Cobalt–Xantphos-Catalyzed, LiCl-Mediated Preparation of Arylzinc Reagents from Aryl Iodides, Bromides, and Chlorides

Meng-Yi Jin and Naohiko Yoshikai*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: A cobalt-Xantphos-catalyzed, LiCl-mediated system has been developed for the direct and expedient preparation of arylzinc reagents in THF from the corresponding aryl iodides, bromides, and chlorides. Owing to the use of THF as a versatile solvent, the thusformed arylzinc reagents displayed a high degree of compatibility with a variety of conventional as well as newly emerging metal-catalyzed crosscoupling reactions.



INTRODUCTION

The preparation of organozinc reagents is an important synthetic task owing to the versatility of the reagents in a wide range of C-C bond-forming reactions.¹ In light of operational simplicity and atom efficiency, direct insertion of zinc into organic halides is the most attractive method. Furthermore, with the continuous development of transition-metal catalysis of organozinc reagents beyond conventional Pd and Cu catalysis,^{2,3} their preparative methods featuring convenience, broad substrate scope, and wide applicability are highly desirable. However, existing methods, particularly for arylzinc reagents, have not yet displayed all of the aforementioned features. Early methods, except the one employing less convenient Rieke zinc,⁴ required the use of aryl iodides and highly polar solvents,^{5,6} the latter being potentially detrimental to subsequent transition-metal-catalyzed reactions. The LiCl-mediated zinc insertion in THF recently developed by the Knochel group⁷ has gained popularity among the synthetic community due to its convenience and wide applicability.^{2,8} Nevertheless, the substrates used are limited to aryl iodides and highly activated aryl bromides. While the preparation of arylzinc reagents from the corresponding bromides and chlorides has been achieved by the CoBr2-catalyzed method of Gosmini and co-workers,⁹ the use of acetonitrile as the solvent (and pyridine as the cosolvent for aryl chlorides) narrows the potential applicability of the resulting zinc reagents. We report herein a cobalt-Xantphos-catalyzed, LiCl-mediated system that allows for the expedient synthesis of arylzinc reagents in THF from a series of aryl iodides, bromides, and chlorides (Scheme 1). Furthermore, the thus-formed arylzinc reagents have proven to be applicable to conventional as well as newly

Scheme 1. Cobalt-Xantphos-Catalyzed, LiCl-Mediated Zinc Insertion into Aryl Halides



emerging cross-coupling reactions catalyzed by various transition metal complexes (i.e., Cu, Pd, Fe, Rh).

RESULTS AND DISCUSSION

Optimization of Reaction Conditions. Prompted by Gosmini's work on CoBr₂-catalyzed zinc insertion in acetonitrile,⁹ we set out to explore cobalt complexes that could accelerate the Knochel zinc insertion in THF. We initially focused on the zinc insertion into 4-iodoanisole 1, which was reported to complete after 90 h at 50 °C.7 Screening of a variety of cobalt precatalysts and ligands led us to find that a combination of CoCl₂ and Xantphos greatly accelerates the reaction. Thus, the reaction of 1 with $Zn \cdot LiCl$ (1.5 equiv/1.0 equiv; zinc was preactivated by 1,2-dibromoethane and Me₃SiCl) in the presence of $CoCl_2$ and Xantphos (5 mol % each) in THF completed within 16 h at 20 °C, and after quenching with 1 M HCl afforded anisole 2 in 97% yield, together with a small amount of a homocoupling

Received: December 7, 2010 Published: March 08, 2011

Table 1. Zinc Insertion into 4-Iodoanisole^a



| | | | | 3 | yield ^{<i>v</i>} (%) | | |
|-----------------|------------------------|------------------|------|---------|-------------------------------|--------|--|
| entry | CoX_n | ligand | LiY | 2 | 3 | 1 | |
| 1 | CoCl ₂ | Xantphos | LiCl | 97 (12) | 2 (3) | 0 (84) | |
| 2 | | | LiCl | 9 | 0 | 89 | |
| 3 | CoCl ₂ | | LiCl | 5 | 0 | 95 | |
| 4 | | Xantphos | LiCl | 10 | 0 | 90 | |
| 5 | CoCl ₂ | DPEphos | LiCl | 89 | 11 | 0 | |
| 6 | $CoCl_2$ | dppbz | LiCl | 67 | 3 | 27 | |
| 7 | $CoCl_2$ | dppf | LiCl | 40 | 5 | 52 | |
| 8 | $CoCl_2$ | dppe | LiCl | 29 | 0 | 67 | |
| 9 ^c | $CoCl_2$ | PPh ₃ | LiCl | 5 | 0 | 95 | |
| 10 | $CoCl_2$ | bpy | LiCl | 26 | 17 | 46 | |
| 11 | CoCl ₂ | phen | LiCl | 51 | 47 | 0 | |
| 12 | CoBr ₂ | Xantphos | LiCl | 95 | 2 | 0 | |
| 13 | CoI ₂ | Xantphos | LiCl | 96 | 1 | 0 | |
| 14 | $Co(acac)_2$ | Xantphos | LiCl | 94 | 2 | 0 | |
| 15 | $Co(acac)_3$ | Xantphos | LiCl | 94 | 4 | 0 | |
| 16 | $CoCl_2$ | Xantphos | LiBr | 99 | <1 | 0 | |
| 17 | CoCl ₂ | Xantphos | LiI | 97 | 2 | 0 | |
| 18 | CoCl ₂ | Xantphos | | 2 | 0 | 97 | |
| 19 ^d | $CoCl_2$ | Xantphos | LiCl | 97 | 1 | 0 | |
| $20^{e,f}$ | CoCl ₂ | Xantphos | LiCl | 98 (9) | 2 (3) | 0 (88) | |
| $21^{f,g}$ | $CoCl_2(Xantphos)$ | | LiCl | (6) | (<1) | (93) | |

^{*a*} Reaction was performed on a 2 mmol scale. ^{*b*} Determined by GC using *n*-tridecane as an internal standard. Values in parentheses refer to yields obtained for reactions quenched with I₂. ^{*c*} 10 mol % of PPh₃ was used. ^{*d*} 10 mol % of Xantphos was used. ^{*e*} 2.5 mol % of CoCl₂ and Xantphos were used. ^{*f*} Reaction completed in 8 h. ^{*g*} 2.5 mol % of CoCl₂(Xantphos) was used.

product 3 (Table 1, entry 1). When the same reaction was quenched with I_2 , 1 was recovered in 84% yield. This confirmed efficient zinc insertion. Unlike the Gosmini protocol,^{9b-d} individually, CoCl₂ (and other cobalt salts) or Xantphos did not exhibit any rate acceleration in THF (entries 2–4).

Although other diphosphines such as DPEphos, dppbz, dppf, and dppe also accelerated the zinc insertion, their effects were less pronounced than that of Xantphos (entries 5–8). Monodentate phosphines such as PPh₃ were not effective (entry 9). The use of bipyridine and phenanthroline ligands resulted in the formation of considerable amounts of **3** (entries 10 and 11). Other cobalt sources such as CoBr₂, CoI₂, Co(acac)₂, and Co(acac)₃ performed equally well as CoCl₂ (entries 12–15).

| Гab | le | 2. | Zinc | Insertion | into | Unactivated | l Ary | l Ioc | lides' | • |
|-----|----|----|------|-----------|------|-------------|-------|-------|--------|---|
|-----|----|----|------|-----------|------|-------------|-------|-------|--------|---|

| | | | yield ^{b} (%) | | |
|--------------------------------|---|----------|-------------------------------------|-----|------|
| entry | Ar-I | time (h) | ArZnI | ArH | ArAr |
| 1 | 4-MeC ₆ H ₄ I | 6 | 86 | 9 | 4 |
| 2 | 3-MeC ₆ H ₄ I | 6 | 84 | 11 | 3 |
| 3 ^{<i>c</i>,<i>d</i>} | 2-MeC ₆ H ₄ I | 16 | 16 | 81 | 0 |
| 4 ^{<i>c,d</i>} | 2,4,6-Me ₃ C ₆ H ₂ I | 24 | 0 | 95 | 0 |
| 5 | 3-MeOC ₆ H ₄ I | 5 | 83 | 12 | 4 |
| 6 ^{<i>c</i>} | 2-MeOC ₆ H ₄ I | 6 | 90 | 10 | 0 |
| 7^c | $2,4-(MeO)_2C_6H_3I$ | 7 | 92 | 7 | 1 |
| 8 | 4-Me ₂ NC ₆ H ₄ I | 12 | 67 | 4 | 8 |
| 9 | 3-NCC ₆ H ₄ I | 8 | 89 | 5 | 5 |
| 10 | 3-EtO ₂ CC ₆ H ₄ I | 5 | 91 | 8 | 1 |
| | | | | | |

^{*a*} Reaction conditions in Table 1, entry 20, were employed unless otherwise noted. ^{*b*} Determined by GC after iodolysis. For each reaction, full conversion of the starting material was confirmed by GC. ^{*c*} 5 mol % of CoCl₂ and 5 mol % of Xantphos were used. ^{*d*} Reaction was run at 50 °C.

LiBr and LiI also assisted the zinc insertion, while the absence of a lithium salt resulted in no rate acceleration (entries 16-18). Change of the cobalt/Xantphos ratio from 1:1 to 1:2 did not affect the reaction (entry 19). A catalyst loading of 2.5 mol % was sufficient for full conversion of 1 within 8 h (entry 20). A preformed complex, CoCl₂(Xantphos),¹⁰ showed a similar catalytic activity to the in situ generated catalyst (entry 21). Note that reactions performed in polar solvents such as DMF and acetonitrile gave much poorer results, affording the product 2 in 31% and 38% yields, respectively. No reaction took place when toluene was used as the solvent.

Zinc Insertion into Aryl lodides, Bromides, and Chlorides. The optimized catalytic system (Table 1, entry 13) was applicable to a series of unactivated aryl iodides (Table 2). Thus, 4- and 3-iodotoluenes underwent zinc insertion smoothly within 6 h to afford the corresponding zinc reagents in ca. 85% yields (entries 1 and 2). The reaction of 2-iodotoluene completed within 16 h at 50 °C with a catalyst loading of 5 mol %. However, toluene was formed as the main product (entry 3). Similarly, 2-iodomesitylene afforded the reduction product exclusively (entry 4). A methoxy group on the 3- or 2-position did not interfere with the reaction (entries 5-7). A strongly donating dimethylamino substituent was also tolerated (entry 8). In addition, moderately reactive 3-cyano- and 3-ethoxycarbonyl-substituted iodides afforded the corresponding functionalized arylzinc reagents in good yields (entries 9 and 10).

The Co–Xantphos catalyst also allowed the facile conversion of a variety of aryl bromides to the corresponding arylzinc reagents (Table 3). Thus, bromobenzene underwent complete conversion within 14 h, affording PhZnBr in 82% yield (entry 1). Electron-withdrawing halogen and CF₃ substituents accelerated the reaction, affording the zinc reagents within 5-6 h (entries 2-7). Note that the C–Cl bonds of 1-bromo-3,5-dichlorobenzene remained intact at room temperature (entry 7; see also entry 16). Electron-rich or neutral aryl bromides also afforded the corresponding zinc reagents in good yield, albeit after longer reaction times (entries 8-11). In addition, activated substrates such as ethyl 4-bromobenzoate reacted smoothly within 5 h (entry 12). Unexpectedly, the reaction of 3-bromobenzonitirle was rather sluggish, and afforded the zinc reagent in a moderate yield after 35 h (entry 13).

 Table 3. Zinc Insertion into Aryl Bromides and Chlorides^a

| | | | yield ^{b} (%) | | |
|----------------------------|--|----------|-------------------------------------|-----|------|
| entry | Ar-X | time (h) | ArZnX | ArH | ArAr |
| 1 | C ₆ H ₅ Br | 14 | 82 | ND | 3 |
| 2 | 4-F ₃ CC ₆ H ₄ Br | 6 | 89 | 7 | 4 |
| 3 | $3,5-(CF_3)_2C_6H_3Br$ | 6 | 90 | ND | 0 |
| 4 | 3-FC ₆ H ₄ Br | 5 | 87 | 6 | 2 |
| 5 ^c | $3,4$ - $F_2C_6H_3Br$ | 5 | 92 | <7 | <1 |
| 6 ^{<i>c</i>} | C ₆ F ₅ Br | 5 | 95 | <5 | 0 |
| 7^c | 3,5-Cl ₂ C ₆ H ₃ Br | 5 | 96 | <4 | 0 |
| 8 | 4-PhC ₆ H ₄ Br | 10 | 87 | 5 | 0 |
| 9 | $1 - C_{10}H_7Br$ | 24 | 79 | 20 | 0 |
| 10 | 4-MeOC ₆ H ₄ Br | 14 | 82 | 10 | 4 |
| 11^d | 2-MeOC ₆ H ₄ Br | 22 | 79 | 21 | 0 |
| 12^e | 4-EtO ₂ CC ₆ H ₄ Br | 5 | 85 | 9 | 6 |
| 13^d | 3-NCC ₆ H ₄ Br | 35 | 68 | 14 | 9 |
| 14 ^c | 2-bromothiophene | 5 | 89 | <5 | <4 |
| 15 ^c | 3-bromothiophene | 8 | 92 | <6 | <2 |
| 16 | 2-bromo-5-chlorothiophene | 5 | 83 | 4 | 3 |
| 17^c | 3-bromoquinoline | 20 | 80 | <1 | 0 |
| $18^{c,d,f}$ | 2-chlorothiophene | 24 | 86 | 9 | 5 |
| 19 ^{<i>c,d,f</i>} | 3-chlorothiophene | 24 | 85 | 9 | 3 |
| 20 ^{<i>c,d,g</i>} | 3-EtO ₂ CC ₆ H ₄ Cl | 24 | 60 | 19 | 15 |
| $21^{c,d,g}$ | 3-F ₃ CC ₆ H ₄ Cl | 24 | 62 | 14 | 15 |

^{*a*} Reaction conditions in Table 1, entry 20, were employed unless otherwise noted. ^{*b*} Determined by GC after iodolysis unless otherwise noted. ND = not detemined. ^{*c*} Reaction was run on a 4–5 mmol scale, and yield of ArZnX was determined by iodine titration.^{11 d} 5 mol % of CoCl₂ and 5 mol % of Xantphos was used. ^{*c*} 5 mol % of Xantphos was used. ^{*f*} Reaction was run at 50 °C. ^{*g*} Reaction was run at 80 °C.

Scheme 2



A smooth zinc insertion was also observed for heteroaryl bromides. Thus, bromothiophenes underwent complete conversion within 5-8 h to afford the thienylzinc reagents in 83-92% yields (entries 14-16). 3-Quinolylzinc bromide was obtained in 80% yield after 20 h (entry 17). Unfortunately, the attempted zinc insertion to 2-bromopyridine afforded mostly pyridine as the reduced product (data not shown).

Preliminary studies demonstrated that the present catalytic system is also effective for aryl chlorides (Table 3). With a catalyst loading of 5 mol %, chlorothiophenes were converted to the corresponding zinc reagents within 24 h at 50 °C in ca. 85% yields (entries 18 and 19). Activated aryl chlorides such as those bearing 3-ethoxycarbonyl and 3-trifluoromethyl groups participated in the reaction at 80 °C to afford the zinc reagents in moderate yields of ca. 60% (entries 20 and 21). Unactivated substrates such as 4-chloroanisole reacted very sluggishly (<30% conversion under the same conditions).

To probe the source of the hydrogen atom in the reduction product, we performed a labeling experiment (Scheme 2). The





reaction of 2-iodomesitylene in THF- d_{8} , followed by quenching with 1 M HCl, afforded deuterated mesitylene with a deuterium incorporation rate of 76%, demonstrating that hydrogen abstraction from THF solvent is the major pathway leading to the reduction product. This observation suggests the radical nature of the reaction (vide infra).

Cross-Coupling Reactions of Arylzinc Reagents. The arylzinc reagents prepared by the present method are amenable to a variety of transition-metal-catalyzed cross-coupling reactions in one pot, without apparent interference from the cobalt catalyst (Table 4). Allylation and acylation reactions in the presence of CuCN·2LiCl¹² were successfully applied to 3-tosyloxyphenylzinc bromide, 3,5-dichlorophenylzinc bromide, and 3-thienylzinc bromide to afford the products 4-6 in good yields (entries 1-3).¹³ The copper catalyst also allowed for the electrophilic trapping of 3,5-bis(trifluoromethyl)phenylzinc bromide with chlorodiphenylphosphine, affording the triarylphopshine 7 in 53% yield (entry 4).¹⁴ Negishi coupling reactions of 4-biphenylzinc bromide, 3-cyanophenylzinc iodide, and 2-methoxyphenylzinc iodide with aryl halides using Pd(PPh₃)₄ or Pd-SPhos catalyst¹⁵ gave the biaryl compounds 8-10 in 65-95% yields (entries 5-7). The preparation and Negishi coupling of 4-biphenylzinc bromide could be performed on a 10 mmol scale without significant decrease in the product yield (entry 5).

Besides the application to the well-established Cu- and Pdcatalyzed reactions, our zinc reagents are ready for use in the emerging cross-coupling reactions. Reactions of 2,4-dimethoxyphenylzinc iodide, 3-quinolylzinc bromide, and 3,4-difluorophenylzinc bromide with primary or secondary alkyl bromides were achieved in good yields by the iron-diamine or irondiphosphine catalyzed protocols of Nakamura and co-workers (entries 8-10).^{3b,g} Note that 3,4-difluorophenylzinc bromide prepared according to the Gosmini method^{9c} failed to participate in the iron-catalyzed cross-coupling reaction (1% GC yield) presumably due to the adverse effect of the acetonitrile solvent, highlighting the advantage of the present protocol. Applications to the Rh-catalyzed three-component coupling with an allene and acetonitrile^{2f} and the MgCl₂-mediated addition to an aldehyde,^{8e} recently reported by the Oshima and Knochel groups, respectively, were also successful (entries 11 and 12).

Proposed Reaction Mechanism. At present, we suggest a mechanistic scenario similar to that proposed by Gosmini and co-workers for CoBr₂-catalyzed zinc insertion (Scheme 3).^{9b,c}

 Table 4. Metal-Mediated Electrophilic Trapping of Arylzinc

 Halides^a



^{*a*} Performed on a 2 mmol scale (starting aryl halide) unless otherwise noted. See the Experimental Section for the detailed procedure for each case. ^{*b*} Based on the starting aryl halide. ^{*c*} Isolated yield based on the electrophile. In parentheses is shown the yield of a 10 mmol scale reaction. ^{*d*} CuCN · 2 LiCl (10–20 mol %) was used. ^{*c*} Pd₂(dba)₃ (0.25 mol %) and S-Phos (1 mol %) were used. ^{*f*} Pd(PPh₃)₄ (2 mol %) was used. ^{*g*} Me₃SiCH₂MgCl (1 equiv), *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (1 equiv), and FeCl₃ (2.5 mol %) were used. ^{*h*} Me₃SiCH₂MgCl (1 equiv), FeCl₃ (2.5 mol %), and dppbz (7.5 mol %) were used. ^{*i*} [RhCl(cod)]₂ (1.25 mol %), *P*'Bu₃· HBF₄ (5 mol %), and KO'Bu (5 mol %) were used. Performed on a 1 mmol scale. ^{*j*} MgCl₂ (1 equiv) was used.

Thus, the reaction may be initiated by reduction of $CoCl_2$ (Xantphos) to a cobalt(I) species by Zn and involves the following steps: (1) oxidative addition of an aryl halide to cobalt(I) to afford an arylcobalt(III) species, (2) reduction of the arylcobalt(III)

species to an arylcobalt(II) species by Zn, (3) transmetalation of the arylcobalt(II) species with zinc(II) halide, which is generated through the preceding reduction steps, to afford arylzinc halide and cobalt(II) halide, and (4) reduction of cobalt(II) halide by Zn to regenerate the cobalt(I) species. On the basis of the deuterium labeling experiment (Scheme 2), we consider that the arylcobalt-(II) species has a radical character. Thus, when the transmetalation between the arylcobalt(II) species and zinc(II) halide is slow, it would behave as an aryl radical to abstract the hydrogen atom from THF, affording the reduction product as the major product (see entries 3 and 4 in Table 2). More details, including the roles of Xantphos and LiCl, will be subjects of further studies.¹⁶

CONCLUSION

In summary, we have developed a Co-Xantphos-catalyzed, LiCl-mediated protocol for the efficient preparation of arylzinc reagents. With Xantphos as the key ligand and THF as the compatible solvent, the present method fulfills the requirements for operational simplicity, broad substrate scope, and applicability to a variety of transition metal-catalyzed cross-coupling reactions in a well-balanced manner. Further investigations into the transition metal-catalyzed metal insertion into organic halides are in progress in our laboratory.

EXPERIMENTAL SECTION

General Procedure for the Zinc Insertion into Aryl Halides. Anhydrous LiCl (84.8 mg, 2 mmol) was placed in a 10 mL Schlenk tube, dried under vacuum (1 mbar) at 150 °C for 20 min, and cooled to room temperature (20 °C) under N2. To the Schlenk tube was added zinc powder (196 mg, 3 mmol), and the heterogeneous mixture of Zn and LiCl was dried under vacuum (1 mbar) at 150 °C for 15 min. While cooling to room temperature, the reaction tube was evacuated and backfilled with N2 for three times. The mixture was suspended with THF (2 mL), followed by the activation of Zn with BrCH₂CH₂Br (10 μ L, 0.1 mmol) and Me₃SiCl (3 µL, 0.02 mmol) and stirring for 5 min. Then Xantphos (28.9 mg, 0.05 mmol) and CoCl₂ (6.5 mg, 0.05 mmol) were added sequentially. After the mixture was stirred for an additional 5 min, an aryl halide (2 mmol) was added in one portion. The reaction was stirred at room temperature and monitored by GC analysis of hydrolyzed aliquots. After complete conversion of the starting material, the reaction was quenched by the addition of I_2 (0.76 g, 3 mmol) and stirred for 30 min. The resulting mixture was analyzed by GC using n-tridecane or *n*-tetradecane as an internal standard to determine the yield of the arylzinc reagent. For some entries in Table 3, the reaction was performed on a 4-5 mmol scale in a 25 mL three-necked round-bottom flask, and the yield of the arylzinc reagent was determined by iodine titration (average of three runs) according to the literature procedure.¹¹

Procedures for Metal-Mediated Electrophilic Trapping of Arylzinc Halides (Table 4). The electrophilic trapping reactions were performed in one pot after preparation of the arylzinc reagents according to the typical procedure (2 mmol scale) unless otherwise noted. The copper (entries 1–4),¹² palladium (entries 5–7),¹⁵ iron (entries 8–10),^{3b,g} rhodium (entry 11),^{2f} and magnesium (entry 12)^{8e}catalyzed/mediated reactions were performed according to the literature procedures with slight modifications in some cases (see below).

3-Allylphenyl 4-methylbenzenesulfonate (4). To 3-tosyloxyphenylzinc bromide (prepared according to the typical procedure, 7 h) was added CuCN·2LiCl (0.20 mL of 1.0 M solution in THF, 0.20 mmol) at -20 °C, followed by the addition of allyl bromide (208.5 mg, 1.72 mmol). The reaction mixture was then stirred at 0 °C for 4 h, followed by the addition of saturated aqueous NH₄Cl solution (4 mL) and 10% aqueous NH₃ solution (2 mL). The resulting mixture was extracted with ethyl acetate (3 × 6 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 50/1, 30/1) afforded the title compound as a colorless oil (479.6 mg, 97%): R_f 0.48 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃) δ 2.43 (s, 3H), 3.29 (d, *J* = 6.8 Hz, 2H), 4.97 (ddt, *J* = 1.6 Hz, 1.6 Hz, 17.2 Hz, 1H), 5.03 (ddt, *J* = 1.2 Hz, 1.6 Hz, 10.0 Hz, 1H), 5.82 (ddt, *J* = 6.8 Hz, 10.0 Hz, 17.2 Hz, 1 H), 6.77–6.78 (m, 1H), 6.80–6.83 (m, 1H), 7.04–7.06 (m, 1H), 7.16–7.20 (m, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 39.5, 116.3, 119.9, 122.4, 127.3, 128.4, 129.3, 129.6, 132.3, 136.2, 141.9, 145.2, 149.6; FTIR (NaCl, neat): 3082, 2980, 2924, 1736, 1639, 1609, 1599, 1483, 1445, 1373, 1294, 1242, 1223, 1190, 1179, 1128, 1094, 1045, 955, 907, 818, 729, 692, 664; HRMS (ESI) calcd for C₁₆H₁₇O₃S [M + H]⁺ 289.0898, found 289.0893.

(3,5-Dichlorophenyl)(phenyl)methanone (5). To 3,5-dichlorophenylzinc bromide (prepared according to the typical procedure, 5 h) was added CuCN+2LiCl (0.40 mL of 1.0 M solution in THF, 0.40 mmol) -20 °C. The resulting mixture was stirred at 0 °C for 10 min, followed by the addition of benzoyl chloride (242.9 mg, 1.73 mmol) at -20 °C. The reaction mixture was then stirred at 20 °C for 2 h, followed by the addition of saturated aqueous NH₄Cl solution (4 mL) and 10% aqueous NH₃ solution (2 mL). The resulting mixture was extracted with ethyl acetate $(3 \times 6 \text{ mL})$. The combined organic phase was washed with brine, dried over Na2SO4, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 100/1) afforded the title compound as a white solid (312.1 mg, 72%): Rf 0.56 (hexane/EtOAc = 3/1); mp 62.2-63.1 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.48–7.52 (m, 2H), 7.54–7.55 (m, 1H), 7.60-7.64 (m, 3H), 7.76-7.78 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 128.1, 128.6, 129.9, 132.0, 133.1, 135.2, 136.2, 140.2, 193.6; FTIR (NaCl, CHCl₃) 3076, 1663, 1597, 1562, 1447, 1416, 1395, 1314, 1275, 1180, 1161, 1099, 974, 872, 810, 756 (overlapped with CHCl₃ band), 719, 692, 652; HRMS (ESI) calcd for C₁₃H₈³⁵Cl₂O [M + H]⁺ 251.0030, found 251.0025.

Thiophen-3-yl(4-(trifluoromethyl)phenyl)methanone (6). To 3-thienylzinc bromide (prepared according to the typical procedure, 8 h) was added CuCN · 2LiCl (0.40 mL of 1.0 M solution in THF, 0.40 mmol) at -20 °C. The resulting mixture was stirred at 0 °C for 10 min, followed by the addition of 4-(trifluoromethyl)benzoyl chloride (343.8 mg, 1.65 mmol) at -20 °C. The reaction mixture was then stirred at 20 °C for 2 h, followed by the addition of saturated aqueous NH₄Cl solution (4 mL) and 10% aqueous NH₃ solution (2 mL). The resulting mixture was extracted with ethyl acetate (3 \times 6 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 100/1, 70/1) afforded the title compound as a white solid (337.2 mg, 80%): Rf 0.51 (hexane/ EtOAc = 3/1; mp 113.8-114.9 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, J = 2.8 Hz, 5.2 Hz, 1H), 7.60 (dd, J = 1.2 Hz, 5.2 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.92–7.94 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 123.6 (q, ${}^{1}J_{C-F}$ = 271 Hz), 125.4 (q, ${}^{3}J_{C-F}$ = 3.6 Hz), 126.7, 128.3, 129.5, 133.6 (q, ${}^{2}J_{C-F}$ = 32 Hz), 134.6, 140.7, 141.6, 188.7; FTIR (NaCl, CHCl₃) 3103, 1639, 1508, 1420, 1408, 1325, 1277, 1206, 1171, 1153, 1134, 1119, 1109, 1067, 1013, 972, 856, 831, 754 (overlapped with CHCl₃ band), 706, 687; HRMS (ESI) calcd for $C_{12}H_8F_3OS [M + H]^+$ 257.0248, found 257.0253.

(3,5-Bis(trifluoromethyl)phenyl)diphenylphosphine (7). To 3,5-bis(trifluoromethyl)phenylzinc bromide (prepared according to the typical procedure) was added CuCN·2LiCl (0.40 mL of 1.0 M solution in THF, 0.40 mmol) at -20 °C. The resulting mixture was stirred at 0 °C for 10 min, followed by the addition of chlorodiphenylphosphine (355.4 mg, 1.61 mmol) at -20 °C. The reaction mixture was stirred at 20 °C for 2 h, followed by the addition of saturated aqueous

NH₄Cl solution (4 mL) and 10% aqueous NH₃ solution (2 mL). The resulting mixture was extracted with ethyl acetate (3 \times 6 mL). The combined organic phase was washed with brine, dried over Na2SO4, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane) afforded the title compound as a colorless oil (340.8 mg, 53%): Rf 0.47 (hexane/EtOAc = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.36 (m, 4H), 7.39–7.43 (m, 6H), 7.71 (d, ${}^{3}J_{\rm H-P}$ = 6.0 Hz, 2H), 7.83 (s, 1H); 13 C NMR (100 MHz, CDCl₃) δ 122.4 (septet, ${}^{3}J_{C-F}$ = 3.7 Hz), 123.2 (q, ${}^{1}J_{C-F}$ = 271 Hz), 129.0 (d, ${}^{3}J_{C-P} = 7.5$ Hz), 129.7, 131.6 (dq, ${}^{3}J_{C-P} = 5.9$ Hz, ${}^{2}J_{C-F} =$ 33 Hz), 133.0 (dq, ${}^{2}J_{C-P} = 20$ Hz, ${}^{3}J_{C-F} = 3.4$ Hz), 133.8 (d, ${}^{2}J_{C-P} = 20$ Hz), 134.9 (d, ${}^{1}J_{C-P} = 10$ Hz), 142.1 (d, ${}^{1}J_{C-P} = 18$ Hz); ${}^{31}P{}^{1}H$ NMR (162 MHz, CDCl₃): δ –4.6; FTIR (NaCl, neat) 3073, 3057, 1740, 1614, 1477, 1435, 1356, 1279, 1184, 1134, 1105, 1096, 1026, 999, 897, 843, 745, 696, 681, 665; HRMS (ESI) calcd for $C_{20}H_{14}F_6^{31}P [M + H]^+$ 399.0737, found 399.0737.

3-Methoxy-1,1':4',1''-terphenyl (8). To 4-biphenylzinc bromide (prepared according to the typical procedure, 10 h) was added a THF solution of Pd₂(dba)₃/SPhos (0.25 mL, 0.02 M/0.08 M, 0.005 mmol/0.020 mmol) at 20 °C, followed by the addition of 1-iodo-3methoxybenzene (1.41 mL of 1.13 M solution in THF, 372.1 mg, 1.59 mmol). THF (0.34 mL) was added to rinse the walls of the tube. The reaction mixture was stirred for 20 min and then quenched with saturated aqueous NH₄Cl solution (4 mL), followed by extraction with ethyl acetate $(3 \times 5 \text{ mL})$. The combined organic phase was washed with brine, dried over Na2SO4, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 80/1) afforded the title compound as a white solid (394.6 mg, 95%). The same reaction was also performed on a 10 mmol scale in a 100 mL three-necked flask to afford the title compound in 88% yield. The spectral data showed good agreement with the literature data (see the Supporting Information).¹⁷

Ethyl 3'-Cyano(1,1'-biphenyl)-4-carboxylate (9). To 3-cyanophenylzinc iodide (prepared according to the typical procedure, 8 h) was added Pd(PPh₃)₄ (47.0 mg, 0.04 mmol) at 20 °C, followed by the addition of ethyl 4-iodobenzoate (1.34 mL of 1.19 M solution in THF, 439.0 mg, 1.59 mmol). THF (0.8 mL) was added to rinse the walls of the tube. The reaction mixture was stirred for 2 h and quenched with saturated aqueous NH₄Cl solution (4 mL), followed by extraction with ethyl acetate (3×5 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 10/1) afforded the title compound as a white solid (352.3 mg, 88%). The spectral data showed good agreement with the literature data (see the Supporting Information).¹⁸

2-(2-Methoxyphenyl)pyridine (10). To 2-methoxyphenylzinc iodide (prepared according to the typical procedure, 6 h) was added a THF solution of $Pd_2(dba)_3$ /SPhos (0.25 mL, 0.02 M/0.08 M, 0.005 mmol/0.020 mmol) at 20 °C, followed by the addition of 2-bromopyridine (1.33 mL of 1.20 M solution in THF, 252.8 mg, 1.60 mmol). THF (0.42 mL) was added to rinse the walls of the tube. The reaction mixture was stirred for 7 h and quenched with saturated aqueous NH₄Cl solution (4 mL). Saturated aqueous NaHCO₃ solution (4 mL) was added, followed by extraction with ethyl acetate (3 × 8 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 10/1, 8/1) afforded the title compound as a colorless oil (192.3 mg, 65%). The spectral data showed good agreement with the literature data (see the Supporting Information).¹⁹

Ethyl 5-(2,4-Dimethoxyphenyl)pentanoate (11). To 2,4dimethoxyphenylzinc iodide (prepared according to the typical procedure, 7 h) was added Me_3SiCH_2MgCl (0.89 M solution in THF, 2.2 mL, 2.0 mmol) at 0 °C. The resulting mixture was stirred for 2 h, followed by the addition of TMEDA (0.30 mL, 2.0 mmol), ethyl 5-bromovalerate (186.5 mg, 0.89 mmol), and FeCl₃ (0.1 M solution in THF, 0.5 mL, 0.05 mmol). The reaction mixture was warmed to 30 °C, stirred for 6 h, and then quenched with saturated aqueous NH₄Cl solution (5 mL). The resulting mixture was extracted with ethyl acetate (3 \times 5 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 25/1, 20/1, 15/1) afforded the title compound as a colorless oil (220.8 mg, 93%): R_f 0.30 (hexane/EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃) δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.54–1.70 (m, 4H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.55 (t, *J* = 7.4 Hz, 2H), 3.78 (s, 6H), 4.12 (q, J = 7.2 Hz, 2H), 6.41 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 24.7, 29.0, 29.5, 34.2, 55.1, 55.2, 60.0, 98.4, 103.6, 122.9, 129.8, 158.2, 159.0, 173.8; FTIR (NaCl, neat) 2938, 2860, 2835, 1732, 1614, 1587, 1506, 1464, 1439, 1418, 1373, 1288, 260, 1207, 1180, 1155, 1121,1038, 935, 924, 833, 785, 665; HRMS (ESI) calcd for $C_{15}H_{23}O_4 [M + H]^+$ 267.1596, found 267.1593.

3-Cyclohexylquinoline (12). To 3-quinolylzinc bromide (prepared according to the typical procedure, 20 h) was added Me₃SiCH₂MgCl (0.89 M solution in THF, 2.2 mL, 2.0 mmol) at 0 °C. The resulting mixture was stirred for 2 h, followed by the addition of TMEDA (0.30 mL, 2.0 mmol), bromocyclohexane (146.0 mg, 0.90 mmol), and FeCl₃ (0.1 M solution in THF, 0.5 mL, 0.05 mmol). The reaction mixture was warmed to 30 °C, stirred for 6 h, and then quenched with saturated aqueous NH₄Cl solution (5 mL). The resulting mixture was extracted with ethyl acetate (3 \times 5 mL). The combined organic phase was washed with brine, dried over Na2SO4, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 20/1, 15/1, 10/1) afforded the title compound as a colorless oil (172.3 mg, 91%): Rf 0.21 (hexane/ EtOAc = 10/1); ¹H NMR (400 MHz, CDCl₃) δ 1.26–1.37 (m, 1H), 1.41-1.59 (m, 4H), 1.78-1.84 (m, 1H), 1.89-1.93 (m, 2H), 1.98-2.01 (m, 2H), 2.73 (tt, I = 3.3 Hz, 11.5 Hz, 1H), 7.51 (ddd, I = 0.8 Hz, 6.8 Hz, 8.4 Hz, 1H), 7.64 (ddd, J = 1.2 Hz, 6.8 Hz, 8.4 Hz, 1H), 7.77 (dd, J = 0.8 Hz, 8.4 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.82 (d, I = 2.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 25.9, 26.7, 34.1, 42.0, 126.4, 127.4, 128.2, 128.4, 129.0, 132.2, 140.3, 146.8, 151.3; FTIR (NaCl, neat) 3063, 2924, 2851, 1736, 1639, 1570, 1493, 1449, 1371, 1331, 1263, 1238, 1125, 1047, 1018, 974, 881, 860, 787, 752; HRMS (ESI) calcd for $C_{15}H_{18}N [M + H]^+$ 212.1439, found 212.1439.

(3,4-Difluorophenyl)cycloheptane (13). The reaction was performed with a slight modification of the original procedure. To (3,4-difluorophenyl)zinc bromide (prepared according to the typical procedure, 5 h) was added Me₃SiCH₂MgCl (0.92 M solution in THF, 2.2 mL, 2.0 mmol) at 0 °C. The resulting mixture was stirred for 2 h, followed by the addition of 1,2-bis(diphenylphosphino)benzene (DPPBz, 67.0 mg, 0.15 mmol) and bromocycloheptane (189.4 mg, 1.07 mmol) at 0 °C. After 10 min, FeCl₃ (0.25 mL, 0.20 M solution in THF, 0.05 mmol) was added at the same temperature. The reaction mixture was stirred at 60 °C for 5 h. After the mixture was cooled to ambient temperature, aqueous ammonium chloride (saturated, 5.0 mL) was added. The resulting mixture was extracted with Et_2O (3 × 5 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 100/1) afforded the title compound as a colorless oil (169.5 mg, 75%). The spectral data showed good agreement with the literature data (see the Supporting Information).^{3g}

3-(1-(3-Fluorophenyl)vinyl)nonan-2-one (14). The reaction was performed with a slight modification of the original procedure. To a heterogeneous mixture of [RhCl(cod)]₂ (6.4 mg, 0.013 mmol), P⁴Bu₃. HBF₄ (14.6 mg, 0.050 mmol), and KO⁴Bu (5.8 mg, 0.052 mmol) was added a supernatant solution of (3-fluorophenyl)zinc bromide (prepared

according to the typical procedure) (1.0 mL, 0.85 mmol, 0.85 M in THF) under nitrogen. Then, acetonitrile (20.2 mg, 0.492 mmol) and nona-1,2-diene (98.8 mg, 0.795 mmol) were added. The mixture was stirred at 25 °C for 2 h, followed by the addition of saturated aqueous NH₄Cl solution (4 mL). The resulting mixture was extracted with ethyl acetate $(3 \times 5 \text{ mL})$. The combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/ EtOAc = 100/1, 50/1) afforded the title compound as a colorless oil (91.2 mg, 71%): $R_f 0.19$ (hexane/EtOAc = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 0.86 (t, J = 7.0 Hz, 3H), 1.25–1.28 (m, 8H), 1.60–1.65 (m, 1H), 1.88–1.94 (m, 1H), 2.12 (s, 3H), 3.52 (t, J = 7.4 Hz, 1H), 5.21 (s, 1H), 5.49 (s, 1H), 6.97-7.02 (m, 1H), 7.06-7.10 (m, 1H), 7.13-7.16 (m, 1H), 7.27–7.33 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.0, 22.5, 27.6, 28.4, 29.2, 30.8, 31.6, 58.6, 113.4 (d, ${}^{2}J_{C-F}$ = 22.1 Hz), 114.6 (d, ${}^{2}J_{C-F}$ = 21.2 Hz), 116.2, 122.0 (d, ${}^{4}J_{C-F}$ = 2.6 Hz), 130.0 (d, ${}^{3}J_{C-F} = 8.4 \text{ Hz}$, 143.5 (d, ${}^{3}J_{C-F} = 7.3 \text{ Hz}$), 145.9, 162.9 (d, ${}^{1}J_{C-F} = 244.4$ Hz), 208.1; FTIR (NaCl, neat) 3088, 2955, 2928, 2855, 1715, 1611, 1580, 1487, 1435, 1354, 1265, 1196, 1163, 908, 874, 787, 725, 652; HRMS (ESI) calcd for $C_{17}H_{24}FO [M + H]^+$ 263.1811, found 263.1808.

(3-Chlorophenyl)(3,4-difluorophenyl)methanol (15). To 3,4-difluorophenylzinc bromide (prepared according to the typical procedure) was added a THF/toluene solution (8/3, 4.5 mL) of MgCl₂ (0.45 M, 2.0 mmol) at 20 $^\circ\text{C}.$ The resulting mixture was stirred for 2 h, followed by the addition of 3-chlorobenzaldehyde (237.5 mg, 1.69 mmol). The reaction mixture was stirred for 6 h. Then, the reaction mixture was cooled to 0 °C, quenched with saturated aqueous NH₄Cl solution (5 mL), and extracted with ethyl acetate (3 \times 5 mL). The combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (eluent: hexane/EtOAc = 20/1, 15/1, 10/ 1) afforded the title compound as a colorless oil (312.8 mg, 73%): R_f 0.22 $(hexane/EtOAc = 5/1); {}^{1}H NMR (400 MHz, CDCl_3) \delta 2.30 (brs, 1H),$ 5.76 (s, 1H), 7.05-7.24 (m, 4H), 7.26-7.31 (m, 2H), 7.36 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 74.4, 115.4 (d, ²J_{C-F} = 18 Hz), 117.2 (d, ²J_{C-F} = 17 Hz), 122.4 (dd, ⁴J_{C-F} = 3.5 Hz, ³J_{C-F} = 6.4 Hz), 124.5, 126.4, 128.0, 130.0, 134.5, 139.9 (t, ⁴J_{C-F} = ³J_{C-F} = 4.2 Hz), 144.8, 149.7 (dd, ²J_{C-F} = 13 Hz, ¹J_{C-F} = 247 Hz), 150.2 (dd, ²J_{C-F} = 13 Hz), 127.2 (dz, ²J_{C-F} = 13 Hz), 128.2 (dz, ²J_{C-F} = ¹J_{C-F} = 247 Hz); FTIR (NaCl, neat) 3420, 2988, 1707, 1638, 1622, 1612, 1574, 1518, 1474, 1433, 1375, 1279, 1207, 1192, 1113, 1045, 959, 943, 881, 824, 799, 766, 750, 719, 691; HRMS (ESI) calcd for $C_{13}H_9^{35}ClF_2O^{23}Na [M + Na]^+ 277.0208$, found 277.0201.

ASSOCIATED CONTENT

Supporting Information. General experimental information and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author *E-mail: nyoshikai@ntu.edu.sg.

E-mail: nyosnikai@ntu.edu.sg.

ACKNOWLEDGMENT

We thank the National Research Foundation, Singapore (NRF-RF2009-05 to N.Y.) and Nanyang Technological University for generous financial support and Boon-Hong Tan for technical assistance.

REFERENCES

(1) (a) Knochel, P.; Singer, R. D. Chem. Rev. 1993, 93, 2117.
(b) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. In

Handbook of Functionalized Organometallics; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, p 251. (c) Knochel, P.; Calaza, M. I.; Hupe, E. In Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; p 619. (d) Organozinc Reagents; Knochel, P., Jones, P., Eds.; Oxford University Press: New York, 1999. (e) Negishi, E.-i.; Gagneur, S. In Handbook of Organopalladium Chemistry for Organic Synthesis; Negishi, E.-i., Ed.; Wiley: New York, 2002; Vol. 1, p 597.

(2) For examples using Knochel-type reagents (RZnI·LiCl), see: (a) Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. Org. Lett. **2008**, *10*, 2681. (b) Manolikakes, G.; Schade, M. A.; Hernandez, C. M.; Mayr, H.; Knochel, P. Org. Lett. **2008**, *10*, 2765. (c) Gong, H.; Gagné, M. R. J. Am. Chem. Soc. **2008**, *130*, 12177. (d) Murakami, K.; Yorimistu, H.; Oshima, K. Org. Lett. **2009**, *11*, 2373. (e) Han, C.; Buchwald, S. L. J. Am. Chem. Soc. **2009**, *131*, 7532. (f) Yoshida, Y.; Murakami, K.; Yorimitsu, H.; Oshima, K. J. Am. Chem. Soc. **2010**, *132*, 8878. (g) Sumida, Y.; Yorimitsu, H.; Oshima, K. Org. Lett. **2010**, *12*, 2254. (h) Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R. M.; Zipse, H.; Mayer, P.; Knochel, P. Nat. Chem. **2010**, *2*, 125.

(3) For examples using other types of organozinc reagents, see: (a) Zhou, J.; Fu, G. C. J. Am. Chem. Soc. **2003**, *125*, 12527. (b) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. Synlett **2005**, 1794. (c) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. Chem.—Eur. J. **2006**, *12*, 4749. (d) Yeung, C. S.; Dong, V. M. J. Am. Chem. Soc. **2008**, *130*, 7826. (e) Li, B.-J.; Li, Y.-Z.; Lu, X.-Y.; Liu, J.; Guan, B.-T.; Shi, Z.-J. Angew. Chem., Int. Ed. **2008**, *47*, 10124. (f) Smith, S. W.; Fu, G. C. J. Am. Chem. Soc. **2008**, *130*, 12645. (g) Hatakeyama, T.; Kondo, Y.; Fujiwara, Y.; Takaya, H.; Ito, S.; Nakamura, E.; Nakamura, M. Chem. Commun. **2009**, *1216*. (h) Cahiez, G.; Foulgoc, L.; Moyeux, A. Angew. Chem., Int. Ed. **2009**, *48*, 2969. (i) Çalimsiz, S.; Sayah, M.; Mallik, D.; Organ, M. G. Angew. Chem., Int. Ed. **2010**, *49*, 2014.

(4) (a) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. J. Org. Chem. **1991**, 56, 1445. (b) Rieke, R. D. Aldrichim. Acta **2000**, 52, 52. (c) Kim, S. H.; Rieke, R. D. Tetrahedron **2010**, 66, 3135.

(5) (a) Takagi, N.; Hayama, S.; Isokawa Bull. Chem. Soc. Jpn. 1980, 53, 3691. (b) Majid, T. N.; Knochel, P. Tetrahedron Lett. 1990, 31, 4413.
(c) Takagi, K. Chem. Lett. 1993, 469. (d) Takagi, K.; Shimoishi, Y.; Sasaki, K. Chem. Lett. 1994, 2055. (e) Amano, M.; Saiga, A.; Ikegami, R.; Ogata, T.; Takagi, K. Tetrahedron Lett. 1998, 39, 8667.

(6) Zinc insertion in ethereal solvents without any assistance required rather harsh conditions and displayed a narrow substrate scope: Ikegami, R.; Koresawa, A.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2003**, *68*, 2195.

(7) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

(8) (a) Boudet, N.; Sase, S.; Sinha, P.; Liu, C.-Y.; Krasovskiy, A.; Knochel, P. J. Am. Chem. Soc. 2007, 129, 12358. (b) Sase, S.; Jaric, M.; Metzger, A.; Makakhov, V.; Knochel, P. J. Org. Chem. 2008, 73, 7380.
(c) Kobayashi, K.; Kondo, Y. Org. Lett. 2009, 11, 2035. (d) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. Chem.—Eur. J. 2009, 15, 7192. (e) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. Angew. Chem, Int. Ed. 2010, 49, 4665. (f) Schade, M. A.; Manolikakes, G.; Knochel, P. Org. Lett. 2010, 12, 3648.

(9) (a) Gosmini, C.; Rollin, Y.; Nedelec, J.-Y.; Perichon, J. J. Org. Chem. 2000, 65, 6024. (b) Fillon, H.; Gosmini, C.; Perichon, J. J. Am. Chem. Soc. 2003, 125, 3867. (c) Kazmierski, I.; Gosmini, C.; Paris, J.-M.; Perichon, J. Tetrahedron Lett. 2003, 44, 6417. (d) Gosmini, C.; Amatore, M.; Claudel, S.; Perichon, J. Synlett 2005, 2171. (e) Kazmierski, I.; Gosmini, C.; Paris, J.-M.; Périchon, J. Synlett 2006, 881.

(10) Grutters, M. M. P.; Müller, C.; Vogt, D. J. Am. Chem. Soc. 2006, 128, 7414.

(11) Krasovskiy, A.; Knochel, P. Synthesis 2006, 890.

(12) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. J. Org. Chem. 1988, 53, 2390.

(13) The allylation reaction in the absence of CuCN \cdot 2LiCl was very sluggish.

(14) The reaction did not take place in the absence of CuCN, while a similar but uncatalyzed reaction in acetonitrile was reported: Le Gall, E.; Aïssi, K. B.; Lachaise, I.; Troupel, M. *Synlett* **2006**, 954.

(15) Milne, J. E.; Buchwald, S. L. J. Am. Chem. Soc. 2004, 126, 13028.

(16) For a mechanistic study on LiCl-mediated zinc insertion, see: Liu, C.-Y.; Wang, X.; Furuyama, T.; Yasuike, S.; Muranaka, A.; Morokuma, K.; Uchiyama, M. *Chem.—Eur. J.* **2010**, *16*, 1780 and references cited therein.

(17) Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Tetrahedron* **2006**, *62*, 7521.

(18) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. J. Org. Chem. **2008**, 73, 7380.

(19) Ackermann, L.; Potukuchi, H. K.; Kapdi, A. R.; Schulzke, C. *Chem.—Eur. J.* **2010**, *16*, 3300.