Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3847–3850

Chemo-, regio- and stereoselective addition of triorganoindium reagents to acetates of Baylis–Hillman adducts: a new strategy for the synthesis of (*E*)- and (*Z*)-trisubstituted alkenes

Brindaban C. Ranu,* Kalicharan Chattopadhyay and Ranjan Jana

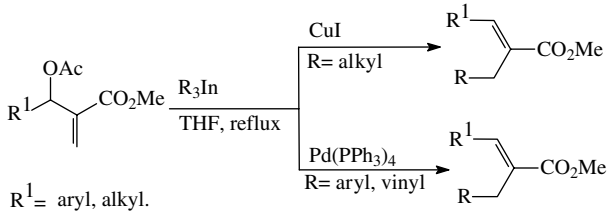
Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India

Received 6 February 2007; revised 17 March 2007; accepted 28 March 2007
Available online 3 April 2007

Abstract—The addition of several trialkyl or triarylindium reagents to the acetates of Baylis–Hillman adducts proceeds readily under the catalysis of copper and palladium derivatives. The reactions of trialkylindiums are catalyzed efficiently by CuI whereas additions of triarylindiums produce better results with $Pd(PPh_3)_4$. The reactions with 3-acetoxy-2-methylenealkanoates provide (*E*)-alkenes, whereas similar reactions with 3-acetoxy-2-methylenealkanenitriles lead to (*Z*)-alkenes. All the reactions are highly regio- and stereoselective and high yielding.

The Baylis–Hillman reaction[1] is a unique carbon–carbon bond forming reaction producing synthetically useful multifunctional molecules having wide applications.[2] Several reports[3] have described the stereoselective synthesis of trisubstituted alkenes using acetates of Baylis–Hillman adducts. Some of these reported procedures involve Grignard reagents,[3a] potassium organotrifluoroborates catalyzed by $Pd(OAc)_2$,[3b] $[Rh(Cod)Cl]_2$,[3c] organosilanes in the presence of $Pd_2(dba)_3$,[3d] alkyl halides in the presence of Zn/aqueous NH_4Cl solution[3e] and Friedel–Crafts reaction with benzene catalyzed by concd H_2SO_4.[3f] However, these procedures have limitations with regard to addition of either only alkyl[3e] or aryl moieties,[3b–f] long reaction times[3c,e] and complexity of the reagents.[3b,c] The increasing interest in organoindium reagents because of their environmentally benign characteristics and their synthetic utility for carbon–carbon bond formation has led to the development of several new indium reagents.[4] Triorganoindium has high potential and has been found to be capable of participating in various reactions.[5] As a part of our continued activities in the area of indium-mediated reactions,[6] we report here a very efficient and convenient synthesis of trisubstituted alkenes by the addition of trialkyl- or triarylindium derivatives to the acetates of Baylis–Hillman adducts catalyzed by CuI and $Pd(PPh_3)_4$ (Scheme 1).

The addition of triorganoindiums to allyl derivatives is usually carried out using Pd-catalysts.[5] Thus, in our initial attempts, the reaction of tributylindium with 2-(acetoxy-phenyl-methyl)-acrylic acid methyl ester was investigated with different Pd-catalysts such as $Pd(PPh_3)_4$, $Pd_2(dba)_3/PPh_3$ and $Pd(OAc)_2/PPh_3$. However, all these catalysts failed to transfer the alkyl group to the olefinic moiety and a rearranged product (**B**) (Table 1) was formed by nucleophilic hydride attack followed by elimination of OAc. This may be explained by the fact that β-H elimination is faster in an *n*-Bu moiety than C–C bond formation under Pd-catalysis. However, when the reaction was tried with Ph_3In, product **A** was formed rapidly by phenyl transfer under identical conditions. In the search for a suitable catalyst for alkyl transfer, we investigated Cu-catalysts following a report by

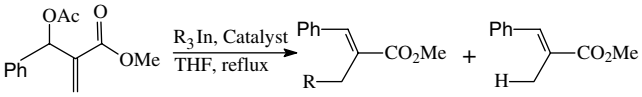


Scheme 1.

Keywords: Triorganoindium; Baylis–Hillman adduct; Trisubstituted alkene; Copper(I) iodide; Tetrakistriphenylphosphine palladium.
* Corresponding author. Tel.: +91 33 2473 4971; fax: 91 33 2473 2805; e-mail: ocbcr@iacs.res.in

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.03.154

Table 1. Study of the effect of catalyst on the reaction of triorganoindiums with 2-(acetoxy-phenyl-methyl)-acrylic acid methyl ester



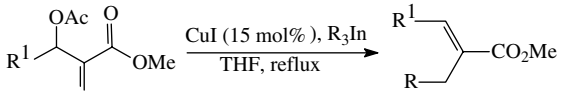
A **B**

Entry	Catalyst	R	Yield[a] (%)	Ratio of **A**:**B**
1	$Pd_2(dba)_3$, PPh_3	*n*-Bu	50	0:100
2	$Pd(OAc)_2$, PPh_3	*n*-Bu	45	0:100
3	$Pd(PPh_3)_4$	*n*-Bu	72	0:100
4	CuI	*n*-Bu	82	100:0
5	CuBr·SMe_2	*n*-Bu	75	100:0
6	$Cu(OTf)_2$	*n*-Bu	20	100:0
7	CuI	Ph	10	100:0
8	CuI, BF_3·etherate	Ph	—	—
9	$Cu(OTf)_2$	Ph	—	—
10	CuCN	Ph	—	—
11	$Pd(PPh_3)_4$	Ph	70	100:0
12	CuI	Ph–≡–	—	—
13	$Pd(PPh_3)_4$	Ph–≡–	—	—

[a] Yields refer to those of pure isolated products characterized by IR, ^1H and ^{13}C NMR spectroscopic data.

Sarandeses[5b] in which $Cu(OTf)_2$ was successfully used for the cross coupling of trialkyl- and triarylindiums to cinnamyl bromide although it did not work for cinnamyl acetate. We also found that $Cu(OTf)_2$ was not very efficient in tributylindium addition to a Baylis–Hillman acetate, however, CuI produced very encouraging results. Thus, it was decided to carry out the reactions of trialkylindiums under CuI catalysis and those of triarylindiums with $Pd(PPh_3)_4$.

Table 2. Addition of trialkylindiums to acetates of Baylis–Hillman adducts catalyzed by CuI

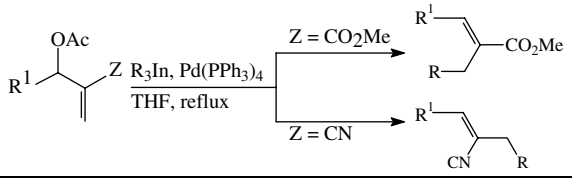


Entry	R^1	R	Time (h)	Yield[a] (%)	Reference
1	Ph	*n*-Bu	6.0	82	3a
2	Ph	Me	5.0	60	11
3	*p*-MeO–C_6H_4	*n*-Bu	6.5	78	3e
4	*p*-O_2N–C_6H_4	*n*-Bu	5.5	75	
5	*p*-Cl–C_6H_4	*n*-Bu	5.0	80	
6	*p*-MeCO–C_6H_4	*n*-Bu	6.0	75	
7	*n*-C_3H_7	*n*-Bu	5.5	85	

[a] Yields refer to those of pure isolated products fully characterized by spectroscopic data.

The experimental procedure is very simple.[7] Several diversely substituted 3-acetoxy-2-methylenealkanoates (acetates of Baylis–Hillman adducts)[8] underwent very easy reactions with trimethyl and tri-*n*-butylindiums[9] in the presence of CuI to produce the corresponding (*E*)-2-substituted alken-2-enoates. The results are summarized in Table 2. The presence of electron donating and electron withdrawing groups on the aromatic ring of the adduct (entries 3 and 4, Table 2) did not make any difference with regard to reactivity and yields of products. The addition of trialkylindiums was also highly chemoselective as the keto-carbonyl present in the substrate in entry 6, Table 2 and entry 4, Table 3 remained intact even when excess trialkylindium was

Table 3. Addition of triarylindiums to acetates of Baylis–Hillman adducts catalyzed by $Pd(PPh_3)_4$



Entry	R^1	Z	R	Time (h)	Yield[a] (%)	Ratio of *E*:*Z* isomers	Reference
1	Ph	CO_2Me		3.5	75	95:5	3b
2	Ph	CO_2Me		4.0	70	100:0	12
3	*p*-Cl–C_6H_4	CO_2Me		3.0	72	80:20	3d
4	*p*-MeCO–C_6H_4	CO_2Me		4.0	70	90:10	
5	*p*-Me–C_6H_4	CN		3.5	72	0:100	
6	Ph	CN		3.2	75	0:100	3b
7	Ph	CN		3.5	70	5:95	13

[a] Yields refer to those of pure isolated products fully characterized by spectroscopic data.

used. It should be mentioned that no existing procedures have addressed the compatibility of carbonyl groups present in the molecule.[3]

A number of triaryl- and trivinylindiums were subjected to additions with several acetates of Baylis–Hillman adducts under the catalysis of $Pd(PPh_3)_4$ using this procedure to provide the corresponding products. The results are reported in Table 3. In accordance with the results obtained by other groups,[3] the acetates of Baylis–Hillman carboalkoxy adducts produced mainly (*E*)-alkenes (entries 1–4, Table 3) whereas Baylis–Hillman nitrile adducts led to (*Z*)-isomers (entries 5–7, Table 3) exclusively, or stereoselectively. The stereochemistry of the products was established by comparing NMR parameters for the olefinic and methylene protons with literature values.[3] It was observed that small amounts (2–5%) of the corresponding homocoupled products from triarylindiums were also formed in these reactions.

In general, the reactions were high yielding. THF was found to be the most suitable solvent and the reactions were carried out under reflux. As is evident from the results, aryl transfer from the triarylindiums proceeded smoothly under Pd-catalysis, whereas alkyl transfer occurred via CuI catalysis. Although Pd-catalysis is well documented,[3,5] Cu-catalysis in alkyl additions to Baylis–Hillman acetates is less explored. It may be assumed that the trialkylindium undergoes transmetallation with CuI and subsequently the organocuprate forms a π-complex with the Baylis–Hillman acetate adduct in which the cuprate fragment is bound *anti* to the acetate moiety. Reductive elimination of alkylcopper through a σ-copper(III) species with retention of configuration gives rise to the S_N2' product.[10] It is worth mentioning that $Cu(OTf)_2$-catalyzed coupling of triorganylindiums to cinnamyl bromide provided both S_N2 and S_N2' products and that $Cu(OTf)_2$ did not initiate addition to cinnamyl acetate. Significantly, this CuI-catalyzed reaction led only to S_N2' products.

In conclusion, we have developed a general and efficient method for the addition of triorganoindiums to Baylis–Hillman acetate adducts to provide (*E*)- and (*Z*)-trisubstituted alkenes stereoselectively. Substrates bearing carboalkoxy moieties produced (*E*)-alkenes, whereas those having a nitrile group gave (*Z*)-alkenes. This protocol is applicable to both alkyl and aryl transfer under CuI and $Pd(PPh_3)_4$ catalysis, respectively. The use of triorganoindiums in this addition reaction made this procedure chemoselective being inert to carbonyl groups, which is not likely to be achieved with Grignard reagents.

Acknowledgements

We are pleased to acknowledge financial support from the CSIR [Grant No. 01(1936)/04/EMR-1], New Delhi, for this project. K.C. and R.J. also thank the CSIR for their fellowships.

References and notes

1. Baylis, A. B.; Hillman, M. E. D. German Patent 2,155,113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q.
2. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891, and references cited therein; (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1998**, *44*, 4653–4670.
3. (a) Basavaiah, D.; Sarma, P. K. S.; Bhavani, A. K. D. *Chem. Commun.* **1994**, 1091–1092; (b) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, *5*, 3803–3805; (c) Navarre, L.; Darses, S.; Genet, J.-P. *Adv. Synth. Catal.* **2006**, *348*, 317–322; (d) Kabalka, G. W.; Dong, G.; Venkataiah, B.; Chen, C. *J. Org. Chem.* **2005**, *70*, 9207–9210; (e) Das, B.; Banerjee, J.; Mahender, G.; Majhi, A. *Org. Lett.* **2004**, *6*, 3349–3352; (f) Basavaiah, D.; Krishnamacharyulu, H. R. S.; Pandiaraju, S. *Tetrahedron Lett.* **1997**, *38*, 2141–2144.
4. (a) Cintas, P. *Synlett* **1995**, 1087–1096; (b) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643–5668; (c) Li, C.-J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149–11176; (d) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015–3019; (e) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347–2356; (f) Ghosh, R. *Indian J. Chem.* **2001**, *40B*, 550–557; (g) Podelech, J.; Maier, T. C. *Synthesis* **2003**, 633–655; (h) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *68*, 1959–1982.
5. (a) Metza, J. T., Jr.; Terzian, A.; Minehan, T. *Tetrahedron Lett.* **2006**, *47*, 8905–8910; (b) Rodriguez, D.; Sestelo, J. P.; Sarandeses, L. A. *J. Org. Chem.* **2003**, *68*, 2518–2520; (c) Reveiros, R.; Rodriguez, D.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **2006**, *8*, 1403–1406; (d) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155–4160; (e) Baker, L.; Minehan, T. *J. Org. Chem.* **2004**, *69*, 3957–3960; (f) Pena, M. A.; Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246–2247; (g) Lee, P. H.; Lee, S. W.; Lee, K. *Org. Lett.* **2003**, *5*, 1103–1106; (h) Fausett, B. W.; Liebeskind, L. S. *J. Org. Chem.* **2005**, *70*, 4851–4853; (i) Perez, I.; Sestelo, J. P.; Maestro, M. A.; Mourino, A.; Sarandeses, L. A. *J. Org. Chem.* **1998**, *63*, 10074–10076.
6. (a) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270–6272; (b) Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2000**, *41*, 531–533; (c) Ranu, B. C.; Samanta, S.; Hajra, A. *Synlett* **2002**, 987–989; (d) Ranu, B. C.; Das, A.; Samanta, S. *Synlett* **2002**, 727–730; (e) Ranu, B. C.; Dey, S. S.; Hajra, A. *Tetrahedron* **2002**, *58*, 2529–2532; (f) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **2003**, *59*, 813–819; (g) Ranu, B. C.; Samanta, S. *J. Org. Chem.* **2003**, *68*, 7130–7132; (h) Ranu, B. C.; Das, A.; Hajra, A. *Synthesis* **2003**, 1012–1014; (i) Ranu, B. C.; Samanta, S. *Tetrahedron* **2003**, *59*, 7901–7906; (j) Ranu, B. C.; Mandal, T.; Samanta, S. *Org. Lett.* **2003**, *5*, 1439–1441; (k) Ranu, B. C.; Mandal, T. *J. Org. Chem.* **2004**, *69*, 5793–5795; (l) Ranu, B. C.; Mandal, T. *Synlett* **2004**, 1239–1242; (m) Ranu, B. C.; Das, A. *Tetrahedron Lett.* **2004**, *45*, 6875–6877; (n) Ranu, B. C.; Jana, R.; Samanta, S. *Adv. Synth. Catal.* **2004**, *346*, 446–450; (o) Ranu, B. C.; Das, A. *Adv. Synth. Catal.* **2005**, *347*, 712–714; (p) Ranu, B. C.; Chattopadhyay, K.; Banerjee, S. *J. Org. Chem.* **2006**, *71*, 423–425; (q) Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2006**, *47*, 2859–2861; (r) Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2006**, *47*, 5677–5680; (s) Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2006**, *47*, 6911–6914.
7. *Representative procedure for the addition of tributylindium to 2-[acetoxy-(4-acetylphenyl)-methyl]-acrylic acid methyl ester* (Table 2, entry 6). A solution of 2-[acetoxy-(4-acetylphenyl)-methyl]-acrylic acid methyl ester (276 mg,

1 mmol) and tributylindium (1.2 mmol) in THF (3 mL) was heated under reflux for 6 h (TLC) in the presence of CuI (28 mg, 15 mol %). The reaction mixture was then quenched with a few drops of H_2O and extracted with Et_2O (3×6 mL). The extract was washed with aqueous HCl (0.5 N), brine, water and dried over Na_2SO_4. Evaporation of the solvent gave a crude product, which was purified by column chromatography over silica gel (hexane–ethyl acetate 98:2) to furnish 3-(4-acetylphenyl)-2-pentylacrylic acid methyl ester (205 mg, 75%) as a yellow semi-solid; IR (neat): 2954, 2929, 2860, 1714, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86–0.89 (m, 3H), 1.29–1.30 (m, 4H), 1.49–1.54 (m, 2H), 2.45–2.50 (m, 2H), 2.60 (s, 3H), 3.81 (s, 3H), 7.41 (d, $J = 8.07$ Hz, 2H), 7.62 (s, 1H), 7.96 (d, $J = 8.07$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.4, 26.7, 27.7, 29.0, 31.9, 52.1, 128.5 (2C), 128.6, 129.3 (2C), 135.8, 136.5, 140.7, 168.6, 197.5. Anal. Calcd for $C_{17}H_{27}O_3$: C, 74.42; H, 8.08. Found: C, 74.39; H, 8.01.

This procedure was followed for the reactions of all the substrates listed in Tables 2 and 3. The products (entries 1–3, Table 2) and entries (1, 2, 3, 6 and 7, Table 3) were identified by comparison of their spectroscopic data (IR, ^1H NMR and ^{13}C NMR) with those reported (see references in Tables 2 and 3). New compounds (entries 4–7, Table 2) and entries (4 and 5, Table 3) were characterized from their spectroscopic data and elemental analysis. These data are presented below:

3-(4-Nitrophenyl)-2-pentyl-acrylic acid methyl ester (entry 4, Table 2): Yellow semi-solid; IR (neat) 2954, 2929, 1517, 1597, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85–0.90 (m, 3H), 1.25–1.32 (m, 4H), 1.49–1.59 (m, 2H), 2.44–2.49 (m, 2H), 3.84 (s, 3H), 7.47 (d, $J = 8.8$ Hz, 2H), 7.64 (s, 1H), 8.25 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz)δ 14.3, 22.7, 28.0, 29.2, 32.1, 51.8, 124.1 (2C), 130.1 (2C), 136.4, 137.5, 142.9, 147.8, 168.5. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.91; H, 7.01; N, 5.15.

3-(4-Chloro-phenyl)-2-pentyl-acrylic acid methyl ester (entry 5, Table 2): Yellow semi-solid; IR (neat) 3026, 3001, 1714, 1404 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85–0.90 (m, 3H), 1.30–1.33 (m, 4H), 1.46–1.54 (m, 2H), 2.44–2.49 (m, 2H), 3.80 (s, 3H), 7.26 (d, $J = 8.3$ Hz, 2H), 7.35 (d, $J = 8.3$ Hz, 2H), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 22.2, 27.4, 28.7, 31.8, 51.9, 128.6 (2C), 130.3 (2C), 134.1, 134.2, 134.3, 137.2, 168.6. Anal. Calcd for $C_{15}H_{19}ClO_2$: C, 67.54; H, 7.18. Found: C, 67.49; H, 7.17.

2-Pentyl-hex-2-enoic acid methyl ester (entry 7, Table 2): Yellow oil; IR (neat) 2956, 2871, 1716, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84–0.97 (m, 6H), 1.24–1.73 (m, 8H), 2.13 (q, $J = 7.3$ Hz, 2H), 2.26 (t, $J = 6.9$ Hz, 2H), 3.7 (s, 3H), 6.7 (t, $J = 15.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 14.3, 22.4, 22.8, 27.1, 29.3, 30.9, 32.1, 51.9, 132.9, 142.9, 168.9. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.36; H, 11.05.

3-(4-Acetyl-phenyl)-2-benzyl acrylic methyl ester (entry 4, Table 3): Yellow semi-solid; IR (neat) 2952, 2929, 1715, 1682, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, 3H), 3.75 (s, 3H), 3.93 (s, 2H), 7.15–7.31 (m, 6H), 7.43–7.45 (m, 2H), 7.91–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.7, 33.3, 52.4, 126.4, 127.9 (2C), 128.6 (2C), 128.7 (2C), 129.1, 129.4 (2C), 130.1, 132.8, 139.0, 140.0, 168.3, 197.5. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.28; H, 6.07.

(*Z*)-2-(4-Methyl-benzyl)-3-*p*-tolyl-acrylonitrile (entry 5, Table 3): Yellow semi-solid; IR (neat) 3024, 2860, 2208, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 2.35 (s, 3H), 3.63 (s, 2H), 6.90 (s, 1H), 7.14–7.23 (m, 6H), 7.61 (d, $J = 8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2, 21.5, 41.8, 109.8, 118.5, 128.8 (2C), 128.9 (2C), 129.6 (2C), 129.7 (2C), 131.0, 133.8, 137.0, 140.5,143.9. Anal. Calcd for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.11; H, 7.01; N, 5.52.

8. (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795–796; (b) Basavaiah, D.; Gowriswari, V. V. L. *Synth. Commun.* **1987**, *17*, 587–591.
9. Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267–1269.
10. Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186–204, and references cited therein.
11. Murakami, M.; Ishida, N.; Miura, T. *Chem. Commun.* **2006**, 643–645.
12. Datta, A.; Ila, H.; Junjappa, H. *Tetrahedron* **1987**, *43*, 5367–5374.
13. Thibornet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319–3322.