

Improved Nickel-Catalyzed Cross-Coupling Reaction Conditions between *ortho*-Substituted Aryl Iodides/Nonaflates and Alkylzinc Iodides in Solution and in the Solid-Phase

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Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

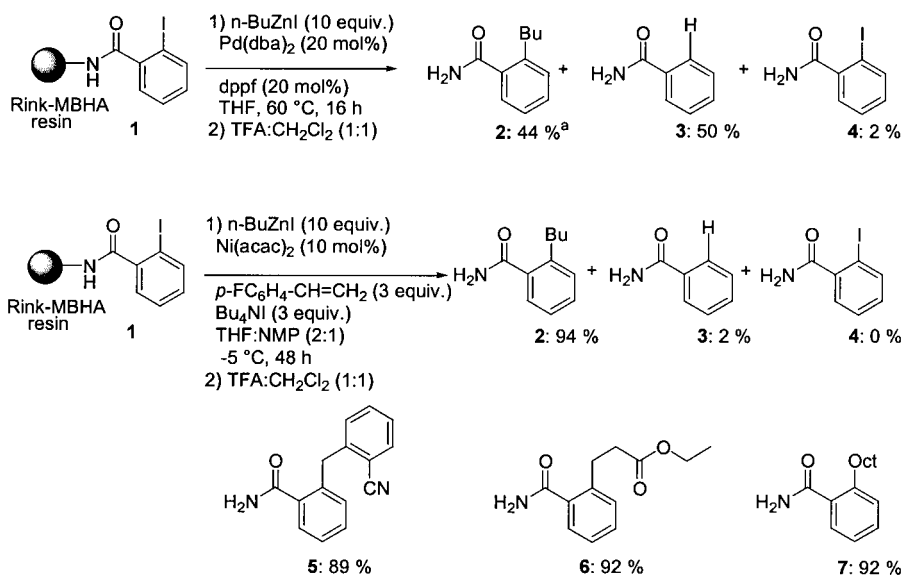
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Abstract—*ortho*-Substituted aryl iodides and nonaflates undergo nickel-catalyzed cross-coupling reactions with functionalized alkylzinc iodides in the solid-phase as well as in solution providing high HPLC purities and good yields. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

The palladium or nickel-catalyzed cross-coupling reaction between organometallic reagents and organic halides is an important method for preparing polyfunctional molecules.¹ Especially useful is the cross-coupling between aryl halides and alkyl organometallics. In this respect, the Negishi-

cross-coupling reaction using alkylzinc halides has given excellent results.^{2,3} Unfortunately, this palladium-catalyzed cross-coupling leads to poor reactions in the solid-phase when *ortho*-substituted functionalized aryl iodides are used. These substrates are important for the elaboration of broad-range libraries of compounds using combinatorial chemistry techniques.⁴ Thus, the reaction of the resin-bound

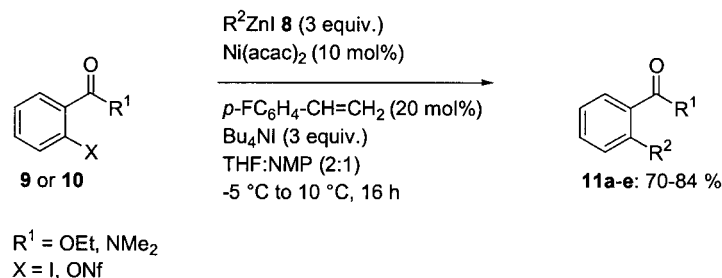


^aPurities were determined by HPLC analysis.

Scheme 1.

Keywords: nickel catalysis; cross-coupling; solid-phase; salt effect.

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Scheme 2.

ortho-iodobenzamide **1** with butylzinc iodide (10 equiv.) in the presence of $Pd(dba)_2$ (20 mol%), $dppf$ (20 mol%) in THF (60°C , 16 h) furnishes, after cleavage from the resin using TFA in CH_2Cl_2 , the desired cross-coupling product (**2**) in 40% HPLC purity accompanied by the reduced starting material (**3**) in over 50% HPLC purity as well as 2% of unchanged 2-iodobenzamide (**4**). Recently, we have shown that nickel-catalyzed cross-coupling reactions with dialkyl-

zincs were for the first time possible by using 4-fluorostyrene as a promotor.⁵ These reaction conditions also proved advantageous for the cross-coupling reaction between benzylic zinc halides⁶ and alkyl iodides, as well as between arylzinc derivatives and alkyl iodides.⁷ Herein, we report that this nickel-catalysis further allows considerable improvement of the cross-coupling between *ortho*-substituted aryl iodides or nonaflates and a range of alkylzinc iodides.

Table 1. *ortho*-Substituted aryl esters or amides **11a–e** obtained by a $Ni(acac)_2$ catalyzed cross-coupling between alkylzinc iodides and *ortho*-substituted aryl nonaflates or iodides

Entry	Aryl iodide of type 9 or nonaflate 10	Organozinc iodide of type 8	Product of type 11	Yield (%) ^a
1		PentZnI		79
2	9a			72
3	9a			83
4		PentZnI		73
5	9b			70
6		PentZnI		84

^aIsolated yield of analytically pure product

Results and Discussion

A resin attached aryl iodide **1** undergoes a smooth cross-coupling with butylzinc iodide (10 equiv.) in the presence of Ni(acac)₂ (10 mol%), 4-fluorostyrene (3 equiv.) and Bu₄NI (3 equiv.) in THF:NMP (2:1) at –5°C (48 h). After cleavage from the resin the desired cross-coupling product (**2**) is obtained with 94% purity as determined by HPLC analysis. Under these conditions, less than 2% of the reduced starting material (**3**) is found (Scheme 1).

This behavior appears to be general and long-chain alkylzinc iodides like octylzinc iodide or functionalized organozinc reagents⁸ such as 2-cyanobenzylzinc bromide or 2-ethoxycarbonylethylzinc iodide undergo the nickel-catalyzed cross-coupling on the solid-phase with similar purities after cleavage from the resin leading to the expected amides **5–7** in 89–92% HPLC purity. Further, this nickel-catalyzed cross-coupling reaction finds application in solution. In this case, the organozinc iodide of type **8** and Bu₄NI are still used in excess (3 equiv.), but the promoter (4-fluorostyrene) is added only in substoichiometric amount (20 mol%). Both aryl iodides of type **9** or aryl triflates like **10** are good substrates. All the cross-coupling reactions are completed between –5 and 10°C within 16 h leading to the expected *ortho*-substituted products **11a–e** in 70–84% isolated yields (Scheme 2).

Calibration experiments in solution leaving out either the Bu₄NI or 4-fluorostyrene lead to longer reaction times and complex reaction mixtures. Leaving out both components surprisingly enhances the reaction rate, but also affords reaction mixtures. Thus, the optimized reaction conditions requested both additives. Ethyl 2-iodobenzoate (**9a**) undergoes a highly efficient cross-coupling with various functionalized organozinc iodides (entries 1–3 of Table 1). The corresponding dimethylamide (**9b**) similarly reacts under the standard conditions with pentylzinc iodide (entry 4) leading to the *ortho*-substituted amide **11d** in 73% yield. The cross-coupling with a functionalized organozinc reagent such as PivO(CH₂)₅ZnI affords the amide **11e** in 70% yield (entry 5 of Table 1). Interestingly, recently introduced aryl nonaflates^{3b} such as **10** react well with pentylzinc iodide, furnishing the expected product **11a** in 84% yield (entry 6). The aryl iodide **9a** and the nonaflate **10** react with similar rates.

Conclusion

In conclusion, we have optimized the reaction conditions allowing cross-coupling reactions with *ortho*-substituted aryl iodides and nonaflates. This nickel-catalyzed reactions proceeds well in solution and in the solid-phase.

Experimental

General methods

All reactions were carried out under an argon atmosphere in flame-dried glassware. THF was distilled under argon from sodium/benzophenone. NMP was distilled under argon from

calcium hydride. Commercially available materials were used without further purification. Reactions were monitored by gas chromatography (GC) analysis of worked up reaction aliquots or by HPLC analysis of cleaved aliquots for the solid-phase. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm) precoated with a fluorescent indicator. Column chromatography was performed with 40–63 μm silica gel (Merck). GC analysis was performed on a bonded 5% phenylmethylpolysiloxane DB 5 capillary column (Mega-bore, 15 m, 0.53 mm id, 2.65 μm df). NMR spectra were recorded on a 200 or 300 MHz NMR spectrometer. Infrared spectroscopy was performed with a Perkin–Elmer FT-IR-spectrometer ‘Spectrum 1000’. The ionization method used for mass spectrometry was electron impact (EI, 70 eV). Elemental analyses were performed by the Microanalytical Service Laboratory of Universität München.

Preparation of alkylzinc iodides of type **8** (pentylzinc iodide)

A 25 ml two-necked flask equipped with a dropping funnel, reflux condenser and a stirring bar was charged with cut zinc foil (Merck quality) (1.77 g, 27 mmol), flame dried and flushed with argon. THF (1 ml) and 1,2-dibromoethane (51 mg, 0.27 mmol) was added and the zinc activated by heating to reflux with a heat gun, then allowing to cool down. This procedure was repeated until foam no longer formed as result of heating. The mixture was heated to 50°C before dropwise addition of pentyl iodide (1.77 g, 9 mmol) in THF (4 ml). The mixture was kept at 50°C until complete conversion is reached (checked by GC analysis, approx. 4 h). The solution was used directly for reactions on the solid-phase or concentrated to 6–7 M under vacuum for reactions in solution.

Preparation of resin-attached 2-iodobenzamide (1). Commercially available Fmoc-protected Rink-MBHA-resin (15.0 g, 0.56 mmol Fmoc/g) was suspended in DMF (100 ml) and piperidine (45 ml, 455 mmol) was added. The mixture was shaken for 1 h at rt. The resin was filtered, sequentially washed four times with DMF, MeOH and THF, followed by four washings with CH₂Cl₂ and dried overnight at 55°C affording the unprotected amide resin (12.9 g, 0.64 mmol/g). Unprotected amide resin (3.00 g, 1.92 mmol) was suspended in CH₂Cl₂ (40 ml) and allowed to swell for 5 min. 2-Iodobenzoic acid (1.44 g, 5.8 mmol) and *N,N'*-diisopropylcarbodiimide (0.73 g, 5.8 mmol) were added and the mixture was shaken for 16 h at rt. Then the resin was filtered, sequentially washed four times with THF, DMF and MeOH, followed by four washings with CH₂Cl₂ and dried overnight at 55°C leading to the loaded resin **1** (3.38 g, 0.49 mmol/g).

Typical procedure A: nickel-catalyzed cross-coupling between butylzinc iodide and aryl iodides in the solid-phase. Preparation of 2-butylbenzamide (2). Resin-attached 2-iodobenzamide **1** (200 mg, 0.49 mmol/g, 0.098 mmol) and Bu₄NI (110 mg, 0.30 mmol) were placed in a dry, argon flushed 10 ml—Schlenk flask equipped with a rubber septum. A solution of Ni(acac)₂ (2.6 mg, 10.1 μmol) in NMP (0.5 ml) and THF (0.5 ml) was added and the resin was allowed to swell for 5 min. 4-Fluorostyrene (35 mg,

0.29 mmol) was added and the mixture was cooled to -30°C . Then butylzinc iodide (0.5 ml, 2.0 M in THF, 1.0 mmol) was added dropwise with stirring. The reaction mixture was warmed up to 0°C and stirred for 48 h. After the reaction was completed as monitored by HPLC, the resin was filtered, sequentially washed four times with THF, DMF and MeOH, followed by four washings with CH_2Cl_2 and dried at 55°C overnight. To determine the yield and purity, 100 mg of the product resin was placed in a 5 ml—syringe equipped with a filter plate and TFA: CH_2Cl_2 1:1 (3 ml) was added for cleavage. The mixture was shaken for 20 min. The filtrate was transferred into a flask and the solvents were removed in vacuo leading to the cross-coupling product **2** with 94% HPLC purity as a white solid (8.4 mg, 94%), mp: $80\text{--}82^{\circ}\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ 7.34 (d, $J=9$ Hz, 1H), 7.27 (d, $J=6$ Hz, 1H), 7.21–7.15 (m, 2H), 6.36 (br s, 1H), 5.82 (br s, 1H), 2.75 (m, 2H), 1.55–1.51 (m, 2H), 1.33–1.26 (m, 2H), 0.85 (t, $J=7.5$ Hz). MS (EI, 70 eV): 177 (36), 148 (100), 131 (40), 116 (27), 105 (23), 91 (24), 77 (26). HRMS: calcd 177.1154, found: 177.1149. The products 5–7 were prepared according to this method.

2-(Cyanobenzyl)benzamide (5). Prepared from resin **1** (200 mg, 0.098 mmol) and 2-cyanobenzylzinc bromide (0.9 ml, 1.1 M, 1 mmol). Reaction time: 72 h at 10°C . Cleavage with TFA from 100 mg of resin yielded **5** in 89% HPLC purity as white crystals (10.3 mg, 89%), mp: $139\text{--}143^{\circ}\text{C}$. ^1H NMR (200 MHz, CDCl_3): δ 7.65 (d, $J=6.6$ Hz, 1H), 7.58–7.23 (m, 6H), 7.15–7.08 (d, $J=6.6$ Hz, 1H), 5.98 (br s, 2H), 4.41 (br s, 2H). MS (EI, 70 eV): 236 (4), 219(100), 207(14), 190 (36), 165 (12). HRMS: calcd 236.0950, found: 236.0947.

2-(2-Carboethoxyethyl)benzamide (6). Prepared from resin **1** (200 mg, 0.098 mmol) and 2-ethoxycarbonyl ethylzinc iodide (0.5 ml, 2 M, 1 mmol). Reaction time: 60 h at 10°C . Cleavage with TFA from 100 mg of resin yielded **6** in 92% HPLC purity as a colourless oil (9.5 mg, 87%). ^1H NMR (200 MHz, CDCl_3): δ 7.50–7.24 (m, 4H), 5.92 (br s, 2H), 4.08 (q, $J=6.6$ Hz, 2H), 3.10 (m, 2H), 2.74 (m, 2H), 1.18 (t, $J=6.6$ Hz, 3H). MS (EI, 70 eV): 221 (6), 205 (48), 191 (11), 176 (100), 159 (24), 148 (42), 131 (73), 116 (19), 103 (42), 77 (25). HRMS: calcd 221.1052, found 221.1049.

2-Octylbenzamide (7). Prepared from resin **1** (200 mg, 0.098 mmol) and octylzinc iodide (0.5 ml, 2 M, 1 mmol). Reaction time: 60 h at 5°C . Cleavage with TFA from 100 mg of resin yielded the amide **7** in 92% HPLC purity as a white solid (11.0 mg, 96%), mp: $95\text{--}98^{\circ}\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ 7.33 (d, $J=7.5$ Hz, 1H), 7.28 (d, $J=6.9$ Hz, 1H), 7.20–7.11 (m, 2H), 6.13 (br s, 1H), 5.78 (br s, 1H), 2.74 (t, $J=7.8$ Hz, 2H), 1.55–1.52 (m, 2H), 1.24–1.17 (m, 10H), 0.80 (t, $J=6.6$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 193.9, 141.4, 130.3, 127.0, 125.7, 33.4, 31.8, 31.7, 29.6, 29.4, 29.2, 22.6, 14.1. MS (EI 70 eV): 233 (60), 217 (5), 204 (3), 148 (100), 135 (60). HRMS: calcd 233.1780, found: 233.1776.

Typical procedure B: nickel-catalyzed cross-coupling between alkylzinc iodide and aryl iodides in solution. Preparation of ethyl 2-pentylbenzoate (11a). A dried and argon-flushed 10 ml two-necked flask was charged

with $\text{Ni}(\text{acac})_2$ (77 mg, 0.3 mmol). Dry THF (2 ml), NMP (1 ml), ethyl 2-iodobenzoate **9a** (825 mg, 3 mmol), 4-fluorostyrene (74 mg, 0.6 mmol) and Bu_4NI (3.3 g, 9 mmol) were successively added at rt. The reaction mixture was cooled to -35°C before slowly adding a solution of pentylzinc iodide (1.3 ml, 7 M, 9 mmol). The reaction mixture was then allowed to warm up to 0°C . The conversion was complete in 16 h, after which it was quenched with saturated aqueous NH_4Cl solution (2 ml) and extracted with ether (4 \times 50–75 ml). The combined organic phase was dried (MgSO_4) and the solvents removed in vacuo. Flash chromatography on silica gel (pentane/ether 20:1) furnished the cross-coupling product **11a** as a colourless oil (521 mg, 79%). IR (KBr): 2958 (m), 2931 (m), 1721 (s), 1251 (s), 1098 (s) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 7.78–7.15 (m, 4H), 4.28 (q, $J=7.1$ Hz, 2H), 2.85 (t, $J=7.8$ Hz, 2H), 1.51–1.25 (m, 9H), 0.84–0.80 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 168.4, 144.8, 132.0, 131.2, 130.8, 130.4, 126.0, 61.1, 34.8, 32.3, 32.0, 23.0, 14.7, 14.4. MS (EI, 70 eV): 220 (70), 175 (100), 131 (98), 91 (48). Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$: C, 76.33; H, 9.15. Found: C, 76.19; H, 9.17. The products **11b–e** were prepared according to this method.

Alternatively **11a** can be prepared from ethyl 2-carbetoxyphenyl nonaflate **10** (1.35 g, 3 mmol). Reaction time: 16 h at 0°C (554 mg, 84%).

Ethyl 2-cyclohexylbenzoate (11b). Prepared from ethyl 2-iodobenzoate **9a** (825 mg, 3 mmol) and cyclohexylzinc iodide (1.5 ml, 6 M, 9 mmol). Reaction time: 16 h at 10°C . Purification by flash chromatography (pentane/ether 9:1) yielded **11b** as a colourless oil (495 mg, 72%). IR (KBr): 2927 (s), 2852 (m), 1719 (s), 1228 (s), 1119 (m), 1072 (m) cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ 7.73–7.21 (m, 4H), 4.37 (q, $J=7.1$ Hz, 2H), 3.39–3.22 (m, 1H), 1.87–1.38 (m, 10H), 1.40 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 169.0, 148.7, 131.8, 130.9, 130.1, 127.1, 125.8, 61.4, 40.7, 34.8, 27.4, 27.0, 14.7. MS (EI, 70 eV): 232 (54), 186 (100), 168 (94), 157 (49), 145 (44), 135 (23), 91 (37). Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$: C, 71.55; H, 8.68. Found: C, 71.15; H, 8.73.

Ethyl 2-(2-ethoxycarbonyl-ethyl)-benzoate (11c). Prepared from ethyl 2-iodobenzoate **9a** (825 mg, 3 mmol) and 2-(ethoxycarbonyl)ethylzinc iodide (1.5 ml, 6 M, 9 mmol). Reaction time 16 h at 0°C . Purification by flash chromatography (pentane/ethyl acetate 95:5) yielded **11c** as a colourless oil (622 mg, 83%). IR (KBr): 2983 (m), 1732 (s), 1716 (s), 1257 (s), 1080 (m) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 7.84–7.18 (m, 4H), 4.28 (q, $J=7.1$ Hz, 2H), 4.03 (q, $J=7.1$ Hz, 2H), 3.19 (t, $J=7.8$ Hz, 2H), 2.57 (t, $J=7.8$ Hz, 2H), 1.31 (t, $J=7.1$ Hz, 3H), 1.14 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 173.3, 167.7, 142.7, 132.4, 131.5, 131.2, 130.2, 126.8, 61.3, 60.7, 36.3, 30.3, 14.6, 14.6. MS (EI, 70 eV): 250 (3), 205 (42), 176 (100), 148 (52), 131 (53). Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18; H, 7.25. Found: C, 67.12; H, 7.16.

2-Pentyl-*N,N*-dimethylbenzamide (11d). Prepared from 2-iodo-*N,N*-dimethylbenzamide **9b** (822 mg, 3 mmol) and pentylzinc iodide (1.3 ml, 7 M, 9 mmol). Reaction time: 16 h at -5°C . Purification by flash chromatography (pentane/ethyl acetate 7:3) yielded **11d** as a colourless oil

(674 mg, 70%). IR (KBr): 2929 (s), 1640 (s), 1393 (s), 1084 (m), 1065 (m) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 7.03–6.89 (m, 4H), 2.87 (s, 3H), 2.56 (s, 3H), 2.31 (br s, 2H), 1.35 (br s, 2H), 1.06 (m, 4H), 0.63 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 171.9, 139.5, 136.7, 129.8, 129.1, 126.2, 39.1, 34.9, 33.3, 32.1, 30.8, 22.8, 14.3. MS (EI, 70 eV): 219 (42), 176 (100), 131 (98), 91 (62). Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{ON}$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.23; H, 9.83; N, 6.40.

2-(5-(Pivaloyloxy)-pentyl)-*N,N*-dimethylbenzamide (11e). Prepared from 2-iodo-*N,N*-dimethylbenzamide **9b** (822 mg, 3 mmol) and 5-(pivaloyloxy)pentylzinc iodide (1.5 ml, 6 M, 9 mmol). Reaction time: 16 h at 10°C. Purification by flash chromatography (pentane/ethyl acetate 4:1) yielded **11e** as a colourless oil (484 mg, 73%). IR (KBr): 2935 (m), 1726 (s), 1640 (s), 1395 (m), 1285 (m), 1158(s) cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 7.25–7.04 (m, 4H), 3.96 (t, $J=7.2$ Hz, 2H), 3.04 (s, 3H), 2.73 (s, 3H), 2.52 (b, 2H), 1.62–1.53 (m, 4H), 1.29–1.18 (m, 2H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3): δ 180.5, 173.4, 140.7, 138.4, 131.4, 130.8, 128.0, 128.0, 66.2, 40.7, 36.6, 34.8, 32.4, 30.5, 29.2, 27.8. MS (EI, 70 eV): 319 (39), 271 (34), 226 (100), 176 (97), 131 (41), 57 (77). Anal. Calcd for $\text{C}_{19}\text{H}_{29}\text{O}_3\text{N}$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.32; H, 8.78; N, 4.28.

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References

1. *Metal-catalyzed Cross-Coupling Reactions*, Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.
2. (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (d) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955.
3. (a) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201. (b) Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203.
4. Rottländer, M.; Knochel, P. *J. Comb. Chem.* **1999**, *1*, 181.
5. (a) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2387. (b) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544.
6. Piber, M.; Jensen, A. E.; Rottländer, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323.
7. Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186.
8. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.