of the transition state (Figure 4). Titanium metal chelation with sulfonyl oxygen is also proposed. Walsh and co-workers have documented such metal chelation by X-ray

(9) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

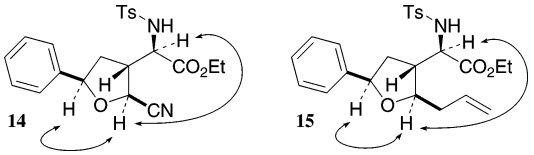


Figure 3. Observed NOE effects on **14** and **15**.

crystallography.[10] Multicomponent reaction with *N*-tosyl imino ester **1** and dihydrofuran presumably proceeds through transition state model **B** (*exo*) as opposed to model **A** (*endo*). Model **B** is preferred because of the absence of the developing nonbonded interaction between the tetrahydrofuran ring and the chelated titanium metal. The observed stereochemical outcome in various reactions is consistent with the proposed models.

In summary, the $TiCl_4$-promoted multicomponent coupling reaction of *N*-tosyl imino ester, cyclic enol ethers, and carbon nucleophiles has provided stereocontrolled access to unnatural THP- and THF-containing amino acids with multiple stereocenters. The overall protocol is practical and quite efficient. Further studies and applications are currently under investigation.

(10) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423.

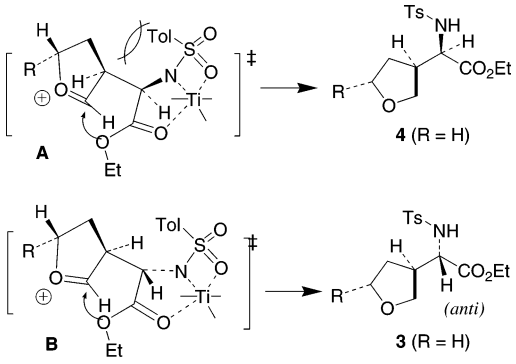


Figure 4. Stereochemical models.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for compounds **3**−**10** and **13**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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