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Preparation of *N*-protected allylic amines and α-methylene-β-amino acids from vinylalumination/Baylis–Hillman products via tandem S_N2' substitution–Overman rearrangement

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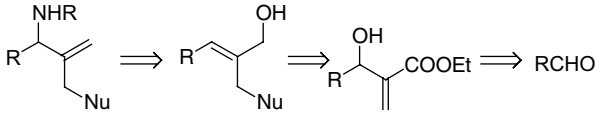
Abstract—S_N2' reaction on the acetates obtained from vinylalumination or Baylis–Hillman products, followed by in situ reduction afforded allylic alcohols. Upon conversion to trichloroacetimidates and [3,3]-sigmatropic rearrangement, the corresponding *N*-protected β-substituted allylic amines were obtained in good yields. Utilization of hydroxy group as the nucleophile furnished allylic hydroxy esters, which were converted to protected α-methylene-β-amino acids via Overman rearrangement.

Allylic amines are very useful synthons in organic synthesis.[1] They are used in the preparation of various synthetic intermediates; they are also attractive starting materials for the synthesis of amino acids.[1,2] Owing to their importance, there have been many literature reports[1] for the preparation of allylic amines and [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates (Overman rearrangement) is a well-established protocol.[3] The resulting allylic amides can be conveniently deprotected into the parent amines under either acidic or basic conditions.[4] Preparation of β-amino acids is of particular interest to medicinal and bioorganic chemists[5] as various β-amino acid moieties can be found in taxoids, β-lactam antibiotics, HIV-protease inhibitors, and other compounds.[6] Moreover, high proteolytic stability of β-amino acids makes them excellent substrates for peptidomimetics.[7]

Vinylalumination[8] using [α-(ethoxycarbonyl)vinyl]diisobutylaluminum, prepared from ethyl propiolate and diisobutylaluminum hydride (DIBAL-H) in the presence of 4-methylmorpholine-*N*-oxide (NMO), is an attractive alternative to Baylis–Hillman protocol[9] due to shorter reaction times and tolerance of wider array of carbonyls. Our ongoing work involving applications of the vinylalumination products[8a,10] prompted us to investigate the preparation of *N*-protected-β-substituted allylic amines from α-methylene-β-hydroxy esters. We envisaged the protocol as a two-step synthesis, with the first step involving the S_N2' reaction of the acetates with various nucleophiles, followed by an in situ reduction of the esters to furnish primary allylic alcohols. In the second step, the obtained allylic alcohols would be converted to trichloroacetimidates and subjected to [3,3]-sigmatropic rearrangement to afford the allylic amides. The retrosynthetic analysis is shown in Scheme 1. Among the chosen representative nucleophiles, only S_N2' addition of carbon is well recognized.[9,11] The other, viz. nitrogen,[9,12] hydride,[13] and sulfur[14] are known, but remain rather obscure. Herein we report the results of our investigation.

Vinylalumination or Baylis–Hillman reaction of acetaldehyde and benzaldehyde provided the allylic alcohols in high yields. The obtained alcohols were acetylated



Scheme 1. Retrosynthetic analysis.

Keywords: β-Amino acids; Allylic amines; S_N2' reaction; Allylic alcohols; Vinylalumination; Baylis–Hillman reaction.

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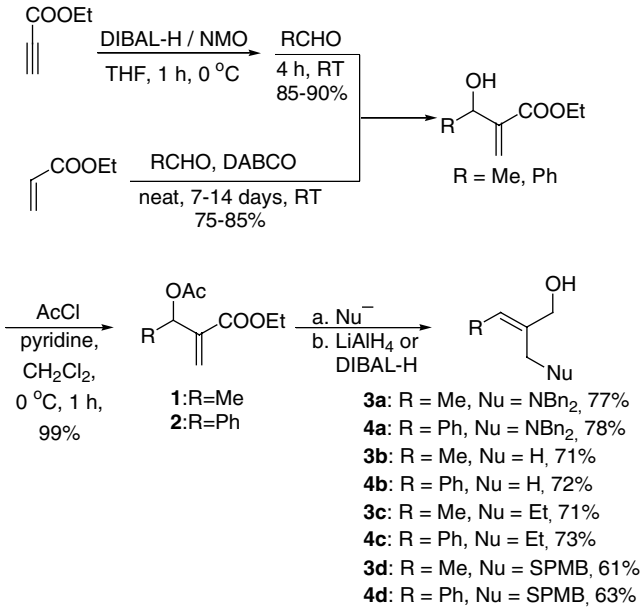


Scheme 2. Synthesis of allylic alcohols.

to give quantitative yields of the corresponding acetates **1** and **2** (Scheme 2).

The reaction of dibenzylamine with **1** and **2**, in the presence of triethylamine, followed by in situ reduction with $LiAlH_4$ at 0 °C furnished the desired hydroxy amines **3a** and **4a** in good yields (Table 1, entries 1 and 2). The reductions with DIBAL-H were sluggish and required over 6 h at rt. Analysis of the obtained amino alcohols with ^1H NMR spectroscopy revealed that **3a** and **4a** were obtained as ~1:1 mixtures of *E*- and *Z*-isomers, which could be separated on silica gel. We were not concerned about the isomer ratio since both **3a** and **4a** were rearranged to a terminal methylene later. Hydride nucleophile was installed by the treatment of **1** and **2** with $LiAlH_4$ to give the corresponding alcohols **3b** and **4b** in good yields (Table 1, entries 3 and 4).[13] This treatment resulted in a simultaneous reduction of the ester moiety. The acetates **1** and **2**, upon reaction with ethylmagnesium bromide, followed by the reduction with $LiAlH_4$, afforded the alcohols **3c** and **4c**, respectively (Table 1, entries 5 and 6). (4-Methoxyphenyl)methanethiol added easily to the acetates **1** and **2** in the presence of triethylamine to give quantitative yields of the expected allylic thioether esters. However, upon reduction with $LiAlH_4$, only the starting thiol was recovered in 96% yield. Fortunately, treatment of the S_N2'-substitution products with DIBAL-H at −18 °C furnished **3d** and **4d**, albeit in somewhat diminished yields (Table 1, entries 7 and 8).

Table 1. Synthesis of protected β-substituted allylic amines

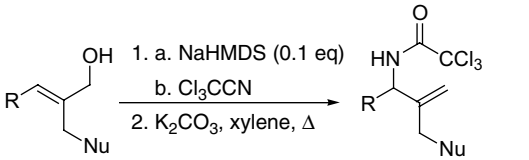
Entry	Acetate		Nu	Alcohol		Amide	
	#	R		#	Yld, %[a]	#	Yld, %[a]
1	**1**	Me	NBn_2	**3a**	77[b]	**5a**	73
2	**2**	Ph	NBn_2	**4a**	78[b]	**5a**	72
3	**1**	Me	H	**3b**	71	**5b**	78
4	**2**	Ph	H	**4b**	72	**6b**	77
5	**1**	Me	Et	**3c**	71	**5c**	76
6	**2**	Ph	Et	**4c**	73	**6c**	75
7	**1**	Me	SPMB	**3d**	61[c]	**5d**	70
8	**2**	Ph	SPMB	**4d**	63[c]	**6d**	73
9	**1**	Me	'OH'[d]	**7e**	65	**9e**	71
10	**2**	Ph	'OH'[d]	**8e**	70	**10e**	73

[a] All yields are of isolated, pure products.
[b] Obtained as ~1:1 mixtures of separable *E*- and *Z*-isomers.
[c] Reduction with DIBAL-H at −18 °C was required.
[d] The hydroxy nucleophile was inserted via other routes (see text).

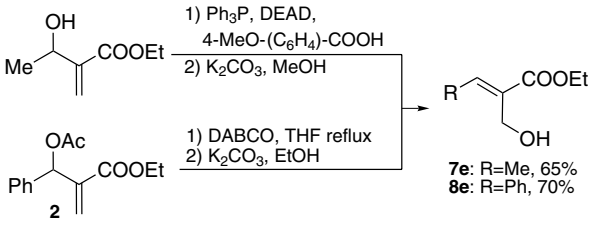
The allylic alcohols **3a–d** and **4a–d** were converted to the corresponding trichloroacetimidates by the treatment with 0.1 equiv of sodium bis(trimethylsilyl)amide (NaHMDS) in THF at −42 °C, followed by the addition of trichloroacetonitrile and warming to room temperature. Although in the vast majority of the literature reports the acetimidates are prepared using DBU or NaH as the base,[3] we found that, in our system, the best results were obtained with NaHMDS. The use of catalytic amounts of the solid NaH was quite inconvenient for small scale preparations and DBU was required in a stochiometric amount and provided the trichloroacetimidates along with the unreacted base, which necessitated purification hence leading to diminished yields. On the other hand, NaHMDS solution was easy to add in catalytic amounts and furnished clear reaction mixtures that did not require rigorous purification. After removal of the solvent under reduced pressure, the obtained crude acetimidates were diluted with xylene and refluxed in the presence of K_2CO_3[15] for 4–10 h (reactions monitored by TLC), furnishing the desired β-substituted allylic amides **5a–d** and **6a–d** in good yields (Scheme 3). The preparation of *N*-protected allylic amines is summarized in Table 1.

Since direct installation of the oxygen nucleophile was not facile, as a surrogate we used S_N2' Mitsunobu conditions[16] for the aliphatic substrate and rearrangements of the acetate devised by Foucault and Le Guemmout[17] for the aromatic acetate **2** to obtain the allylic hydroxy esters **7e** and **8e**, respectively (Scheme 4; Table 1, entries 9 and 10).

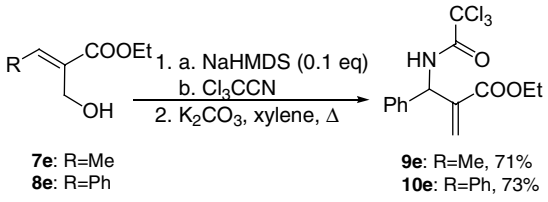
Due to the importance of β-amino acids,[5–7] we chose to convert hydroxy esters **7e** and **8e** to *N*-protected α-methylene-β-amino acids. Thus, they were subjected to Over-



Scheme 3. Synthesis of *N*-protected β-substituted allylic amines.



Scheme 4. Preparation of allylic esters using oxygen nucleophile.



Scheme 5. Synthesis of protected α-methylene-β-amino acids.

man rearrangement as described above to furnish the corresponding protected β-amino acids **9e** and **10e** in good yields (Scheme 5; Table 1, entries 9 and 10).

In conclusion, we have developed a simple and reliable two-step procedure for the preparation of β-substituted allylic amides and α-methylene-β-amino esters from the acetates of readily accessible vinylalumination or Baylis–Hillman products. We believe that the simplicity of the protocol, tolerance of a wide range of nucleophiles, and the importance of allylic amines make this procedure attractive and it will find applications in organic syntheses.

Representative experimental procedures

Nitrogen nucleophile: To a solution of ethyl 2-[(acetyloxy)(phenyl)methyl]acrylate (**2**; 0.9 g, 3.6 mmol) in CH_2Cl_2 (30 mL) was added triethylamine (0.5 mL, 3.5 mmol) and dibenzylamine (1.0 mL, 7.2 mmol) and the reaction was stirred for 4 h at rt, followed by cooling to 0 °C and addition of $LiAlH_4$ (1 M in THF; 3.6 mL, 3.6 mmol). After stirring at rt for 1 h, followed by quenching with H_2O (5 mL), the product was extracted with Et_2O (3 × 50 mL). After removal of the volatiles, the residue was purified on silica gel (flash; ethyl acetate/hexanes 1:9) to provide a mixture of separable (2*E*) and (2*Z*)-2-{[dibenzylamino]methyl}-3-phenylprop-2-en-1-ol (**4a**) (52:48 *E*/*Z* ratio; 0.95 g, 2.8 mmol, 77% combined yield). For the *E*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.32 (br s, 1H), 3.42 (s, 2H), 3.51 (s, 4H), 4.33 (s, 2H), 6.77 (s, 1H), 7.21–7.43 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 35.3, 57.4, 57.8, 67.6, 125.9, 126.3, 127.2, 127.4, 127.5, 127.8, 127.9, 128.0, 128.3, 129.0, 135.7, 136.9, 137.0. MS (EI): 343 (M^+), 194, 91 ($C_7H_7^+$); (CI): 344 (M+H), 210, 147. *Hydride nucleophile*: To $LiAlH_4$ (0.3 g, 7.9 mmol) diluted with Et_2O (30 mL) and cooled to 0 °C was slowly added EtOH (0.46 mL, 7.9 mmol). The mixture was transferred via canula to a solution of **2** (1.8 g, 7.3 mmol) in Et_2O (30 mL) cooled to −78 °C. Reaction was allowed to warm to rt over 0.5 h, when it was quenched with aq 10% HCl (5 mL). The product was extracted with Et_2O (3 × 30 mL), washed with brine, concentrated in vacuo, and purified on silica gel (ethyl acetate/hexanes 2:8) to furnish 0.75 g of (2*E*)-2-methyl-3-phenylprop-2-en-1-ol (**4b**) (5.1 mmol, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.98 (br s, 1H), 1.91 (s, 3H), 4.20 (s, 2H), 6.54 (s, 1H), 7.24–7.3 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 15.3, 69.0, 125.0, 126.4, 128.2, 128.9, 137.6, 137.7. *Carbon nucleophile*: To a solution of **2** (0.9 g, 3.6 mmol) in Et_2O (15 mL) cooled to −18 °C was added EtMgBr (3 M in Et_2O; 1.2 mL, 3.6 mmol) and the reaction was stirred for 2 h at 0 °C. To the obtained crude ester was added $LiAlH_4$ (1 M in THF; 3.5 mL, 3.5 mmol) and the mixture was stirred for 1 h, while it warmed to rt. After quenching with 10% aq HCl (5 mL), the obtained material was extracted with Et_2O (3 × 30 mL), washed with brine, the volatiles were removed under reduced pressure, and the product as purified on silica gel (ethyl acetate/hexanes 2:8) to furnish (2*E*)-3-phenyl-2-propylprop-2-en-1-ol (**4c**): (0.45 g, 2.6 mmol, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.96 (t, J = 7.4 Hz, 3H), 1.56 (m, 2H), 2.31 (t, J = 7.96 Hz, 2H), 2.60 (s, 1H), 4.24 (s, 2H), 6.58 (s, 1H), 7.26–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.3, 21.7, 30.9, 68.8, 125,3, 126.5, 128.3, 128.7, 137.7, 142.3. *Sulfur nucleophile*: To a solution of **2** (0.3 g, 1.2 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (0.14 mL, 1.1 mmol) and (4-methoxyphenyl)methanethiol (0.25 mL, 1.8 mmol) and the reaction was stirred overnight at rt, followed by cooling to −18 °C and the addition of DIBAL-H (1 M in hexanes; 1.3 mL, 1.3 mmol). The reaction was allowed to warm to rt and was stirred for 6 h, when it was quenched with H_2O (5 mL). The product was extracted with CH_2Cl_2 (1 × 10 mL) and Et_2O (2 × 30 mL), the solvents were removed under reduced pressure, and the material was purified on silica gel (flash; ethyl acetate/hexanes 2:8) to furnish (2*Z*)-2-{[(4-methoxybenzyl)thio]methyl}-3-phenylprop-2-en-1-ol (**4d**; 0.23 g, 0.8 mmol, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.94 (br s, 1H), 3.40 (s, 2H), 3.61 (s, 2H), 3.77 (s, 3H), 4.34 (s, 2H), 6.70 (s, 1H), 6.79 (d, J = 8.58 Hz, 2H), 7.08 (d, J = 8.52 Hz, 2H), 7.24–7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 29.9, 36.2, 55.3, 66.3, 114.0, 127.1, 128.5, 128.8, 129, 130.1, 130.3, 136.7, 137.4, 158.6. MS (EI): 300 (M^+), 205, 121 (MeO–(C_6H_4)–CH_2^+), 107; (CI): 283 (M+H−H_2O), 121 (MeO–(C_6H_4)–CH_2^+); HRMS: 300.1184 (calcd), 300.1184 (actual). *Oxygen nucleophile on aliphatic substrate*: To ethyl 2-(1-hydroxyethyl)acrylate (1.7 g, 10.0 mmol) dissolved in THF (30 mL) was added triphenylphosphine (3.5 g, 13.3 mmol) and 4-nitrobenzoic acid (2.2 g, 13.2 mmol). The mixture was cooled to −78 °C and diethylazodicarboxylate (2.1 mL, 13.2 mmol) was added slowly. The mixture was allowed to warm to rt over 3 h, when it was quenched with satd aq $NaHCO_3$ (10 mL), the product was extracted with Et_2O (3 × 30 mL), washed with brine, evaporated, and purified on silica gel (ethyl acetate/hexanes 1:8) to give (2*E*)-2-(ethoxycarbonyl)-benzoate in 66% yield (1.9 g, 6.5 mmol). The obtained ester was dissolved in MeOH (65 mL), and treated with K_2CO_3 (1.0 g, 7.2 mmol) for 1 h at rt. The reaction was

quenched with H_2O (20 mL), the product was extracted with Et_2O (3×30 mL), washed with brine, and after removal of the solvents under reduced pressure purified on silica gel (flash; ethyl acetate/hexanes 1:7) to furnish **7e** (0.85 g, 6.5 mmol, 65% yield from the alcohol). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.39 (t, $J = 7.12$ Hz, 3H), 1.85 (d, $J = 7.35$ Hz, 3H), 2.8 (br s, 1H), 4.29 (s, 2H), 4.33 (q, $J = 7.15$ Hz, 2H), 6.92 (q, $J = 7.23$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.1, 14.7, 51.7, 56.4, 131.8, 141.0, 167.9. *Oxygen nucleophile on aromatic substrate*: To a solution **2** (2.5 g, 10.1 mmol) in THF (20 mL) was added DABCO (0.8 g, 7.1 mmol) and the reaction was refluxed for 14 h, followed by evaporation of THF. The residue was dissolved in EtOH (100 mL) and treated with K_2CO_3 (3.5 g, 25 mmol) for 14 h at rt, when it was quenched with H_2O (50 mL), the product was extracted with Et_2O (3×50 mL), washed with brine, the solvent was evaporated, and the material was purified on silica gel (flash; ethyl acetate/hexanes 1:7) to give **8e** (1.45 g, 7.0 mmol, 70% yield) ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.39 (t, $J = 7.12$ Hz, 3H), 3.18 (br s, 1H), 4.30 (q, $J = 7.15$ Hz, 2H), 4.52 (d, $J = 5.1$ Hz, 2H), 7.25–7.45 (m, 5H), 7.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.1, 59.9, 57.5, 128.6, 129.3, 129.7, 131.0, 134.6, 142.8, 168.5. *Representative procedure for the rearrangement*: To **4b** (0.2 g, 1.3 mmol) dissolved in THF (15 mL) and cooled to -42 °C was added sodium bis(trimethylsilyl)amide (1 M in THF; 0.13 mL, 0.13 mmol) and the reaction was stirred for 0.2 h, followed by the addition of trichloroacetonitrile (0.15 mL, 1.5 mmol) and stirring for 1 h, while it warmed to rt. The solvent was removed under reduced pressure and the crude material was diluted with xylene (5 mL), K_2CO_3 (0.18 g, 1.3 mmol) was added, and the reaction was stirred for 6 h at reflux. After filtration through Celite, the product was purified on silica gel (flash; ethyl acetate/hexanes 1:99) to give 2,2,2-trichloro-*N*-(2-methyl-1-phenylprop-2-enyl)acetamide (**6b**) (0.3 g, 1.0 mmol, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.72 (s, 3H), 5.08 (d, $J = 14.01$ Hz, 2H), 5.41 (d, $J = 7.95$ Hz, 1H), 6.94 (d, $J = 6.99$ Hz, 1H), 7.35-7.56 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 19.2, 59.2, 111.5, 126.3, 127.4, 128, 137.1, 141.5, 159.7.

References and notes

1. Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.
2. (a) Ichikawa, Y.; Ito, T.; Nishiyama, T.; Isobe, M. *Synlett* **2003**, *7*, 1034; (b) Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291; (c) Bower, J. F.; Jumnah, R.; Williams, A. C.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1411; (d) Burgess, K.; Liu, L. T.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758; (e) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.
3. (a) Sato, H.; Oishi, T.; Chida, N. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 693; (b) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218; (c) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597.
4. (a) Ramachandran, P. V.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2005**, *70*, 0000; (b) Bey, P.; Gerhart, F.; Jung, M. *J. Org. Chem.* **1986**, *51*, 2835; (c) Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1984**, 770.
5. (a) Dougherty, D. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 645; (b) Bittker, J. A.; Phillips, K. J.; Liu, D. R. *Curr. Opin. Chem. Biol.* **2002**, *6*, 367; (c) Yodar, N. C.; Kumar, K. *Chem. Soc. Rev.* **2002**, *31*, 335.
6. (a) Ojima, I.; Lin, S. N.; Wang, T. *Curr. Med. Chem.* **1999**, *6*, 927; (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Viley-VCH: London, 1997, and references cited therein.
7. Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M.-I. *Curr. Med. Chem.* **2002**, *9*, 811.
8. (a) Ramachandran, P. V.; Rudd, M. T.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2003**, *68*, 9310; (b) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Chem. Commun.* **1999**, 1979; (c) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Tetrahedron Lett.* **1999**, *40*, 627; (d) Li, G. G.; Wei, H.-X.; Willis, S. *Tetrahedron Lett.* **1998**, *39*, 4607; (e) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T.; de Alaniz, J. R. *Tetrahedron Lett.* **1998**, *39*, 8791.
9. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.
10. Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M. V. R. *Org. Lett.* **2004**, *6*, 481.
11. (a) GowriSankar, S.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 6949; (b) Amri, H.; Rambaud, M.; Villiéras, J. *J. Organomet. Chem.* **1990**, *384*, 1; (c) Drewes, S. E.; Emslie, N. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079.
12. (a) Nilov, D.; Räcker, R.; Reiser, O. *Synthesis* **2002**, 2232; (b) Hbaïeb, S.; Latiri, Z.; Amri, H. *Synth. Commun.* **1999**, *29*, 981.
13. Basavaiah, D.; Pakalah, K. S. S. *J. Chem. Soc., Chem. Commun.* **1992**, 955.
14. (a) Kamimura, A.; Morita, R.; Matsuura, K.; Omataa, Y.; Shiraib, M. *Tetrahedron Lett.* **2002**, *43*, 6189; (b) Calò, V.; Lopez, L.; Pesce, G. *J. Organomet. Chem.* **1988**, *353*, 405.
15. Nishikawa, T.; Asai, M.; Ohayabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188.
16. (a) Charette, A. B.; Côté, B.; Monroc, S.; Prescott, S. *J. Org. Chem.* **1995**, *68*, 6888; (b) Mitsunobu, O. *Synthesis* **1981**, 1.
17. Foucaud, A.; Le Guemmout, F. *Bull. Soc. Chim. Fr.* **1989**, *3*, 403.