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# Mitsunobu Approach to the Synthesis of Optically Active α,α-Disubstituted Amino Acids

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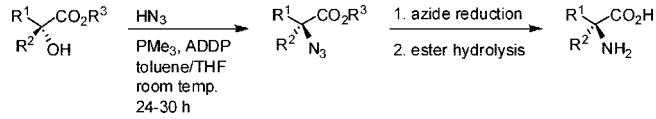
## ABSTRACT




**Chiral tertiary α-hydroxy esters of known stereochemical configuration were transformed to α-azido esters by Mitsunobu reaction with $HN_3$. Optimization of this reaction was shown to proceed at room temperature with high chemical yield using 1,1-(azodicarbonyl)dipiperidine (ADDP) and trimethylphosphine ($PMe_3$). Complete inversion of configuration was observed at the α-carbon. Several α,α-disubstituted amino acids were synthesized in high overall chemical yield and optical purity.**

Quaternary α-amino acids have been incorporated as building blocks into synthetic peptides and in efforts to elucidate and enhance biological activity. α,α-Disubstituted amino acids have been shown to affect the conformation, biological activity, and stability of peptides.[1] Despite their importance in medicinal and biological chemistry, nonproteinogenic nonracemic amino acids remain challenging synthetic targets.

A survey of the chemical literature concerning nonracemic α,α-disubstituted amino acids reveals a variety of synthetic methods.[2] The strategies employed can be classified according to the order of placement of the acid and amino moieties along with two variable functional groups on the α-carbon.[2f]

To date, relatively few examples have been reported in which the amino group is the last to be introduced at the α-carbon. These examples include rearrangements,[3] reactions with electrophilic[4] or nucleophilic[5] nitrogen sources, and reactions involving chiral aziridines.[6] We herein report the use of hydrazoic acid[7] in the Mitsunobu reaction[8] to convert chiral α-hydroxy esters into α,α-disubstituted amino acids. This new route provides two advantages in that the azide acts

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(1) (a) Ripka, W. C.; De Lucca, G. V.; Back, A. C., II; Pottorf, R. S.; Blaney, J. M. *Tetrahedron* **1993**, *49*, 3593–3608. (b) Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389–397. (c) Sagan, S.; Karoyan, P.; Lequin, O.; Chassaing, G.; Lavielle, S. *Current Med. Chem.* **2004**, *11*, 2799–2822.

(2) (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732. (d) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, *512*, 7–5143. (e) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430. (f) Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623.

(3) (a) Tanaka, M.; Oba, M.; Tamai, K.; Suemune, H. *J. Org. Chem.* **2001**, *66*, 2667–2673. (b) Wu, Z.-L.; Li, Z.-Y. *J. Org. Chem.* **2003**, *68*, 2479–2482. (c) Cristau, H.-J.; Marat, X.; Vors, J.-P.; Pirat, J.-L. *Tetrahedron Lett.* **2003**, *44*, 3179–3181.

(4) Smulik, J. A.; Vedejs, E. *Org. Lett.* **2003**, *5*, 4187–4190.

(5) For selected examples involving azide, see: (a) Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 5240–5244. (b) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahetron: Asymmetry* **2001**, *12*, 949–957. (c) Martín, R.; Islas, G.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **2001**, *57*, 6367–6374. (d) Pedregal, C.; Prowse, W. *Bioorg. Med. Chem.* **2002**, *10*, 433–436. (e) Sato, K.-i.; Sekiguchi, T.; Hozumi, T.; Yamazaki, T.; Akai, S. *Tetrahedron Lett.* **2002**, *43*, 3087–3090. (f) Masaki, Y.; Arasaki, H.; Iwata, M. *Chem. Lett.* **2003**, *32*, 4–5. (g) Forman, G. S.; Scaffidi, A.; Stick, R. V. *Aust. J. Chem.* **2004**, *57*, 25–28.

(6) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365.

(7) CAUTION: Hydrazoic acid is toxic and potentially explosive. All procedures using hydrazoic acid should be performed behind a safety shield in a well-ventilated hood.

10.1021/ol802325h CCC: $40.75 
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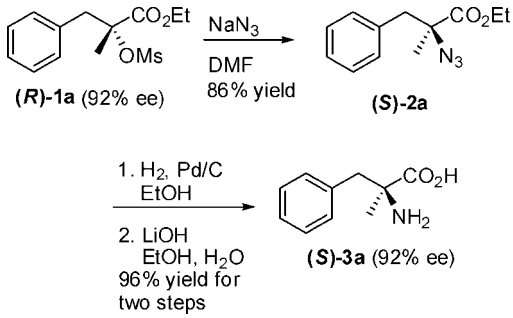
**Scheme 1.** Synthesis of α-Methylphenylalanine from α-Mesylate Ester Using $NaN_3$ in DMF



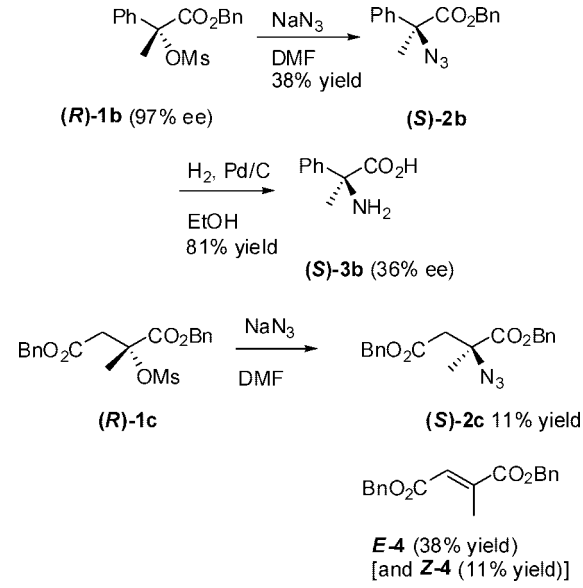

effectively as a masking group eliminating the need for nitrogen protection and readily available chiral starting materials are utilized.

In the course of studying the reactivity of tertiary leaving groups, we discovered that mesylate **(*R*)-1a** reacted smoothly with excess $NaN_3$ at room temperature to give azide **(*S*)-2a** with complete inversion of stereochemical configuration (Scheme 1). Azide reduction and ester hydrolysis gave (*S*)-α-methylphenylalanine [**(*S*)-3a**] in high overall yield. These results were intriguing in light of the fact that $S_N2$ displacements at tertiary centers are rare.[5] However, the scope of this strategy was found to be limited. Mesylate **(*R*)-1b** decomposed rapidly at room temperature, which required that it be reacted immediately with $NaN_3$ in DMF to give moderate yields of azide **(*S*)-2b** (Scheme 2). Simultaneous hydrogenolysis of the benzyl ester and azide reduction gave (*S*)-α-methylphenylglycine [**(*S*)-3b**] in 36% ee, indicating either significant epimerization during formation of the mesylate or an increase in $S_N1$ character of the azide displacement. Mesylate **(*R*)-1c** was also found to be unstable, having a propensity to eliminate to the corresponding α,β-unsaturated derivatives ***E*-** and ***Z*-4** under the reaction conditions as well as on standing at room temperature.

The low yield and poor stereoselectivity in the synthesis of **(*S*)-3b** via the mesylate led to a search for an alternative more general method of accomplishing the azide displacement of tertiary α-hydroxy esters. It was reasoned that the Mitsunobu reaction could be an advantageous alternative since the alcohol is activated *in situ* in the presence of the nucleophile and the activated species is short-lived. In addition, recent reports indicated that the Mitsunobu reaction could take place on chiral tertiary alcohols with high stereoselectivity.[9]

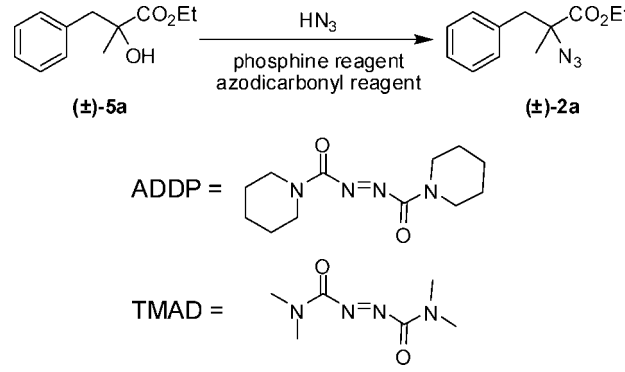
The Mitsunobu reaction was carried out on racemic α-hydroxy ester **(±)-5a** using standard reagents: diethyl

**Scheme 2.** Limitations of the Reaction of $NaN_3$ with Chiral Tertiary α-Mesylate Esters




azodicarboxylate (DIAD), $PPh_3$, and $HN_3$ (Table 1, Entry 1). The azide product was observed by reverse-phase HPLC in 29% conversion from the starting alcohol after 24 h. Optimization of the reaction was performed, studying various

**Table 1.** Optimization of the Azide Mitsunobu Reaction on α-Hydroxy Ester **(±)-5a**

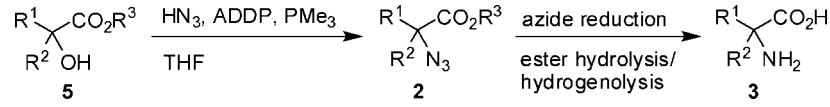


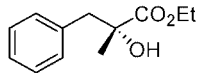
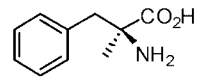
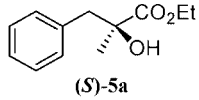
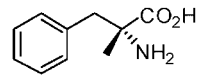
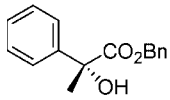
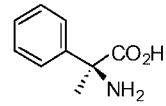
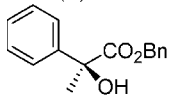
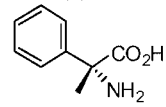
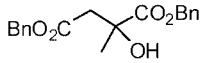
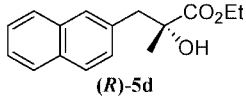
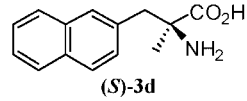
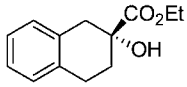
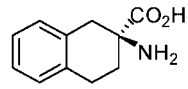
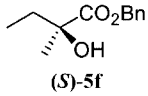
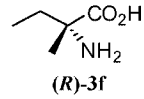

| entry[a] | azodicarbonyl reagent | phosphine reagent | % conversion after 24 h |
|---|---|---|---|
| 1 | DIAD | $PPh_3$ | 29 |
| 2 | ADDP | $PPh_3$ | 0 |
| 3 | ADDP | $PBu_3$ | 64 |
| 4 | ADDP | $PMe_3$ | 89 |
| 5 | TMAD | $PBu_3$ | 81 |
| 6 | TMAD | $PMe_3$ | 56 |
| 7 | DIAD | $PMe_3$ | 0 |
| 8[b] | ADDP | $PMe_3$ | 99 |

[a] Reaction conditions for all entries except entry 8: 1.5 equiv phosphine reagent, 1.5 equiv $HN_3$, 1.5 equiv azodicarbonyl reagent, toluene 0−25 °C. [b] Optimal reaction conditions (entry 8): $PMe_3$ (2 equiv), $HN_3$ (2 equiv), ADDP (2 equiv), THF 0−25 °C.

(8) (a) Mitsunobu, O. *Synthesis* **1981**, *1*, 28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656. (c) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451–8452. (d) Maycock, C. D.; Afonso, C. M.; Barros, T.; Godinho, L. S. *Tetrahedron* **1994**, *50*, 9671–9678. (e) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164. (f) Wiśniewski, K.; Kołdziejczyk, A. S.; Falkiewicz, B. J. *Peptide Science* **1998**, *4*, 1–14. (g) Watanabe, T.; Gridnev, I. D.; Imamoto, T. *Chirality* **2000**, *12*, 346–351. (h) Lee, S. H.; Yoon, J.; Chung, S.-H.; Lee, Y.-S. *Tetrahedron* **2001**, *57*, 2139–2145. (i) Goksu, S.; Secen, H.; Sutbeyaz, Y. *Synthesis* **2002**, 2373–2378. (j) Ko, S. Y. *J. Org. Chem.* **2002**, *67*, 2689–2691.

**Table 2.** Azide Mitsunobu Reaction[a] on Tertiary α-Hydroxy Esters and Conversion to α,α-Disubstituted Amino Acids




| Entry | Alcohol | Alcohol optical purity[b] | Amino Acid | Overall yield (%)[c] | Amino acid optical purity[b] |
|---|---|---|---|---|---|
| 1 |  **(*R*)-5a** | >99% ee |  **(*S*)-3a** | 71 | 99% ee |
| 2 |  **(*S*)-5a** | >99% ee |  **(*R*)-3a** | 62 | >99% ee |
| 3 |  **(*R*)-5b** | 97% ee |  **(*S*)-3b** | 80 | >99% ee |
| 4 |  **(*S*)-5b** | 98% ee |  **(*R*)-3b** | 76 | 98% ee |
| 5 |  **(±)-5c** | — | — | —[d] | — |
| 6 |  **(*R*)-5d** | 90% ee |  **(*S*)-3d** | 65 | 90% ee |
| 7 |  **(R)-5e** | >99% ee |  **(*S*)-3e** | 71 | >99% ee |
| 8 |  **(*S*)-5f** | 94% ee |  **(*R*)-3f** | 90 | 94% ee |

[a] Conditions: $HN_3$ (2 equiv), $PMe_3$ (2 equiv), ADDP (2.2 equiv), THF, 0−25 °C, 24−30 h. See Supporting Information for full experimental details. [b] Optical purities determined by chiral HPLC. [c] Isolated yields. [d] >99% elimination observed by HPLC in Mitsunobu reaction.

combinations of reagents, molar equivalents, solvent, and temperature (Entries 2−8). Tsunoda and Itô et al.[10] reported the use of 1,1-(azodicarbonyl)dipiperidine (ADDP) and N,N,N′,N′-tetramethylazodicarboxamide (TMAD) with $PBu_3$ as alternatives to the DIAD/$PPh_3$ system. The combination of ADDP with $PPh_3$ gave no reaction (Entry 2). By switching from $PPh_3$ to $PBu_3$, a moderate 64% conversion was observed (Entry 3). Using $PMe_3$, conversion to the azide increased to 89% (Entry 4).

It is interesting that TMAD in combination with $PBu_3$ and $PMe_3$ (Entries 5 and 6, respectively) were less efficient than ADDP/$PMe_3$, while DIAD/$PMe_3$ gave no reaction (Entry 7). Since ADDP/$PMe_3$ gave the highest conversion to product in 24 h, the reaction was further optimized by switching to THF as solvent and increasing reagent equivalents[11] (Entry 8: 2.0 equiv of $PMe_3$ and $HN_3$, 2.2 equiv of ADDP). Under these conditions, the reaction proceeded with 99% conversion from alcohol to azide in 24 h.

Following optimization of the chemical yield of the azide Mitsunobu reaction, a variety of chiral α-hydroxy esters (**5a**−**f**) were synthesized (Table 2). Examples containing benzylic substituents (Entries 1,2,6,7) were prepared by Sharpless asymmetric dihydroxylation (AD)[12] of the corresponding α,*β*-unsaturated esters. The resulting diols were

(9) (a) Shi, Y.-J.; Hughes, D. L.; McNamara, J. M. *Tetrahedron Lett.* **2003**, *44*, 3609–3611. (b) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 7359–7367. (c) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451–8452.

(10) (a) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639–1642. (b) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539–542. (c) Itô, S. *Yakugaku Zasshi* **2001**, *121*, 567–583.

converted to the alcohols by catalytic $\beta$−C−O hydrogenolysis in 73−93% yield (see Supporting Information for full experimental details). The chiral alcohols were >90% ee, and could be enriched to >99% ee by a single recrystallization of the preceding diol intermediate. The α-hydroxy esters in entries 3 and 4 [**(*R*)-** and **(*S*)-5b**] were prepared by benzylation of the commercially available chiral atrolactic acid hemihydrates. The (*S*)-α-hydroxybutanoic acid derivative in Entry 8 [**(*S*)-5f**] was obtained by resolution of the racemic acid, followed by benzylation.

The absolute configuration of alcohols **5a**−**f** was determined by comparison of optical rotations with literature values where available or inferred by known stereochemical preferences of the Sharpless AD reaction. The alcohols shown in Table 2 were subjected to the optimized Mitsunobu reaction conditions to generate the corresponding azido derivatives. Hydrogenation of the azides followed by ester hydrolysis or, in the case of benzyl esters, simultaneous hydrogenolysis, gave the optically active α,α-disubstituted amino acids (**3a**−**f**). These amino acids were analyzed by chiral HPLC using literature methods.[13] The azide Mitsunobu reactions on the chiral α-hydroxy esters listed in Table 2 gave high yields of the corresponding α-azido esters with the exception of **(±)-5c** (Entry 5), which resulted in >99% elimination. With the exception of entry 5, the Mitsunobu reactions took place with complete inversion of stereochemical configuration and optical purity was completely conserved. These results are remarkable given that each example has considerable steric hindrance at the α-carbon. In addition, the reactions were carried out at room temperature and were completed in 24−30 h. These examples also demonstrate the utility of the azide Mitsunobu reaction as part of a general method to synthesize nonracemic α,α-disubstituted amino acids from chiral tertiary alcohols. The preparation of new biologically active α,α-disubstituted amino acids utilizing this reaction is under investigation.

**Acknowledgment.** We are grateful to Stefan Thibodeaux, Thomas Perun, and Jonathan Paschal of Eli Lilly and Company for analytical support.

**Supporting Information Available:** Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802325H

(11) Lai, J.-Y.; Yu, J.; Hawkins, R. D.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5691–5694.

(12) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(13) (a) Péter, A.; Török, G.; Armstrong, D. W *J. Chromatogr. A* **1998**, *793*, 283–296. (b) Ekborg-Ott, K. H.; Liu, Y.; Armstrong, D. W. *Chirality* **1998**, *10*, 434–483. (c) Petritis, K.; Valleix, A.; Elfakir, C.; Dreux, M. *J. Chromatogr. A* **2001**, *913*, 331–340.