Synthesis of Unsymmetrical Heterobiaryls Using Palladium-Catalyzed Cross-Coupling Reactions of Lithium Organozincates

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Abstract: Several unsymmetrical heterobiaryls have been synthesized through palladium-catalyzed cross-coupling reactions of lithium triorganozincates. The latter have been prepared by deprotonative lithiation followed by transmetalation using non-hygroscopic $ZnCl_2$·TMEDA (0.33 equiv).

Key words: cross-coupling, heterocycle, metalation, palladium, zinc

The importance of heterobiaryls in natural products and pharmaceutical intermediates and their unique photophysical properties have stimulated tremendous efforts for the development of synthetic methods in the area of aryl–aryl bond formation.[1] Like the Suzuki–Miyaura[2] and Stille[3] reactions, the Negishi[4] cross-couplings of organozincs and aryl halides offer the advantage of stable starting materials and thus are known to tolerate a large range of functional groups. Nevertheless, the latter become more attractive when heteroaryl boronic acids cannot be prepared; in addition, they do not use highly toxic starting materials.

The organozincs are in general prepared by treating the corresponding lithium or magnesium compounds with zinc halides.[5] Alternative methods employ zinc dust or active Rieke zinc (direct insertion).[5,6] Electrochemical methods have also been considered.[7]

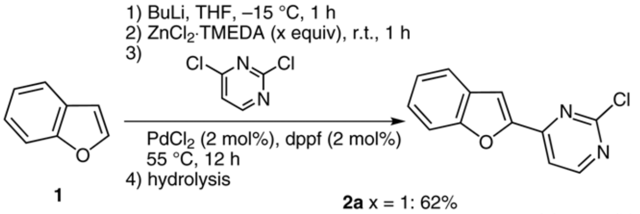
A major drawback of the Negishi coupling procedure lies in obtaining dry zinc chloride or zinc bromide. Mutule and Suma described in 2005 a sequential microwave-assisted Grignard formation–transmetalation–Negishi one-pot reaction using the less hygroscopic TMEDA-chelated zinc chloride.[8] Gauthier and co-workers developed an approach through lithium zincates using only one third equivalent of zinc chloride for the synthesis of 5-aryl-2-furaldehydes from 5-lithio-2-furaldehyde diethyl acetal.[9] Miller and Farrell reported the use of a catalytic amount of zinc chloride to perform nickel- or palladium-catalyzed couplings of aryl Grignard reagents with aryl halides.[10] Other authors completely avoided the use of zinc halide by generating lithium zincates either by iodine–metal exchange[11] or by deprotonation.[12] Herein, we report palladium-catalyzed reactions for which the lithium zincate intermediates are generated by transmetalation of the corresponding lithio compounds using $ZnCl_2$·TMEDA.

We first optimized the procedure for the cross-coupling of zinc compounds obtained from 2-lithiobenzofuran. Benzo[*b*]furan (**1**) was lithiated using butyllithium in tetrahydrofuran (THF) at –15 °C.[13] Transmetalation was performed using 1:1, 3:1, and 4:1 benzofuryllithium/$ZnCl_2$·TMEDA stoichiometries in order to generate the corresponding organozinc, lithium triorganozincate, and dilithium tetraorganozincate, respectively.

Nickel-catalyzed cross-couplings of organozinc compounds have been described.[14] However, the toxicity of nickel salts led us to explore alternative routes.[15]

In 2002 Figadère[16] and Fürstner[17] separately reported iron-catalyzed aryl–heteroaryl cross-coupling reactions starting from aryl Grignard reagents and heteroaryl chlorides. The reactions proceed in good yields when carried out in THF at –30 °C using iron(III) acetylacetonate [$Fe(acac)_3$]. A magnesium trialkylzincate, $Et_3ZnMgBr$, also proved to react with methyl 4-chlorobenzoate when the reaction was conducted similarly.[17] Attempts to perform the reaction between benzofurylzinc chloride and 2,4-dichloropyrimidine in the presence of $Fe(acac)_3$ under the same reaction conditions failed.

We thus turned to palladium-catalyzed reactions (Scheme 1, Table 1).[18] Cross-coupling reactions of all the benzofurylzincs performed with 2,4-dichloropyrimidine at 55 °C in THF with catalytic amounts of palladium(II) chloride and 1,1′-bis(diphenylphosphino)ferrocene (dppf)[19] provided the expected benzofurylpyrimidine **2a**.[20] Whereas a lower 44% yield was obtained with the higher order zincate,[21] similar results were shown using the organozinc



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2a x = 1: 62%
x = 0.33: 56%, 53% (a), 30% (b)
x = 0.25: 44%

Scheme 1 (a) Using PPh_3 (4 mol%) instead of dppf; (b) using PCy_3 (4 mol%) instead of dppf

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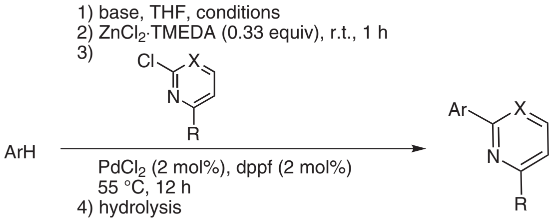
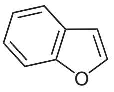
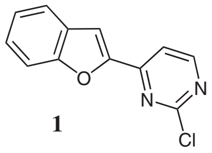
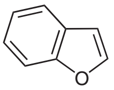
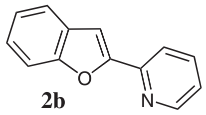
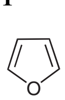
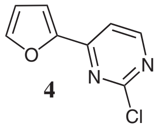
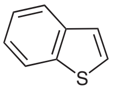
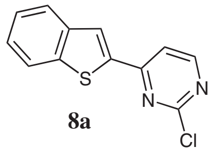
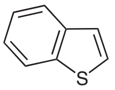
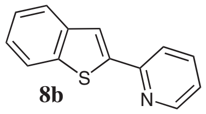
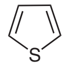
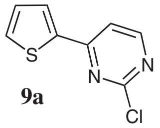
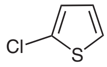
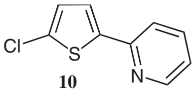
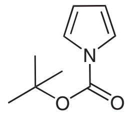
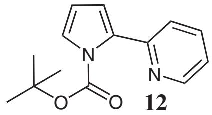
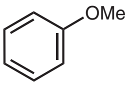
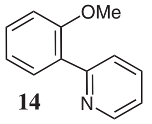
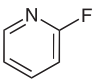
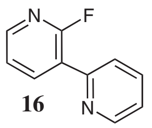
Table 1 Coupling Reactions of Lithium Triarylzincates with Heteroaryl Chlorides



Entry	Substrate	Base, conditions	Product	Yield (%)
1	 **1**	BuLi, –15 °C, 1 h	 **1**	56
2	 **1**	BuLi, –15 °C, 1 h	 **2b**	61, 76[a]
3	 **3**	BuLi, –15 °C, 1 h	 **4**	61
4	 **5**	BuLi, –75 °C, 1 h	 **8a**	29[b]
5	 **5**	BuLi, –75 °C, 1 h	 **8b**	81
6	 **6**	BuLi, –15 °C, 1 h	 **9a**	56
7	 **7**	BuLi, –75 °C, 1 h	 **10**	85
8	 **11**	LiTMP, –75 °C, 1 h	 **12**	61
9	 **13**	BuLi, 25 °C, 2 h	 **14**	64
10	 **15**	LiTMP, –75 °C, 1 h	 **16**	62

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[a] Coupling step performed in the presence of DME (5 equiv).

[b] Since 2,4-dichloropyrimidine reacts rapidly with moisture in air, lower yields can be partly attributed to the presence of pyrimidinone in the starting heteroaryl chloride.

and lithium triorganozincate (62% and 56% yields, respectively). Other ligands such as triphenylphosphine (53%), tri(cyclohexyl)phosphine (30%), 1,3-bis(diphenylphosphino)propane (<20%), and 1,4-bis(diphenylphosphino)-butane (<10%) were tested for the palladium-catalyzed reaction involving lithium tri(2-benzofuryl)zincate, which was preferred for stoichiometry efficiency, but proved less efficient than dppf.[22] The pyridylbenzofuran **2b**[23] was similarly obtained in 61% yield from 2-chloropyridine (Table 1, entry 2).

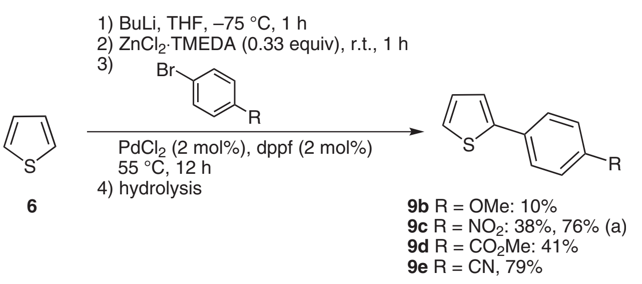
Having optimized the conditions, various aromatic substrates were used in the deprotonation–transmetalation–coupling sequence using 2,4-dichloropyrimidine and/or 2-chloropyridine. Furan (**3**) was similarly lithiated;[24] subsequent transmetalation using $ZnCl_2$·TMEDA (0.33 equiv) and coupling with 2,4-dichloropyrimidine afforded the expected furylpyrimidine **4**[25] (Table 1, entry 3). Benzo[*b*]thiophene (**5**), thiophene (**6**), and 2-chlorothiophene (**7**), which were lithiated using butyllithium in THF at –75 °C, –15 °C, and –75 °C,[26] respectively, gave the bisheterocycles **8a**,[27] **8b**,[28] **9a**,[29] and **10**[30] (entries 4–7). *N*-Boc pyrrole (**11**) was deprotonated upon treatment with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF at –75 °C[31] to give the 2-pyridyl derivative **12**[32] (entry 8) after subsequent transmetalation–coupling reactions. Anisole (**13**) was similarly *ortho* functionalized[33] to afford the 2-pyridyl derivative **14**[34] (entry 9). The reaction also proved convenient for the functionalization of a π-deficient substrate, 2-fluoropyridine (**15**), which was converted to the bipyridine **16**[35] (entry 10) after lithiation using LiTMP in THF at –75 °C,[36] followed by transmetalation and cross-coupling steps.

Since the addition of 1,2-dimethoxyethane (DME) to the reaction mixture proved to improve yields of Negishi cross-coupling products,[37] the palladium-catalyzed reaction between lithium tri(2-benzofuryl)zincate and 2-chloropyridine was performed in the presence of five equivalents of this cosolvent to give the pyridylbenzofuran **2b** in a slightly higher yield (76%, Table 1, entry 2).

Nevertheless, even using these improved conditions, the coupling between the *N*,*N*-diethylbenzamide lithium zincate and 2-chloropyridine failed, a result probably due to the size of the diethylamide group.

In addition, when heteroaryl chlorides were replaced by phenyl chlorides the reactions also failed, even in the presence of electron-withdrawing groups at the phenyl 4-position. We therefore turned to the corresponding bromides[38] which have lower carbon–halogen bond-dissociation energies,[39] and investigated the access to functionalized 2-phenylthiophenes (Scheme 2).

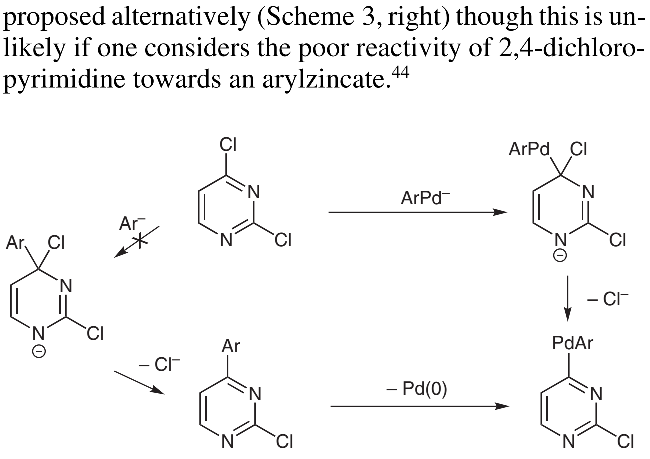
The reaction of lithium tri(2-thienyl)zincate with 4-bromoanisole afforded the expected coupling product **9b**,[40] but in a poor 10% yield due to the competitive formation of 2,2′-bisthiophene (40–50% yield). With bromobenzenes containing electron-withdrawing groups at the 4-position, such as 2-bromo-4-nitrobenzene, methyl 4-bromobenzoate, and 4-bromobenzonitrile, the expected derivatives



Scheme 2 (a) Coupling step performed in the presence of DME (5 equiv)

9c,[41] **9d**,[42] and **9e**[43] were isolated in yields ranging from 38% to 79%.

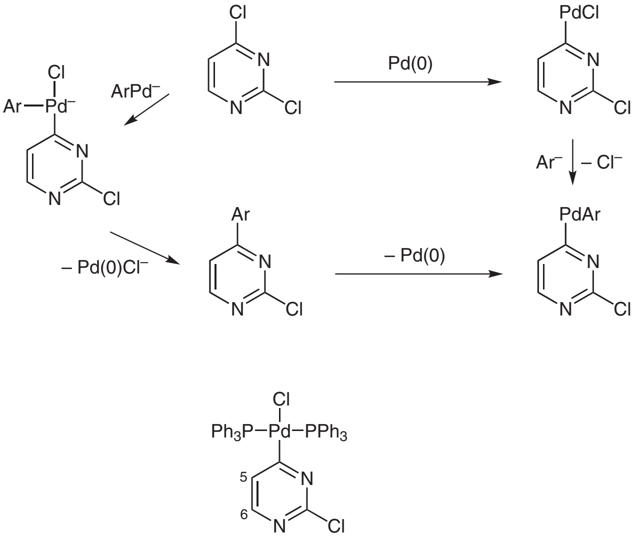
Since 2-chloropyridine and, above all, 2,4-dichloropyrimidine are π-deficient chloro substrates, a reaction mechanism involving a nucleophilic aromatic substitution by an aryl group was suspected (Scheme 3, left). However, this was discarded since the reaction between lithium tri(2-benzofuryl)zincate and 2,4-dichloropyrimidine performed without catalyst did not allow the cross-coupling product **2a** to be formed. A mechanism involving an addition–elimination of an organopalladate as first step can be proposed alternatively (Scheme 3, right) though this is unlikely if one considers the poor reactivity of 2,4-dichloropyrimidine towards an arylzincate.[44]



Scheme 3 Ligands are omitted for clarity

A more classical pathway is an oxidative addition of 2,4-dichloropyrimidine to a Pd(0) complex followed by transmetalation by the nucleophile (Scheme 4, right). However, the oxidative addition could take place either at the 2- or 4-position. To test the regioselectivity of the oxidative addition, the reaction of 2,4-dichloropyrimidine (0.01 mmol) with $Pd(PPh_3)_4$ (0.01 mmol) was followed by ^1H NMR (250 MHz, TMS) and ^{31}P NMR (101 MHz, H_3PO_4) in CD_2Cl_2 at 27 °C. Two ^1H signals of equal magnitude at $\delta = 6.73$ (dt, $J_{HH} = 5.1$ Hz, $J_{PH} = 1.2$ Hz, H_5) and 6.58 (d, $J_{HH} = 5.1$ Hz, H_6) associated to a ^{31}P singlet at $\delta = 22.0$ characterized the formation of complex **17** by oxidative addition at the 4-position, in agreement with the regioselectivity observed in the catalytic reactions.

It should be noted that the presence of a lithium zincate could also allow the formation of an arylpalladate $ArPd(0)L_2^-$,[45] which could regioselectively react with 2,4-



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Scheme 4 Ligands are omitted for clarity

dichloropyrimidine by oxidative addition as depicted in Scheme 4 (left).

In conclusion, we have described the synthesis of unsymmetrical heterobiaryls using palladium-catalyzed cross-coupling reactions of lithium triorganozincates, which have been prepared through one-pot deprotonative lithiation–transmetalation using non-hygroscopic $ZnCl_2$·TMEDA.

Typical Procedure: Preparation of 2-(2-benzo[*b*]thienyl)pyridine (8b)

To a stirred and cooled (–75 °C) solution of benzo[*b*]thiophene (**5**, 0.54 g, 4.0 mmol) in dry THF (5 mL) under argon was added BuLi (about 1.6 M hexanes solution, 4.0 mmol) and, 1 h later, $ZnCl_2$·TMEDA[46] (0.33 g, 1.3 mmol). The mixture was slowly warmed to r.t. (1 h) before addition of 2-chloropyridine (0.45 g, 4.0 mmol), $PdCl_2$ (14 mg, 80 μmol), and dppf (44 mg, 80 μmol). The mixture was cooled before addition of H_2O (0.5 mL) and EtOAc (50 mL), dried over $MgSO_4$, and the solvents were removed under reduced pressure. Compound **8b** was isolated by chromatographic purification on silica gel column (eluent: heptane–CH_2Cl_2, 50:50 to 30:70) as a white powder (1.0 g, 81%).[28]

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(19) For the use of $PdCl_2$(dppf) as a highly effective catalyst for the coupling of organozinc reagents, see: Hayashi, T.; Konishi, M.; Kobri, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

(20) (a) Compound **2a**: pale yellow powder; mp 186 °C. The spectral data were found identical to those previously described, see ref. 20b. ^{13}C NMR (50 MHz, CD_3COCD_3): $\delta = 110.9, 112.4, 115.4, 123.5, 124.7, 128.1, 128.7, 152.2, 156.5, 158.6, 161.8, 162.1$. (b) Strekowski, L.; Harden, M. J.; Grubb, W. B. III.; Patterson, S. E.; Czarny, A.; Mokrosz, M. J.; Cegla, M. T.; Wydra, R. L. *J. Heterocycl. Chem.* **1990**, *27*, 1393.

(21) Slightly lower cross-coupling yields have been observed with higher order zincate compared with lithium triorganozincate, see ref. 9.

(22) No reaction takes place in the absence of transition metal. Note that product **2a** has previously been obtained by addition of 2-benzofuryllithium at the 4-position of 2-chloropyrimidine followed by rearomatization using DDQ in 38% yield, see ref. 20b.

(23) Compound **2b**: white powder; mp 88 °C. The spectral data were found identical to those previously described. See: Mongin, F.; Bucher, A.; Bazureau, J. P.; Bayh, O.; Awad, H.; Trécourt, F. *Tetrahedron Lett.* **2005**, *46*, 7989.

(24) Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216.

(25) Compound **4**: white powder; mp 88 °C. The spectral data were found identical to those previously described, see. ref. 20b. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 113.1, 113.1, 114.5, 146.2, 150.4, 158.1, 159.9, 161.7$.

(26) Benzo[*b*]thiophene has previously been metalated using butyllithium in THF at 0 °C, see: (a) Jen, K.-Y.; Cava, M. P. *J. Org. Chem.* **1983**, *48*, 1449. Thiophene has previously been metalated using butyllithium in THF at temperatures between –20 °C and r.t., see: (b) Surry, D. S.; Fox, D. J.; MacDonald, S. J. F.; Spring, D. R. *Chem. Commun.* **2005**, 2589.

(27) Compound **8a**: pale yellow powder; mp 198 °C. The spectral data were found identical to those previously described, see ref. 20b. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 114.5, 122.9, 125.2, 125.3, 126.3, 126.9, 139.8, 140.1, 141.8, 159.7, 161.9, 162.3$.

(28) Compound **8b**: white powder; mp 126 °C. The physical and spectral data were found identical to those of a commercial sample (Aldrich).

(29) (a) Compound **9a**: white powder; mp 124 °C. The physical data were found identical to those previously described in ref. 29b. ^1H NMR (200 MHz, CD_3COCD_3): $\delta = 7.17$ (dd, $J = 7.5, 5.7$ Hz, 1 H), 7.46 (d, $J = 7.8$ Hz, 1 H), 7.59 (dd, $J = 7.5, 1.5$ Hz, 1 H), 7.82 (dd, $J = 5.7, 1.5$ Hz, 1 H), 8.53 (d, $J = 8.1$ Hz, 1 H). ^{13}C NMR (50 MHz, CD_3COCD_3): $\delta = 113.7, 128.8, 129.2, 131.8, 140.5, 159.5, 161.7, 162.0$. (b) Brown, D. J.; Cowden, W. B.; Strekowski, L. *Aust. J. Chem.* **1982**, *35*, 1209–1214.

(30) Compound **10**: pale yellow powder; mp 67 °C. The spectral data were found identical to those previously described. See: (a) Constable, E. C.; Sousa, L. R. *J. Organomet. Chem.* **1992**, *427*, 125. (b) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron* **2005**, *61*, 4779.

(31) *N*-Boc pyrrole has previously been metalated using LiTMP in THF at –75 °C. See: Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.

(32) Compound **12**: yellow oil. The spectral data were found identical to those previously described: Semmelback, M. F.; Chlenov, A.; Douglas, M. *J. Am. Chem. Soc.* **2005**, *127*, 7759.

(33) Concerning the direct lithiation of anisole, see: Shirley, D. A.; Johnson, J. R.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 209.

(34) Compound **14**: colorless oil. The spectral data were found identical to those previously described: Mongin, F.; Mojovic, L.; Guillamet, B.; Trécourt, F.; Quéguiner, G. *J. Org. Chem.* **2002**, *67*, 8991.

(35) Compound **16**: beige powder; mp <50 °C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.25$–7.37 (m, 2 H), 7.72–7.91 (m, 2 H), 8.25 (d, $J = 3.2$ Hz, 1 H), 8.47–8.58 (m, 1 H), 8.72 (d, $J = 4.8$ Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 122.1$ (d, $J = 4.3$ Hz), 122.6, 123.2, 124.3 (d, $J = 10.4$ Hz), 136.8, 141.6 (d, $J = 3.8$ Hz), 147.7 (d, $J = 15.1$ Hz), 150.0, 151.4 (d, $J = 6.8$ Hz), 160.9 (d, $J = 241$ Hz). HRMS: *m/z* calcd for $C_{10}H_7N_2F$ [M^+]: 174.0593; found: 174.0595.

(36) For the deprotonation of 2-fluoropyridine using a lithium amide, see: (a) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151. (b) Estel, L.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 2740.

(37) See, for example: Riguet, E.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* **1997**, *38*, 4397.

(38) For palladium-catalyzed cross-couplings of arylzinc compounds with aryl bromides, see for example: (a) Amatore, C.; Jutand, A.; Negri, S.; Fauvarque, J.-F. *J. Organomet. Chem.* **1990**, *390*, 389. (b) Bumagin, N. A.; Sokolova, A. F.; Beletskaya, I. P. *Russ. Chem. Bull.* **1993**, *42*, 1926. (c) Borner, R. C.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1994**, 845. (d) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 4578. (e) Hargreaves, S. L.; Pilkington, B. L.; Russell, S. E.; Worthington, P. A. *Tetrahedron Lett.* **2000**, *41*, 1653. (f) Loren, J. C.; Siegel, J. S. *Angew. Chem. Int. Ed.* **2001**, *40*, 754. (g) Alami, M.; Peyrat, J.-F.; Belachmi, L.; Brion, J.-D. *Eur. J. Org. Chem.* **2001**, 4207. (h) Karig, G.; Thasana, N.; Gallagher, T. *Synlett* **2002**, 808. (i) Balle, T.; Andersen, K.; Vedsø, P. *Synthesis* **2002**, 1509. (j) Kondolff, I.; Doucet, H.; Santelli, M. *Organometallics* **2006**, *25*, 5219. (k) Akao, A.; Tsuritani, T.; Kii, S.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* **2007**, 31.

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(40) Compound **9b**: beige powder; mp 104 °C. The spectral data were found identical to those previously described: Takahashi, K.; Suzuki, T.; Akiyama, K.; Ikegami, Y.; Fukazawa, Y. *J. Am. Chem. Soc.* **1991**, *113*, 4576.

(41) Compound **9c**: yellow powder; mp 135 °C. The spectral data were found identical to those previously described: Li, J.-H.; Zhu, Q.-M.; Xie, Y.-X. *Tetrahedron* **2006**, *62*, 10888.

(42) Compound **9d**: white powder; mp 134 °C. The spectral data were found identical to those previously described: Sieber, F.; Wentworth, P. Jr.; Janda, K. D. *J. Comb. Chem.* **1999**, *1*, 540.

(43) Compound **9e**: white solid; mp 88 °C. The spectral data were found identical to those previously described: Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793.

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