One-Pot Synthesis of γ-Diketones, γ-Keto Esters, and Conjugated Cyclopentenones from Nitroalkanes

Roberto Ballini,* Luciano Barboni, Giovanna Bosica, Dennis Fiorini

Dipartimento di Scienze Chimiche dell'Università, Via S. Agostino 1, 62032 Camerino (MC), Italy
Fax +39(737)402297; E-mail: roberto.ballini@unicam.it

Received 28 August 2002; revised 27 September 2002

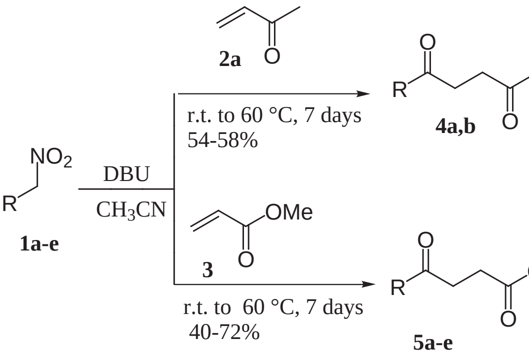
Abstract: Conjugated addition of primary nitroalkanes to α,β-unsaturated ketones or α,β-unsaturated esters, in the presence of two equivalents of DBU, allows the one-pot prepration of γ-diketones or γ-keto esters, respectively. When 2-aryl-1-nitroethane derivatives are employed as starting nitroalkanes in the reaction with α,β-unsaturated ketones, the one-pot formation of cyclopentenones is observed.

Key words: nitroalkanes, γ-diketones, γ-keto esters, cyclopentenones, DBU

The synthesis of complex molecules is traditionally performed by a chain of separate reaction steps, each step requiring its own conditions, reagents, solvent, and catalyst. After each reaction is complete the solvent and the waste products are removed and discarded, and the intermediate product is separated and purified. Now, environmental and economic pressure are forcing the chemical community to search for more efficient ways to perform chemical transformations.[1] These new issues can be addressed by the development of new synthetic methods that, bringing together simple components, generate complex structures in a one-pot procedure, much the same way as nature does.

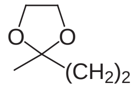
γ-Diketones,[2] are important intermediates for the synthesis of cyclic and heterocyclic compounds such as furans, pyrroles, thiophenes, and pyridazines.[2–7] γ-Keto esters represent a valuable class of compounds as intermediates for various heterocyclic compounds such as lactones, β-lactam antibiotics, isoquinolines and lactonic sex pheromones.[8] The cyclopentenone ring is one of the most recurring structural unit in targets of relevant practical interest.[6,9] Although several methods have been reported for the synthesis of the above compounds,[5,6,10–13] most of these suffer from drawbacks such as the use of harsh conditions, employment of expensive chemicals, tedious procedure, low yields and/or the need of many steps.

Recently we reported an unprecedent, selective Nef conversion of secondary nitroalkanes, promoted under basic conditions, by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a tertiary amidine base.[14] This new discovery, combined with the peculiarity of the aliphatic nitro compounds in the formation of carbon–carbon single bond, under basic conditions,[15] suggested us a new way for a one-pot synthesis of the title compounds. In fact, the reaction of primary nitroalkanes **1** to methyl vinyl ketone (MVK, **2a**) or methyl acrylate (**3**) (Scheme 1), with the help of two equivalents of DBU in MeCN allows, after seven days at room temperature to 60 °C, the one-pot formation of γ-diketones **4** or γ-keto esters **5**, respectively. The yields are from satisfactory to good (40–72%, Table 1), even when functionalized nitroalkanes are employed as starting material. The spectroscopic data of compounds **4** and **5** prepared are given in Table 2.



Scheme 1 Synthesis of γ-diketones **4a**,**b** and γ-keto esters **5a**–**e**

Table 1 One Pot Synthesis of γ-Diketones **4** and γ-Keto Esters **5**

Entry	R	Acceptor	Yield (%)[a,b] of **4**	Yield (%)[a,b] of **5**
a	$CH_3(CH_2)_2$	**2a**	58	–
b	$CH_3(CH_2)_4$	**2a**	54	–
a	$CH_3(CH_2)_2$	**3**	–	60
b	$CH_3(CH_2)_4$	**3**	–	72
c		**3**	–	71
d	$HO(CH_2)_4$	**3**	–	40
e	$PhCH_2$	**3**	–	47

[a] Yield of pure, isolated product.
[b] Satisfactory microanalyses obtained: C ±0.14, H ±0.21.

Synthesis 2002, No. 18, Print: 19 12 2002.
Art Id.1437-210X,E;2002,0,18,2725,2728,ftx,en;Z12102SS.pdf.

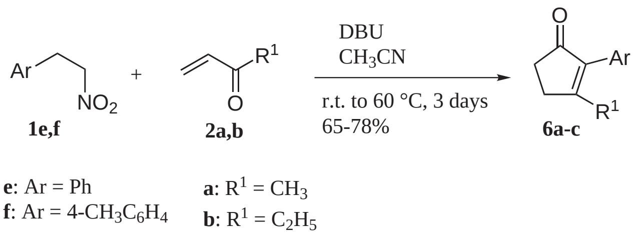
ISSN 0039-7881

Table 2 Spectroscopic Data of γ-Diketones **4a,b** and γ-Keto Esters **5a-e**

Product	IR (film) (cm^{-1})	^{1}H NMR ($\mathrm{CDCl_3}$) δ, J (Hz)	^{13}C NMR (50 MHz, $\mathrm{CDCl_3}$) δ	MS: m/z
4a	1714	0.88 (t, 3 H, $\mathrm{C}H_3\mathrm{CH_2}$, J = 7.5), 1.51–1.64 (m, 2 H, $\mathrm{MeC}H_2\mathrm{CH_2}$), 2.15 (s, 3 H, $\mathrm{CH_3CO}$), 2.40 (t, 2 H, $\mathrm{MeCH_2C}H_2$, J = 7.3), 2.60–2.71 (m, 4 H, $\mathrm{COC}H_2\mathrm{C}H_2\mathrm{CO}$)	209.57 ($\mathrm{CH_2}C\mathrm{OCH_2}$), 207.32 ($\mathrm{CH_2}C\mathrm{OMe}$), 44.70 ($\mathrm{MeCH_2}C\mathrm{H_2CO}$), 36.87 ($C\mathrm{H_2COMe}$), 36.05 ($\mathrm{CO}C\mathrm{H_2CH_2COMe}$), 29.96 ($\mathrm{CO}C\mathrm{H_3}$), 17.28 ($\mathrm{Me}C\mathrm{H_2}$), 13.70 ($C\mathrm{H_3CH_2}$)	142 (M^+), 124, 114, 99, 71, 43 (100)
4b	1715	0.90 (t, 3 H, $\mathrm{C}H_3\mathrm{CH_2}$, J = 6.6), 1.20–1.39 (m, 4 H, $\mathrm{MeC}H_2\mathrm{C}H_2$), 1.51–1.67 (m, 2 H, $\mathrm{CH_2C}H_2\mathrm{CH_2CO}$), 2.20 (s, 3 H, $\mathrm{CH_3CO}$), 2.46 [t, 2 H, $\mathrm{Me(CH_2)_3C}H_2\mathrm{CO}$, J = 7.5], 2.64–2.76 (m, 4 H, $\mathrm{COC}H_2\mathrm{C}H_2\mathrm{CO}$)	209.71 ($\mathrm{CH_2}C\mathrm{OCH_2}$), 207.34 ($\mathrm{CH_2}C\mathrm{OMe}$), 42.81 [$\mathrm{Me(CH_2)_3}C\mathrm{H_2CO}$], 36.90 ($C\mathrm{H_2COMe}$), 36.04 ($\mathrm{CO}C\mathrm{H_2CH_2COMe}$), 31.36 ($\mathrm{MeCH_2}C\mathrm{H_2}$), 29.98 ($\mathrm{CO}C\mathrm{H_3}$), 25.45 [$\mathrm{Me(CH_2)_2}C\mathrm{H_2}$], 23.52 ($\mathrm{Me}C\mathrm{H_2}$), 13.92 ($C\mathrm{H_3CH_2}$)	170 (M^+), 127, 114, 99, 43
5a	1740, 1715	0.92 (t, 3 H, $\mathrm{CH_3}$, J = 7.3), 1.54–1.73 (m, 2 H, $\mathrm{MeC}H_2$), 2.44 (t, 2 H, $\mathrm{MeCH_2C}H_2$, J = 7.3), 2.59 (t, 2 H, $\mathrm{C}H_2\mathrm{CO_2Me}$, J = 6.3), 2.73 (t, 2 H, $\mathrm{COC}H_2\mathrm{CH_2CO_2Me}$, J = 6.2), 3.68 (s, 3 H, $\mathrm{OCH_3}$)	209.00 ($\mathrm{CH_2}C\mathrm{OCH_2}$), 173.29 ($C\mathrm{O_2Me}$), 51.72 ($\mathrm{CO_2}C\mathrm{H_3}$), 44.63 ($\mathrm{MeCH_2}C\mathrm{H_2CO}$), 36.97 ($\mathrm{CO}C\mathrm{H_2CH_2CO_2Me}$), 27.64 ($C\mathrm{H_2CO_2Me}$), 17.22 ($\mathrm{Me}C\mathrm{H_2}$), 13.64 ($C\mathrm{H_3CH_2}$)	158 (M^+), 143, 127, 115 (100), 71, 55, 43
5b	1741, 1716	0.89 (t, 3 H, $\mathrm{C}H_3$, J = 6.6), 1.20–1.40 (m, 4 H, $\mathrm{MeC}H_2\mathrm{C}H_2$), 1.52–1.68 (m, 2 H, $\mathrm{CH_2C}H_2\mathrm{CH_2CO}$), 2.45 [t, 2 H, $\mathrm{Me(CH_2)_3C}H_2\mathrm{CO}$, J = 7.3], 2.59 (t, 2 H, $\mathrm{CH_2C}H_2\mathrm{CO_2Me}$, J = 6.3), 2.73 (t, 2 H, $\mathrm{COC}H_2\mathrm{CH_2CO_2Me}$, J = 6.0), 3.69 (s, 3 H, $\mathrm{OCH_3}$)	209.13 ($\mathrm{CH_2}C\mathrm{OCH_2}$), 173.31 ($C\mathrm{O_2Me}$), 51.76 ($\mathrm{CO_2}C\mathrm{H_3}$), 42.75 [$\mathrm{Me(CH_2)_3}C\mathrm{H_2COCH_2}$], 37.00 ($\mathrm{CO}C\mathrm{H_2CH_2CO_2Me}$), 31.34 ($\mathrm{MeCH_2}C\mathrm{H_2}$), 27.71 ($C\mathrm{H_2CO_2Me}$), 23.47 [$\mathrm{Me(CH_2)_2}C\mathrm{H_2}$], 22.42 ($\mathrm{Me}C\mathrm{H_2}$), 13.89 ($C\mathrm{H_3CH_2}$)	186 (M^+), 155, 130, 115, 98 (100), 71, 55, 43
5c	1736, 1712	1.33 [s, 3 H, $\mathrm{C}H_3\mathrm{C(OCH_2CH_2O)CH_2}$], 2.01 [t, 2 H, $\mathrm{MeC(OCH_2CH_2O)C}H_2\mathrm{CH_2}$, J = 7.5], 2.55 [t, 2 H, $\mathrm{MeC(OCH_2CH_2O)CH_2C}H_2\mathrm{CO}$, J = 7.7], 2.60 (t, 2 H, $\mathrm{COCH_2C}H_2\mathrm{CO_2Me}$, J = 5.9), 2.77 (t, 2 H, $\mathrm{COC}H_2\mathrm{CH_2CO_2Me}$, J = 6.3), 3.68 (s, 3 H, $\mathrm{OCH_3}$), 3.92–3.98 [m, 4H, $\mathrm{MeC(OC}H_2\mathrm{C}H_2\mathrm{O)CH_2}$]	208.09 ($\mathrm{CH_2}C\mathrm{OCH_2}$), 173.07 ($C\mathrm{O_2Me}$), 109.00 [$\mathrm{Me}C\mathrm{(OCH_2CH_2O)CH_2}$], 64.44 ($\mathrm{O}C\mathrm{H_2}C\mathrm{H_2O}$), 51.55 ($\mathrm{CO_2}C\mathrm{H_3}$), 37.03 [$C\mathrm{H_2CO(CH_2)_2CO_2Me}$], 36.74 ($\mathrm{CH_2CO}C\mathrm{H_2CH_2CO_2Me}$), 32.50 [$\mathrm{MeC(OCH_2CH_2O)}C\mathrm{H_2}$], 27.50 ($C\mathrm{H_2CO_2Me}$), 23.71 [$C\mathrm{H_3C(OCH_2)_2OCH_2}$]	215, 199, 127, 87 (100), 71, 55, 43
5d	3506, 1740, 1720	1.23–1.73 (m, 4 H, $\mathrm{HOCH_2C}H_2\mathrm{C}H_2\mathrm{CH_2CO}$), 2.49 [t, 2 H, $\mathrm{HO(CH_2)_3C}H_2\mathrm{CO}$ J = 7.1], 2.61 (t, 2 H, $\mathrm{COCH_2C}H_2\mathrm{CO_2Me}$, J = 5.8), 2.74 (t, 2 H, $\mathrm{COC}H_2\mathrm{CH_2CO_2Me}$, J = 6.1), 3.60–3.70 (m, 3 H, $H\mathrm{OC}H_2\mathrm{CH_2}$), 3.69 (s, 3 H, $\mathrm{OCH_3}$)	209.22 ($\mathrm{CH_2}C\mathrm{OCH_2}$), 173.57 ($\mathrm{CH_2}C\mathrm{O_2Me}$), 62.83 ($\mathrm{HOCH_2}$), 52.02 ($\mathrm{CO_2}C\mathrm{H_3}$), 42.81 [$\mathrm{HO(CH_2)_3}C\mathrm{H_2CO}$], 37.24 [$\mathrm{HO(CH_2)_4CO}C\mathrm{H_2}$], 32.60 [$\mathrm{HOCH_2}C\mathrm{H_2(CH_2)_2CO}$], 27.89 ($\mathrm{COCH_2}C\mathrm{H_2CO_2Me}$), 23.58 [$\mathrm{HO(CH_2)_2}C\mathrm{H_2CH_2CO}$]	173 [M^+ – 18], 141, 115, 88, 59, 55 (100), 41
5e	1738, 1721	2.58 (t, 2 H, $\mathrm{COCH_2C}H_2\mathrm{CO_2Me}$, J = 6.0), 2.78 (t, 2 H, $\mathrm{COC}H_2\mathrm{CH_2CO_2Me}$, J = 6.0), 3.67 (s, 3 H, $\mathrm{OCH_3}$), 3.76 (s, 2 H, $\mathrm{PhC}H_2\mathrm{CO}$), 7.20–7.42 (m, 5 H, $\mathrm{C_6H_5}$)	206.6 ($\mathrm{CH_2}C\mathrm{OCH_2}$), 173.14 ($C\mathrm{O_2Me}$), 134.00 ($C_{\mathrm{Ph}}$), 129.43 ($\mathrm{CH}_{o\text{-}\mathrm{Ph}}$), 128.74 ($\mathrm{CH}_{p\text{-}\mathrm{Ph}}$), 127.09 ($\mathrm{CH}_{m\text{-}\mathrm{Ph}}$), 51.78 ($\mathrm{CO_2}C\mathrm{H_3}$), 50.05 ($\mathrm{Ph}C\mathrm{H_2}$), 36.44 ($\mathrm{CO}C\mathrm{H_2CH_2CO_2Me}$), 27.80 ($C\mathrm{H_2CO_2Me}$)	206 (M^+), 190, 130, 117 (100), 91

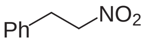
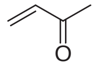
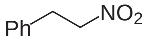
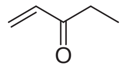
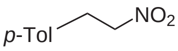
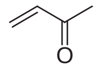
Of great interest is the possibility to realize the one-pot preparation of cyclopentenones **6** by the appropriate choice of the starting nitroalkanes in the reaction with the conjugated enones **2a**,**b** (Scheme 2). In fact we observed that if 2-aryl-1-nitroethane derivatives **1e**,**f** are employed, the Michael addition directly produce, after three days, the cyclic enones **6** in 65–78% yields (Table 3).

In conclusion, the utilization of DBU as base, in the conjugate addition of nitroalkanes to electron-poor alkenes, offers the opportunity to perform the one-pot synthesis of γ-diketones, γ-keto esters and cyclopentenones, under mild conditions and with satisfactory to good overall yields.



Scheme 2 Synthesis of cyclopentenones **6a**–**c**

Table 3 One-Pot Synthesis of Cyclopentenones **6**

Entry	Nitroalkane	Acceptor	Yield (%)[a] of **6**
a	 **1e**	 **2a**	68
b	 **1e**	 **2b**	65
c	 **1f**	 **2a**	78

[a] Yield of pure, isolated product.

^{1}H and ^{13}C NMR were recorded in $CDCl_3$ at 200 and 50 MHz, respectively, on a Varian Gemini 200 spectrometer. Chemical shifts are expressed in ppm downfield from TMS. Mass spectra were determined on a Capillary GC/MS operating in the split mode with He carrier gas with a mass-selective detector (MDS). IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Elemental analyses were performed using a C, H Analyzer Model 185 from Hewlett-Packard. All the reactions were monitored by TLC, and gas chromatographic analyses were performed on a Carlo Erba Fractovap 4160 using a capillary column of duran glass (0.32 mm × 25 m), stationary phase OV1 (film thickness 0.4–0.45 μm). Petroleum ether used had bp 30–60 °C.

γ-Diketones 4 and γ-Keto Esters 5; General Procedure

A solution of the electrophilic acceptor **2a** or **3** (5 mmol) in MeCN (10 mL) was added dropwise to a solution of nitroalkane **1a**–**e** (5 mmol) in MeCN (20 mL) at r.t. The reaction mixture was stirred at r.t. for 6 h, then heated at 60 °C. After 7 d, the solvent was removed under reduced pressure and the oily residue was purified by flash chromatography (EtOAc–petroleum ether as eluent), affording the pure compounds **4** or **5** (Tables 1, 2).

Cyclopentenones 6; General Procedure

A solution of the conjugated enone **2** (5 mmol) in MeCN (10 mL) was added dropwise to a solution of 2-aryl-1-nitroethane derivatives **1e**,**f** (5 mmol) in MeCN (20 mL) at r.t. The obtained solution was stirred at r.t. for 6 h, then heated at 60 °C. After 3 d, the solvent was removed under reduced pressure and the oily residue was purified by flash chromatography (EtOAc–petroleum ether as eluent), affording the pure compounds **6** (Table 3).

3-Methyl-2-phenylcyclopent-2-en-1-one (6a)

R_f 0.32 (cyclohexane–EtOAc, 8:2).

IR (film): 1690, 1635 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.21 (s, 3 H, CH_3), 2.55–2.61 (m, 2 H, CH_2CH_2CO), 2.67–2.73 (m, 2 H, CH_2CH_2CO), 7.25–7.49 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 207.63 (C=O), 171.80 (C=CCO), 140.36 (C=CCO), 129.11 (C_{Ph}), 128.28 (2 C, $CH_{o\text{-}Ph}$), 127.81 ($CH_{p\text{-}Ph}$), 127.60 (2 C, $CH_{m\text{-}Ph}$), 34.84 (CH_2CO), 31.83 (CH_2CH_2CO), 18.38 (CH_3C=C).

MS: *m*/*z* (%) = 172 (M^+), 157, 129 (100), 115.

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.77; H, 6.98.

3-Ethyl-2-phenylcyclopent-2-en-1-one (6b)

R_f 0.35 (cyclohexane–EtOAc, 8:2).

IR (film): 1690, 1630, 1600 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.20 (t, 3 H, *J* = 7.7, CH_3CH_2), 2.52–2.60 (m, 4 H, $MeCH_2$, CH_2CH_2CO), 2.67–2.74 (m, 2 H, CH_2CH_2CO), 7.22–7.44 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 208.09 (C=O), 176.97 (C=CCO), 139.95 (C=CCO), 129.11(C_{Ph}), 128.61 (2 C, $CH_{o\text{-}Ph}$), 128.31 ($CH_{p\text{-}Ph}$), 127.63 (2 C, $CH_{m\text{-}Ph}$), 34.70 (CH_2CO), 28.63 (CH_2CH_2CO), 24.89 (CH_2Me), 12.24 (CH_2CH_3).

MS: *m*/*z* (%) = 186 (M^+), 129 (100), 115.

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.91; H, 7.50.

3-Methyl-2-(4-methylphenyl)cyclopent-2-en-1-one (6c)

R_f 0.34 (cyclohexane–EtOAc, 8:2).

IR (film): 1680, 1630 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.20 (s, 3 H, =CCH_3), 2.38 (s, 3 H, $ArCH_3$), 2.53–2.59 (m, 2 H, $COCH_2CH_2$), 2.64–2.71 (m, 2 H, $COCH_2CH_2$), 7.17–7.30 (m, 4 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 208.02 (C=O), 171.45 (C=CCO), 140.48 (C=CCO), 137.57 (C_{Ar} next to cyclopentenone ring), 129.21 (C_{Ar} substituted with the CH_3 group), 129.10 (2 C, $CH_{m\text{-}Ar}$), 129.03 (2 C, $CH_{o\text{-}Ar}$), 35.01 (CH_2CO), 31.98 (CH_2CH_2CO), 21.48 ($ArCH_3$), 18.55 (=CCH_3).

MS: *m*/*z* (%) = 186 (M^+), 143 (100), 128, 115.

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.77; H, 7.66.

Acknowledgment

Financial support was carried out in the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' supported by MIUR (Ministero dell'Istruzione dell'Università e della Ricerca), Italy and by the University of Camerino.

References

(1) Hall, N. *Science* **1994**, *266*, 32.
(2) (a) Lever, O. W. Jr. *Tetrahedron* **1976**, *32*, 1943.
(b) Bossard, P.; Engster, C. H. *Adv. Heterocycl. Chem.* **1986**, *30*, 384.
(3) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 172.
(4) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*, Vol. 4; Katritsky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, **1984**, 329.
(5) Ellison, R. A. *Synthesis* **1973**, 397.
(6) Ho, T. L. *Synth. Commun.* **1974**, *4*, 265.
(7) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407.
(8) See for example: (a) Cardellach, J.; Font, J.; Ortuno, R. M. *J. Heteroycl. Chem.* **1984**, *21*, 327. (b) Short, K. M.; Mjalli, M. M. A. *Tetrahedron Lett.* **1997**, *38*, 359. (c) Frenette, R.; Monette, M.; Bernstein, M. A.; Young, R. N.; Verhoeven, I. R. *J. Org. Chem.* **1991**, *56*, 3083. (d) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509.
(9) (a) Mikolajaczyc, M.; Mikina, M.; Zurawinski, R. *Pure Appl. Chem.* **1999**, *71*, 473. (b) Collins, P. E.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533. (c) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.

(10) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867.

(11) (a) Trost, B. M.; Pinketon, A. B. *Org. Lett.* **2000**, *2*, 1601. (b) Rajesh, T.; Periasamy, M. *Organometallics* **1999**, *18*, 5709. (c) Langer, P.; Kohler, V. *Org. Lett.* **2000**, *2*, 1597.

(12) (a) Iwasawa, N. *Synlett* **1999**, 13. (b) Mahneteau-Betzer, F.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 5183.

(13) (a) Balaczewsky, P.; Kolajczyk, M. *Org. Lett.* **2000**, *2*, 1153. (b) Sakai, A.; Aoyama, T.; Shiori, T. *Tetrahedron Lett.* **2000**, *41*, 6859.

(14) (a) Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233. (b) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D.; Gil, M. V. *Synlett* **2002**, 1706.

(15) (a) Seebach, D.; Colvin, E. W.; Leher, F.; Weller, T. *Chimia* **1979**, *31*, 1. (b) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. (c) Ono, N.; Kaji, A. *Synthesis* **1986**, 693. (d) Ballini, R.; Bosica, G. In *Recent Research Development in Organic Chemistry*, Vol. 1; Transworld Research Network: Trivandrum, **1997**, 11.