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Synthesis of Dehydro-β-amino esters *via* Highly Regioselective Amination of Allylic Carbonates

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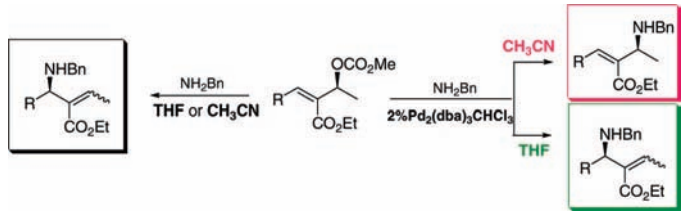
ABSTRACT



The allylic amination of acetates and carbonates affords dehydro-β-aminoesters, which are useful precursors of biologically active compounds. The uncatalyzed reaction proceeds via a S_N2' mechanism. On the other hand, under palladium-catalyzed conditions, the reaction shows a strong solvent-dependent regiocontrol, affording exclusively one of the two possible regioisomers with complete transfer of chirality from the substrates to the products.

Allylic compounds are privileged substrates in organic synthesis, allowing the substitution reaction to be performed with a variety of nucleophiles.[1] The substitution with amines is a very efficient method for C−N bond formation.[2] One of the most interesting aspects of this chemistry is the control of the regio- and the stereoselectivity on the allylic moiety. The reaction may be carried out in the absence of catalyst or under Pd-catalyzed conditions. Depending on the nature of the nucleophile, the substitution can occur via S_N2 or through an S_N2' process.[1b−d] For symmetrically substituted compounds, the step of formation of the metal complex is irrelevant for the regioselectivity of the overall reaction. On the contrary, for substrates bearing different substituents at the two allylic termini, interest increases when the regioselectivity can be controlled.[3] Excellent results have been obtained under metal catalysis by choosing the proper enantiopure ligand.[4] On the other hand, several examples showing a solvent effect on the regioselectivity have been reported.[5] In particular, solvent-dependent regiocontrol has been recently reported in Baylis−Hillman adduct amination[6]

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(1) (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901–1930. (b) Trost, B. M.; Van Vraken, D. L. *Chem. Rev.* **1996**, *96*, 395–442. (c) Pfaltz, A.; Lautens, M. *Comprehensive Asymmetric Catal.* **1999**, *2*, 833–884. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (e) Kar, A.; Argade, N. P. *Synthesis* **2005**, *18*, 2995–3002. (f) Helmchen, G. *Asymmetric Synth.* **2007**, *95*, 95–99.

(2) (a) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4377–4379. (b) Hultzsch, K. C. *Adv. Synth. Cat.* **2005**, *347*, 367–391. (c) Xu, L.-W.; Xia, C. G. *Eur. J. Org. Chem.* **2005**, 633–639. (d) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194–206. (e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365.

(3) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554. (b) Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Shanker, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 5115–5120. (c) Dong, Y.; Teesdale-Spittle, P.; Hoberg, J. O. *Tetrahedron Lett.* **2005**, *46*, 353–355.

(4) (a) Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 116–117. (b) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595–4597. (c) Zheng, W. H.; Sun, N.; Hou, X.-L. *Org. Lett.* **2005**, *7*, 5151–5154. (d) Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 6123–6125.

(5) (a) Kurosawa, H.; Kajimaru, H.; Ogoshi, S.; Yoneda, H.; Miki, K.; Kasai, N.; Murai, S.; Ikeda, I. *J. Am. Chem. Soc.* **1992**, *114*, 8417–8424. (b) Saitoh, A.; Misawa, M.; Morimoto, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1025–1028. (c) Bouquillon, S.; Muzart, J. *Eur. J. Org. Chem.* **2001**, 3301–3305.

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and excellent enantioselective allylic alkylation has been performed by Trost using the (*S*,*S*)-Ln ligand.[7] To the best of our knowledge, less effort has been devoted to substrates bearing substituents on the Cα, C*β*, and C*γ* position of the allylic system.[8] In pursuing our work on the allylic amination,[9] we report herein our preliminary results on the solvent-dependent regiocontrol in amination reaction[10] of racemic or enantiomerically pure acetate **1a** and carbonates **2a**−**c** (Figure 1). The reaction, carried out in the absence of catalyst

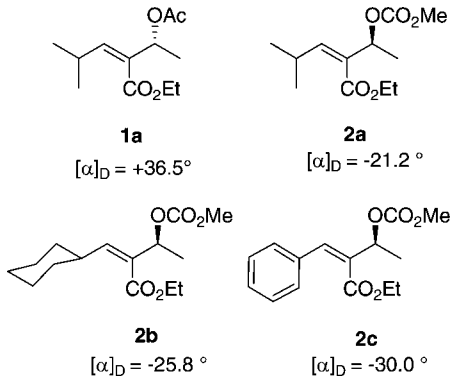


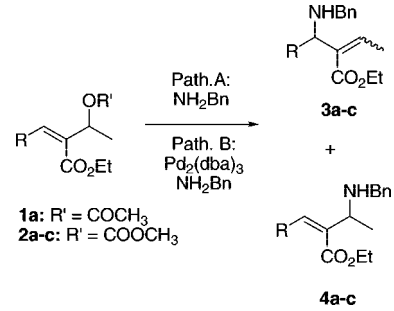
Figure 1. Starting materials for amination reactions.

and under palladium-catalyzed conditions, led to dehydro-*β*-amino esters **3** and **4**,[11] which are interesting precursors of unsaturated *β*-amino acids[12] and α-alkylidene-*β*-lactams.[13]

The optically active amino acetate **1a** was synthesized by kinetic enzymatic resolution of the corresponding alcohol catalyzed by *Pseudomonas Cepacia Lipase*.[14] Carbonates **2a**−**c** have been obtained from the corresponding (*S*)-alcohols by treatment with LiHMDS and methyl chloroformate in dry THF.

The amination reactions were carried out with benzylamine as nucleophile in different solvents, following pathway A or pathway B (Scheme 1). The regioselective nucleophilic

Scheme 1. Pathways A and B

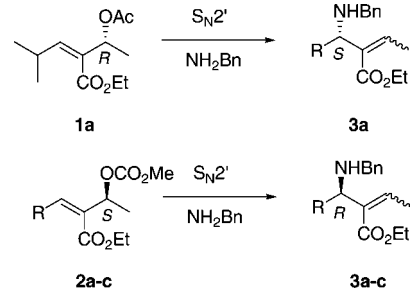


displacement may afford the dehydro-*β*-amino esters **3a**−**c** and **4a**−**c**, respectively.

In our initial experiments, (±)-**1a** and benzylamine were refluxed in CH_2Cl_2, affording (±)-**3a** in 65% yield although in a very long reaction time (Table 1, entry 1). On changing the solvent to THF, faster quantitative conversion to (±)-**3a** was observed (entry 2).

Following the same protocol on enantiomerically enriched (*R*)-**1a**, optically active **3a** was obtained as exclusive

Table 1. Uncatalyzed Amination of **1a** and **2a**−**c**



entry	substrate	solvent[a]	time (h)	**3**[b,c]/**4**
1	(±)-**1a**	CH_2Cl_2	96	>99/1
2	(±)-**1a**	THF	42	>99/1
3	(R)-**1a**	THF	42	>99/1
4	(R)-**1a**	CH_3CN	50	90/10
5	(±)-**2a**	THF	24	>99/1
6	(±)-**2a**	CH_3CN	40	>99/1
7	(S)-**2a**	THF	24	>99/1
8	(S)-**2a**	CH_3CN	40	>99/1
9	(±)-**2b**	THF	24	>99/1
10	(±)-**2b**	CH_3CN	40	95/5
11	(S)-**2b**	THF	24	>99/1
12	(±)-**2c**	THF	24	>99/1
13	(±)-**2c**	CH_3CN	40	88/12
14	(S)-**2c**	THF	24	>99/1[d]

[a] Reactions were carried out in refluxing solvent. [b] Regioisomeric ratio was determined by ^{1}H NMR. Configuration of the double bond in **3** 4/1 *Z*/*E*. [c] Yield of compounds purified by flash chromatography on silica gel >90% (65% only for entry 1). [d] A 12% racemization of the benzylic position was observed by HPLC on chiral column.

(6) (a) Rajesh, S.; Banerij, B.; Iqbal, J. *J. Org. Chem.* **2002**, *67*, 7852–7857. (b) Watson, I. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516–17529.

(7) (a) Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59–72. (b) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2007**, *9*, 3961–3964.

(8) Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, *9*, 927–930.

(9) (a) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Adv. Synth. Cat.* **2005**, *6*, 833–838. (b) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Piccinelli, F.; Tolomelli, A. *Org. Lett.* **2005**, *4*, 533–536.

(10) Ricci, A. *Modern Amination Methods*; Wiley-VCH: Weinheim, Germany, 2000.

(11) (a) Wasek, T.; Olczak, J.; Janecki, T. *Synlett* **2006**, *10*, 1507–1510, and references cited therein. (b) Perlmutter, P.; Tabone, M. *J. Org. Chem.* **1995**, *60*, 6515–6522.

(12) (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117–128. (b) Abdel-Magid, A. F.; Cohen, J. H.; Maryanoff, C. A. *Curr. Med. Chem.* **1999**, *6*, 955–969. (c) Juaristi, E., Ed. *Enantioselective Synthesis of b-amino acids*, 2nd ed.; Wiley-VCH: New York, 2005.

(13) (a) Alcaide, B.; Plumet, J.; Rodriguez-Lopez, J.; Sanchez-Cantalejo, Y. M. *Tetrahedron Lett.* **1990**, *31*, 2493–2496. (b) Buchholz, R.; Hoffmann, H.; Martin, R. *Helv. Chim. Acta* **1991**, *74*, 1213–1220. (c) Toyofuku, M.; Fujiwara, S.-I.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2005**, *127*, 9706–9707. (d) Benfatti, F.; Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Arkivoc* **2005**, *VI*, 136–152.

(14) Benfatti, F.; Cardillo, G.; Gentilucci, L.; Mosconi, E.; Tolomelli, A. *Tetrahedron: Asymmetry* **2007**, 2227–2232.

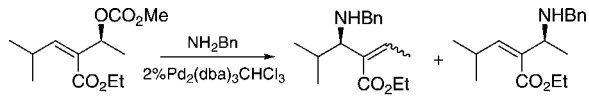
regioisomer in THF, whereas a 90/10 regioisomeric mixture of **3a**/**4a** was observed carrying out the reaction in acetonitrile (entries 3−4). Complete conversion of the starting material to **3a** in reduced reaction time was observed in both solvents starting from the carbonate **2a** (entries 5−6).

On repeating the reaction on (*S*)-**2a**, the chirality of the starting carbonate was completely transferred to the dehydroamino ester **3a** (99% ee determined by chiral HPLC on the pure isolated *Z*-**3a**, entries 7,8). Similar results have been obtained for compounds **2b** and **2c** (entries 9−13), although (*S*)-**2c** afforded enriched **3c** with a partial racemization of the benzylic position (entry 14).

The regiochemistry of the products accounts for a nucleophilic displacement occurring via S_N2' mechanism. Because a *syn* attack is to be predicted for neutral nucleophiles,[15] starting from (*R*)-acetate **1a**, the (*S*) configuration was attributed to the dehydro-*β*-amino ester **3a**, whereas from (*S*)-carbonates **2a**−**c**, the (*R*) configuration was assigned to products **3a**−**c**.

With these results in hand, we treated racemic or (*S*)-**2a** allylic carbonate[16] with benzylamine in the presence of $Pd_2(dba)_3CHCl_3$ catalyst, either in THF or CH_3CN. Selected results are reported in Table 2.

Table 2. Solvent Effect in Pd-Catalyzed Amination of **2a**



2a **3a** **4a**

entry	substrate	solvent[a]	**3a/4a**[b,c] (%)
1	(±)-**2a**	THF	93/7
2	(±)-**2a**	CH_3CN	20/80
3	(S)-**2a**	THF	90/10[d]
4	(S)-**2a**	CH_3CN	20/80[d]
5	(S)-**2a**	CH_3CN + PPh_3	99/1[d]

[a] Reactions were carried out in refluxing solvent (solution 0.1 M of **2**). [b] Regioisomeric ratio was determined by ^1H NMR. Configuration of the double bond in **3** 4/1 *Z*/*E*. [c] Yield of compounds purified by flash chromatography on silica gel >90%. [d] A 90% ee from HPLC on chiral column, starting from (*S*)-**2a** having 90% ee.

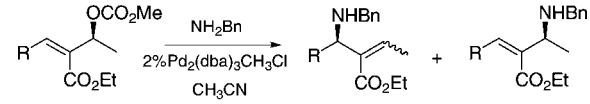
The data reported show that the reaction carried out in THF at reflux gave compound **3a** in 93/7 regioisomeric ratio (entry 1).

When (*S*)-**2a** was used as starting material, the chirality was completely retained, affording **3a** with the same enantiomeric excess of the starting carbonate (entry 3). Complete inversion of the regiochemistry occurred in CH_3CN at reflux, **4a**/**3a** being obtained in 80/20 regioisomeric ratio (entries 2 and 4). Similarly to that observed in THF, the reaction performed in CH_3CN on (*S*)-**2a** gave **4a** in 90% ee (entry 4). To enhance the regioselectivity of the reaction, the amination was performed in the presence of PPh_3.[17] A significant increase of regioselectivity was observed for the reaction carried out in CH_3CN, where **4a** was formed as the exclusive regioisomer (entry 5).

Because both the oxidative addition leading to palladium complex and the nucleophilic attack normally occur stereoselectively with inversion of configuration at the reacting allylic carbon atom, the overall process proceeds with retention of configuration.[18] Therefore, starting from (*S*)-**2a**, the (*R*) configuration was assigned to **3a**, also confirmed by the observed optical rotation, and the (*S*) configuration was assigned to **4a**. Thus, starting from (*S*)-**2a** carbonate, selected conditions gave access to the two different optically active dehydroamino esters (*R*)-**3a** or (*S*)-**4a** through a solvent dependent regioselective control.

On the basis of these results, **2b** and **2c** were reacted in CH_3CN (Table 3, entries 1 and 2) giving **4b** and **4c** in

Table 3. Pd-Catalyzed Amination of **2b**−**c** in CH_3CN



2b: R = Cyclohexyl
2c: R = Ph

3b-c **4b-c**

entry	substrate	solvent[a]	**3/4**[b,c] (%)
1	(S)-**2b**	CH_3CN	15/85[d]
2	(S)-**2c**	CH_3CN	11/89[d]
3	(±)-**2b**	CH_3CN+ PPh_3	5/95
4	(±)-**2c**	CH_3CN+ PPh_3	5/95

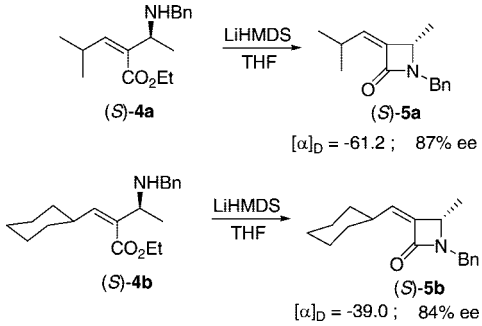
[a] Reactions were carried out in refluxing solvent (solution 0.1 M of **2**). [b] Regioisomeric ratio was determined by ^1H NMR. Configuration of the double bond in **3** 4/1 *Z*/*E*. [c] Yield of compounds purified by flash chromatography on silica gel >90%. [d] 90% ee from HPLC on chiral column, starting from (*S*)-**2** having 90% ee.

satisfactory regioselectivity (>85/15), which was strongly improved when PPh_3 was added to the reaction mixture, in agreement with the above-reported results on the isopropyl derivative (entries 3 and 4). The dehydro-*β*-amino esters were then converted to (*4S*)-α-alkylidene-*β*-lactams to obtain compounds of interest in our research group.[19] To this purpose, (*S*)-**4a**−**b** were easily quantitatively transformed into the corresponding (*Z*)-*β*-lactam (*S*)-**5a**−**b** by treatment with LiHMDS in anhydrous THF at −20 °C (Scheme 2). The *Z* configuration of the double bond was attributed on the basis of vinyl proton ^1H NMR chemical shift (5.33−5.36 ppm)[12b,20] and confirmed by NOE experiments.

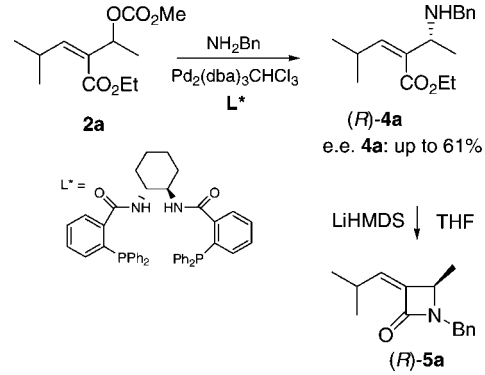
Finally, a preliminary study on the enantioselective variant of this methodology by reaction of (±)-**2a** with benzylamine was performed using different chiral ligands and solvents. In the presence of 5% amount of Pd and 8% amount of

(15) Fukui, K. *Theory of Orientation and Stereoselection*; Springler-Verlag: Berlin, 1975; pp 58−76.
(16) Arcadi, A.; Bernocchi, E.; Cacchi, S.; Caglioti, L.; Marinelli, F. *Gazz. Chim. Ital.* **1991**, *121*, 369–371.
(17) Amatore, C.; Jutand, A.; Meyer, G.; Mottier, L. *Chem.−Eur. J.* **1999**, *5*, 466–473.
(18) Moreno-Manas, M.; Morral, L.; Pleixats, R. *J. Org. Chem.* **1998**, *63*, 6160–6166.
(19) Benfatti, F.; Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Bioorg. Med. Chem. Lett.* **2007**, 1946–1950.

Scheme 2. Synthesis of Alkylidene-β-lactams **5a**−**b**



Scheme 3. Asymmetric Allylic Amination



enantiopure (*R*,*R*)-DACH-Phenyl Trost ligand, a strong effect on the regioselectivity was observed. Compound **4a** was obtained as exclusive product in CH_2Cl_2, whereas it was isolated in 80/20 regioisomeric ratio when the reaction was performed in THF. In both cases, only a moderate 40% ee was observed. Otherwise, decreasing the amount of Pd/ligand (2%/6%) in THF, **4a** was isolated in 30/70 regioisomeric ratio and 61% ee, whereas the major isomer **3a** was obtained in racemic form through uncatalyzed S_N2' reaction (Scheme 3).

The (*R*) absolute configuration of the predominant enantiomer of **4a** was determined by comparison of the HPLC retention times on chiral column and optical rotation values [(*R*)-**4a** $[\alpha]_D = +4$, 61% ee] with (*S*)-**4a** ($[\alpha]_D = -7$, 87% ee). The attribution was further confirmed by the comparison of HPLC of the corresponding β-lactams (*S*)-**5a** and (*R*)-**5a**.

Carrying out the amination of (±)-**2a** in THF in the presence of (*S*,*S*)-DACH-Naphtyl ligand, recently reported by Trost as excellent Pd-ligand in allylic carbonate alkylation,[7b] (±)-**3a** was exclusively isolated, whereas using 8% of (*R*)-BINAP, 89/11 ratio of (±)-**3a**/**4a** was observed. ***(S)*-4a** was obtained as predominant enantiomer in 20% ee.

These results suggest that the dynamic kinetic asymmetric transformation (DYKAT)[7a] of **2** involves a complex sequence of events that deserve further investigation.

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Supporting Information Available: Complete characterizations and selected spectra for **2a**−**c**, **3a**−**c**, **4a**−**c**, **5a**−**b**. HPLC spectra for (*S*)-**5a** and (*R*)-**5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (a) Otto, H. H.; Bergmann, H. J.; Mayrhofer, R. *Arch. Pharm.* **1986**, *319*, 203–216. (b) Anklam, S.; Liebscher, J. *Tetrahedron* **1998**, *54*, 6369–6384.