Pergamon

Tetrahedron 55 (1999) 6097–6108

TETRAHEDRON

One-step Cross-coupling Reaction of Functionalized Alkyl Iodides with Aryl Halides by the Use of an Electrochemical Method

Nobuhito Kurono, Kazuya Sugita, Shingo Takasugi, and Masao Tokuda*

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

Received 17 February 1999; accepted 23 March 1999

Abstract

Organozinc compounds of functionalized alkyl iodide carrying an alkoxycarbonyl, cyano or alkenyl group were prepared in high yields under mild conditions (0°C-r.t., 10min in DMF) by the reaction of iodides with an electrogenerated reactive zinc (EGZn). Cross-coupling of the organozinc compounds with various aryl halides in the presence of 5 mol% $Pd(P(o\text{-}Tol)_3)_2Cl_2$ in THF gave the corresponding cross-coupled products in moderate to high yields. These cross-coupling reactions can be also achieved in one step and in one pot by the use of an electrochemical method utilizing a Pt cathode and Zn anode.

keywords: coupling reactions; electrode; palladium and compounds; zinc and compounds

Introduction

We have already reported a new method for the preparation of reactive zinc by electrolysis and its use in facile isoprenylation[1] and allylation[2] of aldehydes and ketones. Characterization of the electrogenerated reactive zinc (EGZn) shows that it was an aggregation of very fine crystalline zinc particles with a large surface area.[2] Although various methods of zinc activation, such as the reduction of zinc halide with alkaline metal or alkali metal naphthalenide, have been reported,[3] these methods require high temperatures and long reaction times or vigorous stirring during the reaction. On the other hand, Perichon and colleagues recently reported the preparation of a small amount of reactive zinc by a cathodic reduction of zinc bromide in acetonitrile, and they carried out the Blaise reaction in the presence of a catalytic amount of the reactive zinc under electrolytic or nonelectrolytic conditions.[4] As one of our continuing studies on the use of electrogenerated reactive zinc (EGZn) in carbon-carbon bond forming reactions, we examined the usefulness of a method for preparing organozinc compounds

e-mail; tokuda@org-mc.eng.hokudai.ac.jp.

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00281-1

from functionalized alkyl iodides using EGZn and their use in palladium-catalyzed cross-coupling with aryl halides. In this paper, we report that the corresponding organozinc compounds can readily be prepared under mild conditions with a short reaction time by the reaction of EGZn with functionalized alkyl iodides and that a cross-coupling reaction of the organozinc compounds with various aryl iodides readily took place in the presence of a palladium catalyst to give the corresponding cross-coupled products in high yields. We also report that these cross-coupling reactions can be achieved in one-step and in one-pot by using an electrochemical method.

Cross-coupling reactions of organozinc compounds with a variety of organic electrophiles using transition metal catalysts provide efficient methods for chemo- and regioselective formation of carbon-carbon bonds.[5] Usually, organozinc compounds can be prepared by direct reaction of organic halide with activated zinc[3] or by transmetallation of the corresponding organolithium or Grignard reagents with zinc halide.[5] For example, Tamaru and co-workers prepared ethyl 3-(iodozincio)propanoate and ethyl 4-(iodozincio)butanoate by the reaction of ethyl 3-iodopropanoate and ethyl 4-iodobutanoate with a Zn-Cu couple in benzene containing a small amount of DMA or DMF at 60°C for 3-4h.[6a] They utilized these organozinc reagents for a palladium catalyzed cross-coupling reaction with acid chlorides[6a] or aryl iodides.[6b] Similar cross-coupling of ethyl 3- and ethyl 4-(iodozincio)-alkanoates with *N*-heteroaryl halides has also been reported by Sakamoto and co-workers.[7]

Results and Discussion

Cross-coupling Using Electrogenerated Reactive Zinc

Reactive zinc metal was readily prepared by the electrolysis of a DMF solution containing 0.1M Et_4NClO_4 in a one-compartment cell fitted with a platinum plate cathode (2x2 cm^2) and a zinc plate anode (2x2 cm^2). Electrolysis was carried out at a constant current of 60 mA/cm^2 at room temperature under a nitrogen atmosphere. The electrolysis resulted in an anodic dissolution of the zinc anode to give zinc ions, which were reduced at the platinum cathode to give a black, zero valent reactive zinc (Scheme 1).

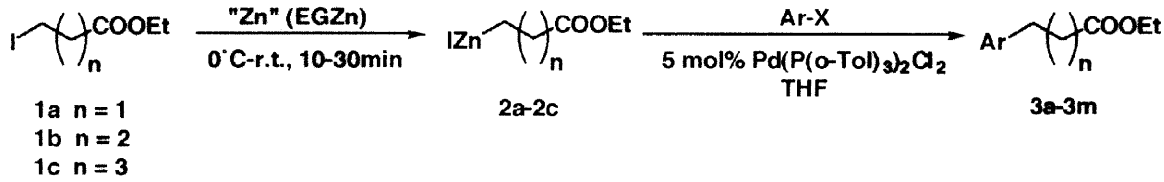
$$\text{Pt cathode - Zn anode} \xrightarrow[\text{0.1M } Et_4NClO_4\text{-DMF}]{\text{electrolysis}} \text{"Zn" (EGZn)}$$

Scheme 1

A solution containing EGZn was directly used in a preparation of functionalized alkylzinc iodide after the zinc anode was removed from the electrochemical cell. The reaction of alkyl iodide with the reactive zinc thus prepared (1.2 equivalents) at room temperature for 10-30 min gave the corresponding alkylzinc iodide in an almost quantitative yield. In the case of ethyl 3-iodopropanoate, a preparation of the corresponding organozinc species was carried out at 0°C. Formation of the organozinc compounds was monitored by GC and was determined by the disappearance of alkyl iodide and by the formation of protonated alkane after hydrolysis with a diluted HCl solution. It was found that organozinc compounds could readily be prepared from functionalized alkyl iodides

under milder conditions than those of previously reported methods. These organozinc compounds can successfully be utilized for the palladium-catalyzed cross-coupling reaction with aryl halides.[6,7]

A DMF solution of alkylzinc iodide (3 mmol) was transferred into a THF solution containing aryl halide (2 mmol) and $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.11 mmol) with a syringe, and the reaction mixture was stirred at 60°C for 3h. All of the cross-coupling reactions were carried out under an argon atmosphere. Usual work-up of the reaction mixture gave the corresponding cross-coupled products in good yields (Scheme 2). Results of the cross-coupling reaction of ethyl iodoalkanoates (**1a-c**) with aryl halides are summarized in Table 1.



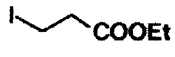
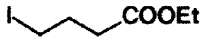
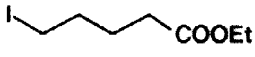
Scheme 2

Ethyl 3-iodopropanoate (**1a**), ethyl 4-iodobutanoate (**1b**), and ethyl 5-iodopentanoate (**1c**) could all be readily converted to the corresponding organozinc compounds (**2a-c**). Cross-coupling of these organozinc compounds with iodo or bromobenzene having electron-withdrawing and electron-donating groups gave the corresponding cross-coupled products (**3a-m**) in high yields. It should be noted that 1-iodo-3,4-dimethoxybenzene and 1-iodo-3,4-methylenedioxybenzene can be successfully used as aryl halide, and the corresponding cross-coupled products (**3g** and **3h**) were obtained in 74% and 90% yields, respectively. Cross-coupling of **2b** with 1-bromo and 2-bromonaphthalene also took place efficiently to give the products **3i** and **3j** in 85% and 79% yields, respectively.

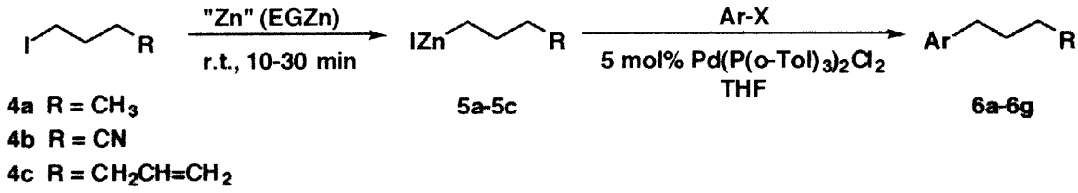
Products **3a**, **3b**, **3d**, and **3e** were also obtained in yields of 90%, 96%, 90%, and 75%, respectively, by the reported procedure using a Zn-Cu couple.[6b] Lower yields of **3a** and **3b** in our procedure are probably due to a formation of ethyl acrylate, a side reaction product, in the preparation step of ethyl 3-(iodozincio)propanoate, since the EGZn was so reactive.

It should be noted that ethyl 5-(iodozincio)pentanoate (**2c**) could effectively be prepared from the corresponding iodoalkanoate (**1c**) by the use of EGZn, although ethyl 3-(iodozincio)propanoate (**2a**) and ethyl 4-(iodozincio)butanoate (**2b**) are known to be relatively stable as metal homoenolate and bishomoenolate. Therefore, we next studied on a preparation of organozinc compounds of iodoalkanes carrying a cyano and an alkenyl group or of simple iodoalkane. It was found that the organozinc compounds **5a**, **5b**, and **5c** could be efficiently prepared from 1-iodobutane (**4a**), 4-iodobutanenitrile (**4b**), and 6-iodo-1-hexene (**4c**) under mild conditions by the use of EGZn. Cross-coupling of these organozinc compounds with various aryl halides under the same conditions as those of Scheme 2 gave the corresponding products (**6a-6g**) in high yields (Scheme 3). Results of these cross-coupling reactions are summarized in Table 2.

Table 1. Cross-coupling Reactions of Ethyl ω-Iodoalkanoate (**1a-c**) with Various Aryl Halides Using Electrogenerated Reactive Zinc (EGZn) [a]

Ethyl Iodoalkanoate	Ar-X	Product	Yield (%)[b]
 **1a**	C_6H_5I	$C_6H_5CH_2CH_2COOEt$ (**3a**)	76
	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4CH_2CH_2COOEt$ (**3b**)	58[c]
	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2COOEt$ (**3c**)	66[c]
 **1b**	C_6H_5I	$C_6H_5CH_2CH_2CH_2COOEt$ (**3d**)	84
	C_6H_5Br	$C_6H_5CH_2CH_2CH_2COOEt$ (**3d**)	85[c]
	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4CH_2CH_2CH_2COOEt$ (**3e**)	90[c]
	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2CH_2COOEt$ (**3f**)	84[c]
	3,4-$(CH_3O)_2C_6H_3I$	3,4-$(CH_3O)_2C_6H_3CH_2CH_2CH_2COOEt$ (**3g**)	74
	(3,4-OCH_2O-)C_6H_3I	(3,4-OCH_2O-)$C_6H_3CH_2CH_2CH_2COOEt$ (**3h**)	90[c]
	1-$C_{10}H_7Br$	1-$C_{10}H_7CH_2CH_2CH_2COOEt$ (**3i**)	85[c]
	2-$C_{10}H_7Br$	2-$C_{10}H_7CH_2CH_2CH_2COOEt$ (**3j**)	79[c]
 **1c**	C_6H_5I	$C_6H_5CH_2CH_2CH_2CH_2COOEt$ (**3k**)	86
	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4CH_2CH_2CH_2CH_2COOEt$ (**3l**)	80
	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2CH_2CH_2COOEt$ (**3m**)	82

a) Organozinc reagent of **1a-c** (3 mmol) was reacted at r.t. for 3h with aryl halides (2 mmol) in THF (20 ml) in the presence of $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.11 mmol).
b) Isolated yields.
c) Cross coupling reaction was carried out at 70°C.



Scheme 3

Table 2. Cross-coupling Reactions of Functionalized Iodoalkanes (**4a-c**) with Various Aryl Halides Using Electrogenerated Reactive Zinc (EGZn) [a]

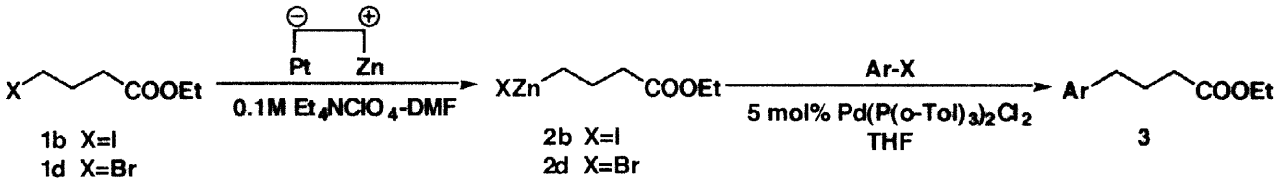
$ICH_2CH_2CH_2R$	Ar-X	Product	Yield (%)[b]
 4a	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4CH_2CH_2CH_3$ (6a)	79
	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2CH_3$ (6b)	48
 4b	C_6H_5I	$C_6H_5CH_2CH_2CH_2CN$ (6c)	66[c]
	C_6H_5Br	$C_6H_5CH_2CH_2CH_2CN$ (6c)	87
	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4CH_2CH_2CH_2CN$ (6d)	87
	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2CH_2CN$ (6e)	78
 4c	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4CH_2CH_2CH_2CH_2CH=CH_2$ (6f)	51
	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2CH_2CH_2CH=CH_2$ (6g)	98

a) Organozinc reagent of **4a-c** (3 mmol) was reacted at 70°C for 3h with aryl halides (2 mmol) in THF (20 ml) in the presence of $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.11 mmol).
b) Isolated yields.
c) Cross-coupling reaction was carried out at r.t. for 3h.

Two-step Procedure for the Cross-coupling Reaction

Organozinc compounds can be prepared directly from haloesters by utilizing an electrochemical method using a zinc anode. Electrolysis of ethyl 4-iodobutanoate (**1b**) in a DMF solution containing 0.1M Et_4NClO_4 with a platinum cathode and a zinc anode gave the corresponding organozinc compound **2b**, which was reacted with aryl halides in the presence of Pd complex to give the corresponding cross-coupled products **3d**, **3e**, and **3f** in 51-79% yields (Scheme 4, Table 3). Bromide can also be converted to the corresponding organozinc compound by the electrochemical method. Electrolysis of ethyl 4-bromobutanoate (**1d**) at 70°C under similar conditions as those

of **1b** followed by a cross-coupling reaction with 4-bromoacetophenone gave **3f** in a 60% yield. Yields of the products **3** obtained by using the present two-step procedure were slightly lower than those obtained by the reactions using EGZn.



Scheme 4

Table 3. Cross-coupling Reactions of Ethyl 4-Haloalkanoate (**1b, 1d**) with Aryl Halides by the Use of an Electrochemical Method using Zinc Anode[a)]

Haloester	Ar-X	Product	Yield (%)[b)]
I(CH2)3COOEt (1b)	C_6H_5I	$C_6H_5CH_2CH_2CH_2COOEt$ (3d)	79
	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4CH_2CH_2CH_2COOEt$ (3e)	51
	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2CH_2COOEt$ (3f)	69
Br(CH2)3COOEt[c)] (1d)	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2CH_2COOEt$ (3f)	60

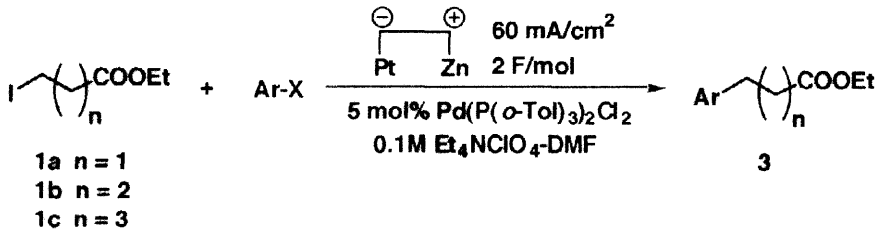
a) Electrolysis of haloester **1b** (3 mmol) was carried out in 0.1M Et_4NClO_4-DMF (15 ml) at 60 mA/cm^2 at r.t. with a Pt cathode and Zn anode. After electrolysis, the DMF solution containing **2b** was reacted at r.t. for 3h with aryl halide (2 mmol) in THF (20 ml) in the presence of $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.11 mmol).

b) Isolated yields.

c) Electrolysis of **1d** was carried out at 70°C. Other reaction conditions were almost the same as those described in footnote a.

One-step and One-pot Cross-coupling Reaction

We found that preparation of organozinc compounds and their cross-coupling with aryl halides can be carried out in a one-step and in a one-pot reaction by utilizing an electrochemical method. Thus, electrolysis of a mixture of ethyl iodoalkanoate (**1a-c**), aryl halide, and 5 mol% Pd complex in a DMF solution containing 0.1M Et_4NClO_4 with a platinum cathode and a zinc anode gave the corresponding cross-coupled products **3** in one step (Scheme 5). When $Ni(PPh_3)_2Cl_2$, $Pd(PPh_3)_2Cl_2$, or $Pd(P(o\text{-}Tol)_3)_2Cl_2$ was used in the present one-step cross-coupling of **1b** with iodobenzene, ethyl 4-phenylbutanoate (**3d**) was obtained in 5, 49, or 67% yield, respectively. A complex



Scheme 5

Table 4. One-step Cross-coupling Reactions of Ethyl ω-Iodoalkanoate (**1a-c**) with Aryl Halides by the Use of an Electrochemical Method using Zinc Anode[a)]

Haloester	Ar-X	Product	Yield (%)[b)]
I-(CH2)2-COOEt (1a)	C_6H_5I	$C_6H_5CH_2CH_2COOEt$ (3a)	49
I-(CH2)3-COOEt (1b)	C_6H_5I	$C_6H_5CH_2CH_2CH_2COOEt$ (3d)	59 (67)[c)]
	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4CH_2CH_2CH_2COOEt$ (3e)	63
	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2CH_2COOEt$ (3f)	21
I-(CH2)4-COOEt (1c)	C_6H_5I	$C_6H_5CH_2CH_2CH_2COOEt$ (3k)	53
	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4CH_2CH_2CH_2COOEt$ (3l)	45
	4-$CH_3COC_6H_4Br$	4-$CH_3COC_6H_4CH_2CH_2CH_2COOEt$ (3m)	43

a) A mixture of iodoester **1a-c** (5 mmol), aryl halide (2 mmol), and 5 mol% $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.11 mmol) in 0.1M Et_4NClO_4-DMF (15 ml) was electrolyzed at 60 mA/cm^2 with a Pt cathode and Zn anode. Electricity passed was 2 F/mol.

b) Isolated yields

c) GC yield is shown in parenthesis.

of $Pd(P(o\text{-}Tol)_3)_2Cl_2$ was found to be the most effective in this one-step reaction. When 1.5 or 2.5 equivalents of **1b** was used in the cross-coupling with iodobenzene, the product **3d** was obtained in 40 or 67% yield, respectively. Electrolysis of a mixture of ethyl iodoalkanoate (**1a-c**) (5 mmol), aryl halide (2 mmol) and $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.11 mmol) in a DMF solution gave the corresponding cross-coupled products in the yields shown in Table 4. Although these yields were lower than those obtained by the procedure using EGZn and the two-step procedure using an electrochemical method, the present one-step and one-pot method is very convenient for the palladium-catalyzed cross-coupling of functionalized iodo compounds with aryl halides. These low yields in this

one-step procedure are probably due to the occurrece of several competing reduction steps. Thus, an electrochemical reduction can take place at a Pd complex, aryl halide, and/or ethyl ω-iodoalkanoate and the most reducible compound is the Pd complex. The Pd(0) species generated by a two-electron reduction might undergo an oxidative addition preferentially to aryl halide and, however, the desired product **3** would not be obtained in this case. We are currently carrying out detailed studies in order to improve the yield and to clarify the reaction pathways of the present one-step cross-coupling reaction.

Experimental

Products were isolated by kugel rohr distillation or TLC (Merck Silica gel PF_{254}). IR spectra were obtained by using on a JASCO IR810 spectrometer (neat between NaCl plates). ^{1}H-NMR Spectra were determined by JEOL JNM EX-270 (270MHz) and JNM-LA400FT NMR (400 MHz) with tetramethylsilane as an internal standard. Gas chromatographic analysis was carried out with a Hitachi G-5000 using a capillary column (OV-17, 20m).

Solvent and Reagents

Commercially available anhydrous *N,N*-dimethylformamide (DMF) and tetrahydrofuran (THF) packed under a nitrogen atmosphere (Kanto Chemical) were used without further purification. Tetraethylammonium perchlorate was prepared as follows. A saturated aqueous solution of 50 g (0.238 mol) of Et_4NBr in 50 ml of water was treated with 24 ml of aqueous 60% $HClO_4$ (0.238 mol). After filtration of the resulting insoluble perchlorate salt, the salt was washed with cold water and dried. Recrystallization from water and drying under reduced pressure gave pure Et_4NClO_4 as white needles in 90% yield. The zinc plate was washed with 2N HCl, methanol, acetone, and dried before electrolysis. Iodobenzene, bromobenzene, 4-bromoanisole are commercially available and were used after distillation. 4-Bromoacetophenone was used without further purification. 3,4-Dimethoxy iodobenzene and 3,4-methylenedioxy iodobenzene were prepared according to a previous described method[8] and were used after purification by distillation under reduced pressure. Ethyl iodoalkanoates and 4–iodobutanenitrile were prepared from the corresponding bromides with NaI in acetone.[9] Iodobutane was used after distillation.

3,4-Dimethoxyiodobenzene: 44% ; b.p. 70 °C / 0.15 mmHg (lit 8 b.p. 68-74 °C / 0.2 mmHg).

3,4-Methylenedioxyiodobenzene: 54% ; b.p. 76°C / 1.0 mmHg (lit 8 b.p. 78.5-79 °C / 0.2 mmHg).

Ethyl 3-iodopropanoate (**1a**). 99% ; b.p. 91°C / 18 mmHg; IR (neat) 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.19 (2H, q, *J*=6.93Hz), 3.33 (2H, t, *J*=7.26Hz), 2.97 (2H, t, *J*=7.26Hz), 1.28 (2H, t, *J*=6.93Hz).
Ethyl 4-iodobutanoate (**1b**). 96% ; b.p. 56 °C / 3.0 mmHg; IR (neat) 1734 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.15 (2H, q, *J*=6.93Hz), 3.24 (2H, t, *J*=6.83Hz) 2.44 (2H, t, *J*=7.07Hz), 2.14 (2H, m), 1.27 (3H, t, *J*=6.93Hz).

Ethyl 5-iodopentanoate (**1c**). 90% ; b.p. 86 °C / 3.0 mmHg; IR (neat) 1735 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 4.13 (2H, q, *J*=6.93Hz), 3.19 (2H, t, *J*=6.77Hz), 2.33 (2H, t, *J*=7.10Hz), 1.90-1.73 (4H, m) 1.26 (3H, t, *J*=6.93Hz).

4-Iodobutane (**4a**). 64%; b.p. 39 °C / 30 mmHg; ^{1}H- NMR ($CDCl_3$) δ 5.76 (1H, m), 5.12 (2H, m), 3.19 (2H, t, *J*=7.26Hz), 2.14 (2H, m).

4-Iodobutanenitrile (**4b**). 94% ; b.p. 55 °C / 1.5 mmHg; IR (neat) 2248 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 3.30 (2H, t,

J=6.6Hz), 2.53 (2H, t, *J*=6.93Hz), 2.14 (2H, m).

6-Iodo-1-hexene (**4c**).

Tosyl chloride (1.2 eq) was added to a solution of 6-hexene-1-ol (10 ml, 83 mmol) in dry pyridine (100 ml) at 0°C. The reaction mixture was kept overnight in a refrigerator. The mixture was filtrated to remove excess tosyl chloride, and extracted with Et_2O (50 ml x 3). Ethereal solution was washed with 18% HCl solution (50 ml x 3), saturated aq.$NaHCO_3$ (50 ml x 3) and saturated aq.NaCl (50 ml x 1), and dried over $MgSO_4$. The solvent was evaporated to give crude tosylate. NaI (2 eq) was added to the solution of the crude tosylate in acetone (50 ml) and heated for 3h under reflux. The reaction mixture was filtrated to remove excess NaI and evaporated to remove acetone. Usual work-up gave crude 6-iodo-1-hexene, which was purified by column chromatography (silica gel, hexane).; 81% ; b.p. 65 °C / 16 mmHg; IR (neat) 1642 cm^{-1}; ^{1}H- NMR ($CDCl_3$) δ 5.79 (1H, m), 5.00 (2H, m), 3.19 (2H, t, *J*=6.93Hz), 2.08 (2H, q, *J*=7.26Hz), 1.84 (2H, qui, *J*=7.26Hz), 1.50 (2H, m) ; EIMS *m/z* (relative intensity) 83 (100), 55 (99), 41 (78); HRMS Calcd for $C_6H_{11}I$ *m/z* 209.9903. Found *m/z* 209.9904.

Preparation of Electrogenerated Reactive Zinc (EGZn)

A normal one-compartment cell equipped with a magnetic stirrer and a serum cap was used. Reactive zinc metal was prepared by the electrolysis of a DMF solution (15 ml) containing 345 mg of Et_4NClO_4 (1.5 mmol) in a one-compartment cell fitted with a platinum plate cathode (2x2 cm^2) and a zinc plate anode (2x2 cm^2). Electrolysis was carried out at a constant current of 60 mA/cm^2 (electricity 2.0 F/mol) at room temperature in an argon atmosphere. A solution containing EGZn was used directly in the reaction after the zinc anode was removed from the electrochemical cell.

General Procedure for Cross-coupling Reaction Using EGZn

Functionalized alkyl iodide (10 mmol) was added to a DMF solution containing EGZn (12 mmol). The reaction mixture was stirred for 10 min at room temperature (at 0°C in the case of ethyl 3-iodopropanoate), which gave the corresponding organozinc iodide. A DMF solution of organozinc iodide (3 mmol) was transferred into a THF solution (20 ml) of aryl halide (2 mmol) and $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.11 mmol), and the mixture was stirred for 3h at room temperature in the case of aryl iodide or stirred at 65°C in the case of aryl bromide. The reaction mixture was quenched with HCl solution and extracted with Et_2O (50 ml x 3). The combined organic layers were washed with H_2O (100 ml x 5) and saturated NaCl solution (100 ml x 1), and dried over $MgSO_4$. Evaporation of Et_2O gave the crude product, which was purified by TLC (silica gel, hexane : ethyl acetate / 4:1).

General Procedure for Two-step Cross-coupling Using an Electrochemical Method

Electrolysis of ethyl 4-iodobutanoate (**1b**) (3 mmol) in 0.1M Et_4NClO_4-DMF (15 ml) at r.t. with a Pt cathode and zinc anode gave the corresponding organozinc compound (**2b**) in high yield. In the case of ethyl 4-bromobutanoate (**1d**), the electrolysis was carried out at 70°C. The resulting organozinc halides (**2b** and **2d**) were subjected to the cross-coupling reaction with aryl halides in the same way as that described above.

General Procedure for One-step and One-pot Cross-coupling Using an Electrochemical Method

A mixture of ethyl iodoalkanoate (**1a-c**) (5 mmol), aryl halide (2 mmol) and $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (0.11 mmol) in 0.1M Et_4NClO_4-DMF (15 ml) was electrolyzed at room temperature with a Pt cathode and Zn anode. Electrolysis was carried out at 60 mA/cm^2, and an electricity of 2 Faradays per mol of iodoalkanoate was passed. Usual work-up of the electrolyzed mixture gave the cross-coupling products (**3a**, **3d-f**, **3k-m**). This procedure involves only one-step and can be carried out in a one-compartment cell (one-pot).

Spectral data of the products are shown below.

Ethyl 3-phenylpropanoate (**3a**). b.p. 85 °C/ 2.6 mmHg; IR (neat) 1737, 1605, 1498 cm^{-1} ; ^{1}H-NMR($CDCl_3$) δ 7.24 (5H, m), 4.12 (2H, q, *J*=7.26Hz), 2.95 (2H, t, *J*=7.59Hz), 2.62 (2H, t, *J*=7.59Hz), 1.23 (3H, t, *J*=7.26Hz) ; EIMS *m/z* (relative intensity) 178 (48), 133 (16), 104 (100), 91 (53); HRMS calcd for $C_{11}H_{14}O_2$. *m/z* 178.1046. Found *m/z* 178.1020; Anal. Calcd for $C_{11}H_{14}O_2$: C,74.13; H, 7.92. Found: C,73.91; H,7.92.

Ethyl 3-(4-methoxy)phenylpropanoate (**3b**). b.p. 79 °C/ 0.16 mmHg; IR (neat) 1736, 1613, 1515, 1248, 1037 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.12 (2H, d, *J*=8.29Hz), 6.82(2H, d, *J*=8.29Hz), 4.12 (2H, q, *J*=7.26Hz), 3.78 (3H, s), 2.89 (2H, t, *J*=7.76Hz), 2.58 (2H, t, *J*=7.76Hz), 1.23(3H, t, *J*=7.26Hz) ; EIMS *m/z* (relative intensity) 208 (31), 134 (39), 121 (100); HRMS Calcd for $C_{12}H_{16}O_3$ *m/z* 208.1141. Found *m/z* 208.1120; Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.17; H, 7.80.

Ethyl 3-(4-acetyl)phenylpropanoate (**3c**). b.p. 108 °C/ 0.25 mmHg; IR (neat) 1735, 1684, 1608, 1571, 1415 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.89 (2H, d, *J*=8.29Hz), 7.30 (2H, dd, *J*=8.29Hz), 4.13 (2H, q, *J*=7.10Hz), 3.01 (2H, t, *J*=7.76Hz), 2.64 (2H, t, *J*=7.76Hz), 2.58 (3H, s), 1.23 (3H, t, *J*=7.10Hz); EIMS *m/z* (relative intensity) 220 (49), 205 (100), 177 (11), 149 (9), 131 (18) ;HRMS Calcd for $C_{13}H_{16}O_3$ *m/z* 220.1151. Found *m/z* 220.1125; Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.68; H, 7.36.

Ethyl 4-phenylbutanoate (**3d**). b.p. 97 °C/ 4 mmHg; IR (neat) 1734, 1498, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.23 (5H, m), 4.12 (2H, q, *J*=7.26Hz), 2.65 (2H, t, *J*=7.59Hz), 2.32 (2H, t, *J*=7.59Hz), 1.96 (2H, quin, *J*=7.59 Hz), 1.25 (3H, t, *J*=7.26Hz) ; EIMS *m/z* (relative intensity) 192 (60), 147 (76), 117(18), 104 (100), 91 (85), 88 (79), 70 (25); HRMS Calcd for $C_{12}H_{16}O_2$ *m/z* 192.1124. Found *m/z* 192.1137; Anal. Calcd for $C_{12}H_{16}O_2$: C,74.97; H, 8.39. Found: C,74.75; H, 8.45.

Ethyl 4-(4-methoxy)phenylbutanoate (**3e**). b.p. 99 °C/ 0.2 mmHg; IR (neat) 1734, 1613, 1514, 1247, 1037cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.09 (2H, dd, *J*=1.98, 4.61Hz), 6.83 (2H, dd, *J*=1.98, 4.61Hz), 4.12 (2H, q, *J*=7.10Hz), 3.78 (3H, s), 2.59 (2H, t, *J*=7.43Hz), 2.30 (2H, t, *J*=7.59 Hz), 1.92 (2H, m), 1.25 (3H, t, *J*=7.10 Hz) ; EIMS *m/z* (relative intensity) 222 (30), 177 (20), 134 (100), 121 (63), 91 (10) ; HRMS Calcd for $C_{13}H_{18}O_3$ *m/z* 222.1198. Found *m/z* 222.1227 ; Anal. Calcd for $C_{13}H_{18}O_3$: C,70.25; H,8.16. Found: C,70.22; H,8.16.

Ethyl 4-(4-acetyl)phenylbutanoate (**3f**). b.p. 126 °C/ 0.18 mmHg; IR (neat) 1734, 1683, 1607, 1571, 1413 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.89 (2H, d, *J*=8.42Hz), 7.28 (2H, d, *J*=8.42Hz), 4.13 (2H, q, *J*=7.26Hz), 2.72 (2H, t, *J*=7.76Hz), 2.59 (3H, s), 2.32 (2H, t, *J*=7.42Hz), 1.99 (2H, m), 1.26 (3H, t, J=7.26Hz) ; EIMS *m/z* (relative intensity) 234 (58), 219 (19), 189 (12), 147 (100), 131 (26), 118 (7), 105 (6), 90 (9) ; HRMS Calcd for $C_{14}H_{18}O_3$ *m/z* 234.1274. Found *m/z* 234.1265; Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.83; H, 7.83.

Ethyl 4-(3,4-dimethoxy)phenylbutanoate (**3g**). b.p. 110 °C/ 0.15 mmHg; IR (neat) 1733, 1608, 1591, 1517, 1465, 1261, 1238 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 6.81-6.71 (3H, m), 4.13 (2H, q, *J*=7.26Hz), 3.87 (3H, s), 3.86 (3H, s), 2.60 (2H, t, *J*=7.26Hz), 2.32 (2H, t, *J*=7.26Hz), 1.94 (2H, qui, *J*=7.26Hz), 1.26 (3H, t, *J*=7.26Hz) ; EIMS *m/z* (relative intensity)252 (77), 207 (27), 164 (100), 151 (75); HRMS Calcd for $C_{14}H_{20}O_4$ *m/z* 252.1355. Found *m/z* 252.1358; Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99 Found: C, 66.40; H, 8.00.

Ethyl 4-(3,4-methylenedioxy)phenylbutanoate (**3h**). b.p. 114 °C/ 0.2 mmHg; IR (neat) 1733, 1610, 1505, 1490, 1248, 1038 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 6.72 (1H, d, *J*=7.92 Hz), 6.67 (1H, d, *J*=1.65Hz), 6.61 (1H, dd, *J*=1.65, 7.92Hz), 5.91 (2H, s), 4.12 (2H, q, *J*=6.93Hz), 2.57 (2H, t, *J*=7.26Hz), 2.29 (2H, t, *J*=7.26Hz), 1.90 (2H, qui, *J*=7.26Hz), 1.25 (3H, t, *J*=6.93Hz) ; EIMS *m/z* (relative intensity) 236 (28), 191 (18), 148 (100), 135 (46), 77 (13); HRMS Calcd for $C_{13}H_{16}O_4$ *m/z* 236.1113. Found *m/z* 236.1081; Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09;

H, 6.83. Found: C, 65.85; H, 6.98.

Ethyl 4-(1-naphthyl)butanoate (**3i**). b.p. 150 °C/0.5 mmHg; IR (neat) 1733, 1598, 1509, 1490, 1460, 799, 790, 779 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 8.07 (1H, d, *J*=7.92Hz), 7.85 (1H, dd, *J*=2.64, 7.91 Hz), 7.72 (1H, d, *J*=7.92 Hz), 7.43 (4H, m), 4.14 (2H, q, *J*=7.26Hz), 3.12 (2H, t, *J*=7.26Hz), 2.41 (2H, t, *J*=7.26Hz), 2.09 (2H, qui, *J*=7.26Hz), 1.26 (3H, t, *J*=6.93Hz); EIMS *m/z* (relative intensity) 242 (43), 197 (15), 167 (4), 154 (100), 141 (36), 128 (3), 115 (11); HRMS Calcd for $C_{16}H_{18}O_2$ *m/z* 242.1287. Found *m/z* 242.1297; Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.34; H, 7.53.

Ethyl 4-(2-naphthyl)butanoate (**3j**). b.p. 125 °C/0.2 mmHg; IR (neat) 1734, 1602, 1508, 1490, 1243, 1027, 854, 819, 748 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.79 (3H, m), 7.61 (1H, s), 7.40 (4H, m), 4.12 (2H, q, *J*=7.26 Hz), 2.82 (2H, t, *J*=7.26Hz), 2.35 (2H, t, *J*=7.26Hz), 2.05 (2H, qui, *J*=7.26Hz), 1.25 (3H, t, *J*=7.26Hz) ; EIMS *m/z* (relative intensity) 242 (32), 197 (14), 154 (100), 141 (24), 115 (9); HRMS Calcd for $C_{16}H_{18}O_2$ *m/z* 242.1283. Found *m/z* 242.1295; Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.29; H, 7.59.

Ethyl 5-phenylpentanoate (**3k**). b.p. 99 °C/1.6 mmHg; IR (neat) 1733, 1497, 700 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.22 (5H, m), 4.12 (2H, q, *J*=7.10Hz), 2.63 (2H, m), 2.32 (2H, m), 1.65 (4H, m), 1.24 (3H, t, *J*=7.10Hz) ; EIMS *m/z* (relative intensity) 206 (10), 160 (100), 132 (12), 117 (27), 104 (29), 91 (58); HRMS Calcd for $C_{13}H_{18}O_2$ *m/z* 206.1320. Found *m/z* 206.1313; Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.36; H, 8.84.

Ethyl 5-(4-methoxy)phenylpentanoate (**3l**). b.p. 110 °C/0.18 mmHg; IR (neat) 1736, 1613, 1514, 1246, 1036 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.08 (2H, dd, *J*=1.98, 6.59Hz), 6.82 (2H, dd, *J*=1.98, 6.59Hz), 4.12(2H, q, *J*=7.26Hz), 3.78 (3H, s), 2.57 (2H, t, *J*=7.26Hz), 2.31 (2H, t, *J*=7.26Hz), 1.64 (4H, m), 1.20 (3H, t, *J*=7.26Hz) ; EIMS *m/z* (relative intensity) 236 (26), 191 (11), 147 (9), 134 (10), 121 (100), 91 (4) ; HRMS Calcd for $C_{14}H_{20}O_3$ *m/z* 236.1414. Found *m/z* 236.1413; Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.94; H, 8.58.

Ethyl 5-(4-acetyl)phenylpentanoate (**3m**). b.p. 135 °C/0.18 mmHg; IR (neat) 1734, 1683, 1607, 1571, 1413cm^{-1} ; ^{1}H-NMR($CDCl_3$) δ 7.88 (2H, d, *J*=8.58Hz), 7.26 (2H, d, *J*=8.58Hz), 4.12 (2H, q, *J*=7.10Hz), 2.69 (2H, m), 2.58 (3H, s), 2.33 (2H, m), 1.66 (4H, m), 1.25 (3H, t, *J*=7.10Hz) ; EIMS *m/z* (relative intensity) 248 (97), 233 (38), 203 (30), 187 (32), 174 (17), 161 (25), 147 (100), 131 (21), 117 (12), 105 (17), 91 (14), 77 (8) ; HRMS Calcd for $C_{15}H_{20}O_3$ *m/z* 248.1360. Found *m/z* 248.1386; Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.44; H 8.21.

4-Butylanisole (**6a**). ^{1}H-NMR($CDCl_3$) δ 7.09 (2H, d, *J*=8.58Hz), 6.82 (2H, d, *J*=8.58Hz), 3.78 (3H, s), 2.55 (2H, t, *J*=7.59 Hz), 1.56 (2H, qui, *J*=7.59Hz), 1.35 (2H, m), 0.92 (3H, t, J=7.59Hz).

4-Butylacetophenone (**6b**). b.p. 71 °C/ 0.25 mmHg; IR (neat) 1684, 1608 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.88 (2H, d, *J*=8.25Hz), 7.26 (2H, d, *J*=8.25Hz), 2.67 (2H, t, *J*=7.59Hz), 2.58 (3H, s), 1.62 (2H, qui, *J*=7.59Hz), 1.36 (2H, m), 0.93 (3H, t, *J*=7.59Hz); EIMS *m/z* (relative intensity) 176 (26), 161 (100), 149 (4), 133 (9), 118 (5), 105 (19), 91 (33), 77 (13) ; HRMS Calcd for $C_{12}H_{16}O$ *m/z* 176.1201. Found *m/z* 176.1211.

4-Phenylbutanenitrile (**6c**). b.p. 75 °C/ 0.2 mmHg; IR (neat) 2244, 1603, 1497 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.25 (5H, m), 2.78 (2H, t, *J*=7.26Hz), 2.32 (2H, t, *J*=7.26Hz), 1.98 (2H, qui, *J*=7.26Hz) ; EIMS *m/z* (relative intensity) 145 (36), 104 (25), 91 (100) ; HRMS Calcd for $C_{10}H_{11}N$ *m/z* 145.0879. Found *m/z* 145.0885; Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.72; H, 7.64; N, 9.61.

4-(4-Methoxyphenyl)butanenitrile (**6d**). b.p. 95 °C/ 0.2 mmHg; ^{1}H-NMR($CDCl_3$) δ 7.10 (2H, dd, *J*=2.97, 11.55Hz), 6.84 (2H, dd, *J*=2.97, 11.55Hz), 3.79 (3H, s), 2.72 (2H, t, *J*=7.26Hz), 2.30 (2H, t, *J*=7.26Hz),

1.95 (2H, qui, *J*=7.26Hz) ; EIMS *m/z* (relative intensity) 175 (17), 121 (100), 91 (15), 77 (15) ; HRMS Calcd for $C_{11}H_{13}ON$ *m/z* 175.1023. Found *m/z* 175.1010; Anal. Calcd for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.20; H, 7.48; N, 7.95.

4-(4-Acetylphenyl)butanenitrile (**6e**). b.p. 120 °C/ 0.15 mmHg; IR (neat) 2246, 1683, 1608, 1499, 1458 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.92 (2H, d, *J*=7.92Hz), 7.30 (2H, d, *J*=7.92Hz), 2.86 (2H, t, *J*=7.26Hz), 2.60 (3H, s), 2.34 (2H, t, *J*=7.26Hz), 2.01 (2H, qui, *J*=7.26Hz) ; EIMS *m/z* (relative intensity) 187 (18), 172 (100), 144 (7), 131 (4), 116 (9) ; HRMS Calcd for $C_{12}H_{13}ON$ *m/z* 187.0967. Found *m/z* 187.0982; Anal. Calcd for $C_{12}H_{13}ON$: C, 76.98; H,7.00; N,7.48. Found: C, 76.43; H, 7.09; N, 7.48.

6-(4-Methoxyphenyl)hexene (**6f**). b.p. 68 °C/ 0.2 mmHg; IR (neat) 1683, 1641, 1608, 1571, 1413, 1359, 1267, 1182 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.09 (2H, d, *J*=8.25Hz), 6.82 (2H, d, *J*=8.25Hz), 5.80 (1H, m), 4.97 (2H, m), 3.78 (3H, s), 2.55 (2H, t, *J*=6.93Hz), 2.05 (2H, m), 1.55 (4H, m) ; EIMS *m/z* (relative intensity) 190 (14), 147 (15), 134 (7), 121 (100), 91 (13) ; HRMS Calcd for $C_{13}H_{18}O$ *m/z* 190.1369. Found *m/z* 190.1363; Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.14; H, 9.69.

6-(4-Acetylphenyl)hexene (**6g**). b.p. 93 °C/ 0.2 mmHg; IR (neat) 1641, 1614, 1585, 1513, 1465, 1442, 1247, 1177, 1039 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 7.87 (2H, dd, *J*=1.32, 8.25Hz), 7.26 (2H, dd, *J*=1.32, 8.25Hz), 5.79 (1H, m), 4.98 (2H, m), 2.67 (2H, t, *J*=7.59Hz)), 2.58 (3H, s), 2.08 (2H, q, *J*= 7.26Hz), 1.57 (4H, m) ; EIMS *m/z* (relative intensity) 202 (27), 187 (100), 134 (34), 131 (19), 117 (11), 91 (21) ; HRMS Calcd for $C_{14}H_{18}O$ *m/z* 202.1358. Found *m/z* 202.1360; Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.06; H, 9.07.

References

(1) Tokuda, M; Mimura, N; Karasawa, T; Fujita, H; Suginome, H. *Tetrahedron. Lett.* **1993**, *34*, 7607.
(2) Tokuda, M; Kurono, N; Mimura, N. *Chem. Lett.* **1996**, 1091.
(3) a) Zhu, L; Wehmeyer, RM; Rieke, RD. *J. Org. Chem.* 1991; 56: 1445-1453. b) Edrick, E; *Tetrahedron* **1987**,*43*, 2203. c) Furstner, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 164. d) Cintas, P. *Activated Metals in Organic Synthesis. CRC Press: Boca Raton.* **1993**, 45.
(4) Zylber, N; Rollin, Y; Dunach, E; Perichon. J. *J. Organometal. Chem.* **1993**, *444*, 1.
(5) Erdik, E. *Tetrahedron*, **1992**, *48*, 9577.
(6) a) Tamaru, Y; Ochiai, H; Nakamura, T; Yoshida, Z. *Tetrahedron. Lett.* **1986**, *27*, 955. b) Tamaru, Y; Ochiai, H; Nakamura, T; Tsubaki, K; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559.
(7) Sakamoto, T; Nishimura, S; Kondo, Y; Yamanaka, H. *Synthesis*, **1988**, 485.
(8) Orito, K; Hatakeyama, T; Takeo, M; Suginome, H. *Synthesis*, **1995**, 1273.
(9) Yasui, K; Tanaka, S; Y, Tamaru. *Tetrahedron*, **1995**, *51*, 6881.