DOI: 10.1002/chem.200600206

A User-Friendly, All-Purpose Pd–NHC (NHC = N-Heterocyclic Carbene) Precatalyst for the Negishi Reaction: A Step Towards a Universal Cross-Coupling Catalyst

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Abstract: We have developed the first user-friendly Negishi protocol capable of routinely cross-coupling all combinations of alkyl and aryl centers. The use of an easily synthesized, air stable, highly active, well-defined precatalyst PEPPSI-IPr (**1**; PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr = diisopropylphenylimidazolium derivative) substantially increases the scope, reliability, and ease-of-use of the Negishi reaction. All organohalides and routinely used pseudohalides were excellent coupling partners, with the use of chlorides, bromides, iodides, triflates, tosylates, and mesylates resulting in high yield of the coupled product. Furthermore, all reactions were performed by using general laboratory techniques, with no glovebox necessary as the precatalyst was weighed and stored in air. Utilization of this methodology allowed for the easy synthesis of an assortment of sterically encumbered biaryls and druglike heteroaromatics, demonstrating the value of the PEPPSI-IPr system. Furthermore, this is also the first time Pd–NHC (NHC = N-heterocyclic carbene) methodology has surpassed the related phosphine-ligated Negishi processes both in activity and use.

Keywords: alkanes · biaryls · C–C coupling · heterocycles · palladium

Introduction

Over the last 30 years, the development of transition-metal-catalyzed cross-coupling reactions transformed the way carbon–carbon bonds are created.[1] Within the current arsenal of transition-metal-catalyzed cross-coupling protocols, palladium processes are amongst the most widely employed and include Hiyama,[2] Kumada,[3] Negishi,[4] Suzuki,[5] and Stille[6] reactions. Central to the success of these transformations are palladium metal centers ligated most often with tertiary phosphines or, recently, N-heterocyclic carbenes (NHC).[7] Although yearly improvements to these supporting ligands are made,[8] advanced ligands[8,9] are still underused, mainly due to sensitivity, difficulty-of-use, limited availability, and expense. Indeed, most synthetic chemists still rely on the reasonably versatile $[Pd(PPh_3)_4]$, first synthesized by Malatesta and Angoletta in 1957.[10] Unfortunately, $[Pd(PPh_3)_4]$ is very unstable and has modest reactivity. Recently the groups of Beller,[11] Herrmann,[12] Nolan,[13] and Sigman[14] have made significant progress towards the development NHC-based palladium catalysts or precatalysts; however, their synthesis is still unattractive.[15] Therefore, it became clear to us that the development of an easily prepared single Pd–NHC precatalyst for routine and advanced cross-coupling reactions would be a significant breakthrough.

Working towards this goal, we recently detailed the synthesis of a new Pd–NHC complex (**1**; Figure 1) and demonstrated the complex's superiority to catalysts generated in situ from the corresponding imidazolium salt and a common Pd source ($[Pd_2(dba)_3]$) in alkyl–alkyl cross-coupling reactions.[16] Here, we now report a comprehensive evaluation of complex **1** in the Negishi cross-coupling reaction (Scheme 1). The Negishi reaction[1,4] owes much of it versatility to the excellent functional group tolerance and high reactivity of organozinc reagents.[17] However, for any Negishi cross-coupling protocol to be employed widely it must fulfil two main criteria: 1) the reaction must be conducted easily and require no special handling, for example, use of a glove

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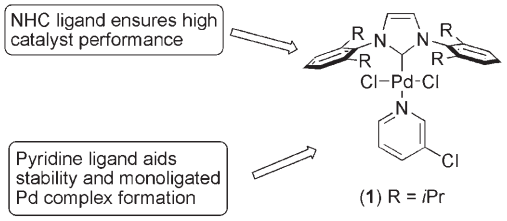
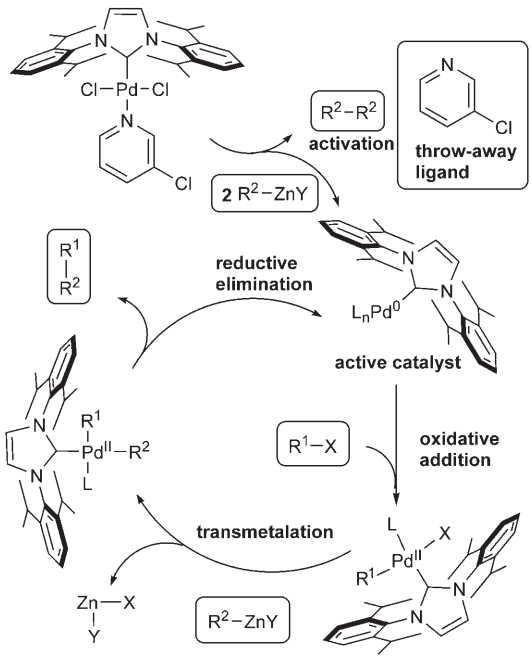


Figure 1. Pyridine-enhanced precatalyst preparation, stabilization and initiation (PEPPSI) precatalyst family. The most active and versatile catalyst, **1** (PEPPSI-IPr), bearing 2,6-diisopropylphenyl substituents at the N atom of the carbene ring is shown.

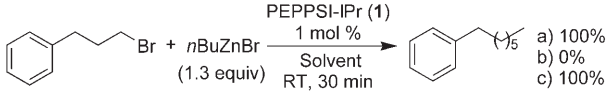


Scheme 1. General, simplified mechanism for Negishi cross-coupling reactions catalyzed by PEPPSI complex **1**.

box; and 2) the protocol must be applicable to a large array of substrates.

Results and Discussion

We previously reported the rapid cross coupling (30 minutes at room temperature) of *n*-butylzinc bromide (*n*BuZnBr) with 1-bromo-3-phenylpropane promoted by **1** (1 mol%; Scheme 2).[16] These studies were performed using *n*BuZnBr

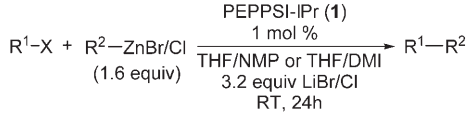


Scheme 2. PEPPSI complex **1** submitted to Negishi cross-coupling reactions: a) THF/NMP, 2:1, *n*BuZnBr prepared from Rieke zinc; b) THF/DMI, 2:1, *n*BuZnBr produced using Hou's protocol; c) THF/DMI, 2:1, *n*BuZnBr produced using Hou's protocol with addition of two equivalents of LiBr.

produced under conditions developed by Rieke et al.[18] However, the use of Rieke zinc to generate organozinc halides can be problematic.[19] Subsequently, Hou disclosed a more convenient route to alkylzinc reagents[20] by heating zinc metal (dust, powder, granule, or shot) and the required bromoalkane in polar aprotic solvents, such as *N*,*N*-dimethylacetamide (DMA), at 80°C.

When we employed *n*BuZnBr, prepared via Hou's protocol, in 1,3-dimethyl-2-imidazolidinone (DMI), complete recovery of the starting alkyl bromide resulted. We reasoned that the lithium halide, formed as a byproduct in the Rieke protocol,[18] was responsible for the activation of the alkylzinc reagent,[21] possibly through formation of a lithium zincate. Indeed, upon addition of two equivalents of LiBr to *n*BuZnBr prepared under Hou's conditions, quantitative conversion to heptylbenzene was achieved (Scheme 2). This information enabled us to couple alkyl chlorides and sulfonates by simply adding LiBr (2 equiv) to the reaction medium. Accordingly, alkyl bromides were successfully coupled in THF/*N*-methylpyrolidinone (NMP) 2:1 or THF/DMI 2:1, whereas alkyl chlorides, mesylates, and tosylates required a solvent ratio of 1:3 in order to achieve high yields. These results invitingly suggest the exciting possibility to selectively couple an alkyl bromide in the presence of an alkyl chloride followed by coupling the chloride in sequential coupling reactions.[22] Intriguingly, alkyl tosylates and mesylates were coupled in high yield (Table 1, entries 4, 5, 15, and 16),

Table 1. Evaluation of PEPPSI complex **1** in the Negishi reaction.

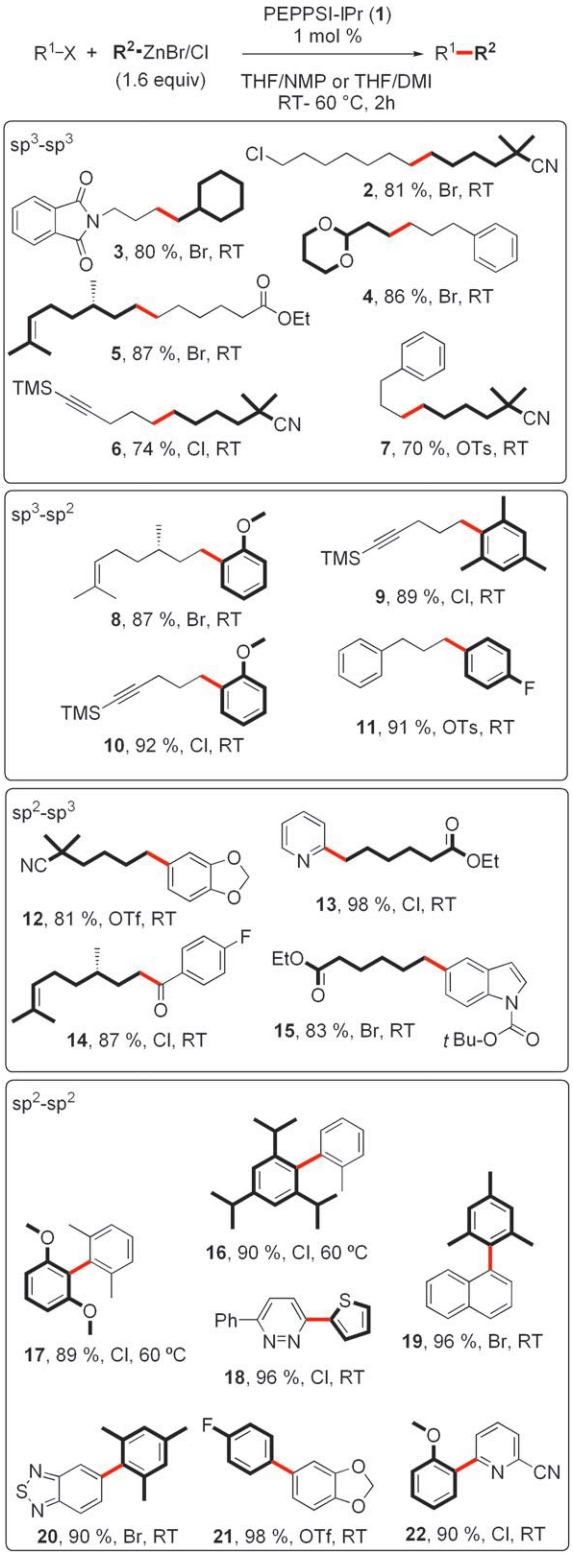


Entry	R^1	X	R^2	Yield [%][a]
1	$Ph(CH_2)_3$	Cl	*n*Bu[c]	88
2	$Ph(CH_2)_3$	Br	*n*Bu[b,g]	100
3	$Ph(CH_2)_3$	I	*n*Bu[c]	68
4	$Ph(CH_2)_3$	OTs	*n*Bu[c]	100
5	$Ph(CH_2)_3$	OMs	*n*Bu[c]	100
6	Ph	Cl	*n*-heptyl[d]	100
7	Ph	Br	*n*-heptyl[b]	100
8	Ph	I	*n*-heptyl[d]	95
9	Ph	OTf	*n*-heptyl[d]	100
10	Ph	OMs	*n*-heptyl[d]	0
11	Ph	OTs	*n*-heptyl[d]	0
12	*n*-heptyl	Cl	Ph[f]	70
13	*n*-heptyl	Br	Ph[e]	100
14	*n*-heptyl	I	Ph[f]	100
15	*n*-heptyl	OTs	Ph[f]	90
16	*n*-heptyl	OMs	Ph[f]	87
17	*p*-tolyl	Cl	p-$MeOC_6H_4$[e]	80
18	*p*-tolyl	Br	p-$MeOC_6H_4$[e]	88
19	*p*-tolyl	I	p-$MeOC_6H_4$[e]	73
20	*p*-tolyl	OTf	p-$MeOC_6H_4$[e]	71
21	*p*-tolyl	OMs	p-$MeOC_6H_4$[e]	0
22	*p*-tolyl	OTs	p-$MeOC_6H_4$[e]	0

[a] GC yield against calibrated internal standard (undecane) performed in duplicate. [b] THF/DMI, 2:1. [c] THF/DMI, 1:3. [d] THF/DMI, 1:2. [e] THF/NMP, 2:1, no LiCl/Br. [f] THF/NMP, 1:2, no LiCl/Br. [g] Yielded 63% after 24 h with a catalyst loading of 0.1 mol%.

in contrast to the corresponding aryl analogues (Table 1, entries 10, 11, 21, and 22). This differing reactivity is unlikely to be due to a more facile oxidative addition in the case of the alkyl tosylate with respect to the aryl tosylate. Rather, an alkyl halide is formed in situ.[23] In contrast, the coupling of aryl zinc reagents with aromatic halides and pseudohalides did not require any additive (Table 1, entries 17–22). Arylhalides and triflates also participated in cross-coupling with alkylzinc reagents in excellent yields (Table 1, entries 6–9). As a whole, the results presented in Table 1 demonstrate that the pyridine-enhanced precatalyst preparation, stabilization and initiation (PEPPSI) complex **1** (PEPPSI-IPr; IPr = diisopropylphenylimidazolium derivative) is able to catalyze the cross-coupling of organochlorides, -bromides, and -iodides; aryl triflates; and alkyl tosylates and mesylates in all possible pairings in high yield at room temperature (Table 1, entries 1–3, 6–8, 12–14, and 17–19). To the best of our knowledge, this is the broadest substrate range ever achieved with a single catalytic protocol.

Encouraged by the results in Table 1, we examined additional substrates to evaluate the functional group and steric tolerance, such as might be seen in the synthesis of materials or biologically active systems. We were delighted to find that functionalization of the reactants did not diminish the generality of this protocol, with sp^3(RX)–sp^3(RZnX), sp^3–sp^2, sp^2–sp^3, and sp^2–sp^2 cross-coupling reactions (Scheme 3) easily accomplished with 1 mol% of PEPPSI-IPr (**1**). Coupling of a range of alkyl bromides, chlorides, and tosylates was achieved at room temperature (Scheme 3, compounds **2**–**7**). Remarkably, by careful choice of reaction conditions it was possible to selectively couple a bromide in the presence of a chloride (Scheme 3, compound **2**). An array of functionality was tolerated including esters, nitriles, amides, and acetals (Scheme 3, **2**–**5**). Noteworthy examples are the coupling of (*S*)-citronellyl bromide in high yield (Scheme 3, compound **8**) and the stability of the TMS group in the reaction conditions (Scheme 3, compounds **6**, **9**, and **10**). The coupling of alkylzinc reagents with aryl halides or aryl triflates occurred in high yield with no transmetalation to the arylzinc observed (Scheme 3, compounds **12**–**15**). Aryl halides, as expected, provided excellent coupling partners. Accordingly, the facile synthesis of a range of druglike heteroaromatics and sterically congested biaryls was accomplished in high yield (Scheme 3, compounds **16**–**22**). A significant entry is the coupling of *o*-chlorotoluene and 2,4,6-triisopropylphenylzinc chloride at 60 °C—the lowest temperature this has been accomplished with any protocol[8] (Scheme 3, compound **16**). *N*-Boc-protected indole (Boc = *tert*-butyloxycarbonyl), pyridine, and multiple heteroatom-containing heterocycles were well tolerated (Scheme 3, compounds **12**, **13**, **15**, **18**, **20**–**22**) Finally, the cross-coupling of a chiral zinc reagent with an acyl chloride (Scheme 3, compound **14**) proceeded without concomitant decarbonylation, demonstrating the mildness of this protocol.



Scheme 3. Complex substrate evaluation: all yields are of isolated product and reactions were performed in duplicate. See the Experimental Section for detailed reaction conditions.

Conclusion

We have developed the first user-friendly Negishi protocol capable of routinely cross-coupling all combinations of alkyl and aryl partners. The use of an easily synthesized, air stable, highly active, well-defined precatalyst **1** substantially increases the scope, reliability and ease-of-use of the Negishi reaction. Additionally, all reactions were performed by using general laboratory techniques, with no glove-box necessary as the precatalyst was weighed and stored in air. This methodology also allowed for the easy synthesis of sterically encumbered biaryls and druglike heteroaromatics, demonstrating the usefulness of the PEPPSI-IPr system. Furthermore, this is also the first time Pd–NHC methodology has surpassed the related phosphine-ligated Negishi processes both in activity and use.[8] The benefits of this protocol as summarized above beckon wide adoption of the PEPPSI-IPr precatalyst in research laboratories and chemical industries.

Experimental Section

General: All reagents were purchased from commercial sources and were used without further purification, unless indicated otherwise. Dry 1-methyl-2-pyrrolidinone (NMP) and 1,3-dimethyl-2-imidazolidinone (DMI) were purchased from Fluka, stored over 4 Å molecular sieves, and handled under argon. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. All reaction vials (screw-cap threaded, caps attached, 17×60 mm) were purchased from Fischer Scientific. $CDCl_3$ was purchased from Cambridge Isotopes. Thin-layer chromatography (TLC) was performed on Whattman 60 F_{254} glass plates and were visualized by using UV light (254 nm), potassium permanganate, or phosphomolybdic acid stains. Column chromatography purification was carried out by using the flash technique on Silicycle silica gel 60 (230–400 mesh). NMR spectra were recorded on a Bruker 400 AV spectrometer or a Bruker 300 AV spectrometer, as indicated. The chemical shifts (δ) for ^{1}H are given in ppm referenced to the residual proton signal of the deuterated solvent. The chemical shifts (δ) for ^{13}C are referenced relative to the signal from the carbon of the deuterated solvent. Gas chromatography was performed on Varian Series GC/MS/MS 4000 System. Optical rotations were measured on a Perkin–Elmer Model 241 polarimeter by using 10 cm cells and the sodium D line at ambient temperature in the solvent specified (concentration c is given as g per 100 mL).

Synthesis of the PEPPSI-IPr complex (1)—medium-scale synthesis: In air a 250 mL beaker was charged with $PdCl_2$ (9.82 g, 55.4 mmol), IPr·HCl (24.5 g, 57.6 mmol), Cs_2CO_3 (98.2 g, 300 mmol) and a stirrer bar. 3-Chloropyridine (150 mL) was added; the beaker was covered with aluminum foil (to prevent solvent evaporation) and heated with vigorous stirring for 16 h at 80 °C directly on the stirrer hotplate. After cooling to RT, the reaction mixture was diluted with CH_2Cl_2 and passed through a short pad of silica gel covered with a pad of Celite eluting with CH_2Cl_2 until the product was completely recovered. Most of the CH_2Cl_2 was removed (rotary evaporator) at RT, and the 3-chloropyridine was recovered for reuse by vacuum distillation (water aspirator vacuum). Complex **1** was isolated after triturating with pentane, decanting the supernatant, and drying in high vacuum. *trans*-Dichloro(1,3-bis-(2,6-diisopropylphenyl)imidazolylidinium)(3-chloro-pyridine)palladium(II) (**1**; 35 g, 93 %) was obtained as a yellow solid after triturating with pentane, decanting the supernatant, and drying under high vacuum. M.p. 240 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, J = 1.6 Hz, 1H), 8.54 (d, J = 5.6 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.37 (d, J = 7.7 Hz, 4H), 7.16 (s, 2H), 7.09 (dd, J = 8.0 Hz, 5.7 Hz, 1H), 3.18 (m, 4H), 1.50 (d, J = 6.7 Hz, 12H), 1.14 ppm (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 150.5, 149.4, 146.7, 137.4, 135.0, 132.0, 130.3, 125.1, 124.3, 124.1, 28.7, 26.3, 23.2 ppm; elemental analysis calcd (%) for $C_{32}H_{40}Cl_3N_3Pd$: C 56.57, H 5.93, N 6.18; found: C 56.90, H 5.99, N 6.52.

Cross-coupling procedures (Scheme 3): All cross-coupling reactions were run with a final solvent volume of 2.4 mL. The specific solvent ratio for each reaction is listed within the experimental results for each compound following the general procedures.

General procedure A (sp^3–sp^3): In air, a vial was charged with **1** (3.4 mg, 1 mol %) and under an inert atmosphere LiBr (139.0 mg, 0.8 mmol) and a stirrer bar were added. The vial was then sealed with a septum and purged with argon after which THF (x mL) and DMI (x mL) or NMP (x mL) were added and the suspension was stirred until the solids dissolved. After this time, the organozinc (0.8 mL, 1.0 M in DMI or NMP, 0.8 mmol) and the organohalide or pseudohalide (0.5 mmol) were added. The septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred for 2 h. After this time, the mixture was diluted with diethyl ether (15 mL) and washed successively with Na_3EDTA solution [1 M; prepared from EDTA (ethylenediaminetetraacetic acid) and 3 equiv of NaOH], water, and brine. After drying (anhydrous $MgSO_4$) the solution was filtered, the solvent removed in vacuo, and the residue purified by flash chromatography.

General procedure B (sp^3–sp^2): In air, a vial was charged with **1** (3.4 mg, 1 mol %) and under an inert atmosphere $ZnCl_2$ (107 mg, 0.8 mmol) and a stirrer bar were added. The vial was then sealed with a septum and purged with argon. THF (x mL) was added followed by the requisite Grignard reagent (0.8 mL, 1.0 M in THF, 0.8 mmol) and stirring continued for 15 minutes at which time a white precipitate formed. Under an inert atmosphere, LiBr (139.0 mg, 1.6 mmol), NMP (x mL) or DMI (x mL) and the organohalide or pseudohalide (0.5 mmol) were added. The septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred for 2 h. After this time, the mixture was diluted with diethyl ether (15 mL) and washed successively with Na_3EDTA solution (1 M prepared from EDTA and 3 equiv of NaOH), water, and brine. After drying (anhydrous $MgSO_4$) the solution was filtered, the solvent removed in vacuo, and the residue purified by flash chromatography.

General procedure C (sp^2–sp^3): In air, a vial was charged with **1** (3.4 mg, 1 mol %) and under an inert atmosphere LiBr (139.0 mg, 1.6 mmol) and a stirrer bar were added. The vial was then sealed with a septum and purged with argon. THF (x mL) and DMI (x mL), or NMP (x mL) were then added and the suspension stirred until the solids had dissolved. After this time, the organozinc (0.8 mL, 1.0 M in DMI or NMP, 0.8 mmol) and the organohalide or pseudo halide (0.5 mmol) were added. The septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred for 2 h. After this time, the mixture was diluted with diethyl ether (15 mL) and washed successively with Na_3EDTA solution (1 M; prepared from EDTA and 3 equiv of NaOH), water, and brine. After drying (anhydrous $MgSO_4$), the solution was filtered, the solvent removed in vacuo, and the residue purified by flash chromatography.

General procedure D (sp^2–sp^2): In air, a vial was charged with **1** (3.4 mg, 1 mol %) and under an inert atmosphere $ZnCl_2$ (0.8 mmol) and a stirrer bar were added. The vial was then sealed with a septum and purged with argon. THF (x mL) was then added followed by the requisite Grignard reagent (0.8 mL, 1.0 M in THF, 0.8 mmol) and stirring continued for 15 minutes, at which time a white precipitate formed. NMP (x mL) was then added followed by the organohalide or pseudo halide (0.5 mmol). The septum was replaced with a Teflon®-lined screw cap under an inert atmosphere and the reaction stirred for 2 h. After this time, the reaction mixture was diluted with diethyl ether (15 mL) and washed successively with Na_3EDTA solution (1 M; prepared from EDTA and 3 equiv of NaOH), water, and brine. After drying (anhydrous $MgSO_4$) the solution was filtered, the solvent removed in vacuo, and the residue purified by flash chromatography.

*Data for compound **2***: Following general procedure A (THF/DMI, 2:1), 13-chloro-2,2-dimethyltridecanenitrile (104 mg, 81 % yield) was isolated (R_f = 0.18, 3 vol % diethyl ether in pentane) as a clear oil. The ^{1}H and ^{13}C NMR spectra were identical to those previously described.[8d]

Data for compound ***3***: Following general procedure A (THF/DMI, 2:1), 2-(5-cyclohexylpentyl)isoindole-1,3-dione (115 mg, 80% yield) was isolated (R_f=0.40, 20 vol% diethyl ether in pentane) as a white solid (m.p. 74–75°C). The alkylzinc bromide reagent was purchased from Aldrich. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.86–7.80 (m, 2H), 7.75–7.67 (m, 2H), 3.68 (t, J=7.2 Hz, 2H), 1.80–1.65 (m, 7H), 1.36–1.27 (m, 4H), 1.25–1.10 (m, 6H), 0.97–0.85 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.4, 133.8, 132.2, 123.1, 38.0, 37.5, 37.3, 33.3, 28.6, 27.1, 26.7, 26.4 ppm; elemental analysis calcd (%) for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, N 4.68; found: C 76.49, H 8.42, N 5.08.

Data for compound ***4***: Following general procedure A (THF/NMP, 2:1), 2-(5-phenylpentyl)[1,3]dioxane (107 mg, 86% yield) was isolated (R_f= 0.20, 5 vol% diethyl ether in pentane) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.29 (t, J=7.2 Hz, 2H), 7.19 (d, J=7.3 Hz, 3H), 4.52 (t, J= 4.8 Hz, 1H), 4.12 (dd, J=11.7, 4.8 Hz, 2H), 3.76 (dt, J=12.6, 2.4 Hz, 2H), 2.63 (t, J=7.5 Hz, 2H), 2.17–2.00 (m, 1H), 1.74–1.55 (m, 4H), 1.50–1.28 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=142.7, 128.4, 128.2, 125.5, 102.3, 66.9, 35.8, 35.1, 31.3, 29.1, 25.8, 23.8 ppm; elemental analysis calcd (%) for $C_{15}H_{22}O_2$: C 76.88, H 9.46; found: C 76.57, H 9.85.

Data for compound ***5***: Following general procedure A (THF/DMI, 2:1), (9*S*,13)-dimethyltetradec-12-enoic acid ethyl ester (123 mg, 87% yield) was isolated (R_f=0.60, 5 vol% diethyl ether in pentane) as a clear viscous oil. $[\alpha]_D^{23}$=+0.84 (c=2.5 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.11 (t, J=6.0 Hz, 1H), 4.13 (q, J=7.1 Hz, 2H), 2.30 (t, J=7.4 Hz, 2H), 2.05–1.90 (m, 2H), 1.75–1.58 (m, 8H), 1.45–1.20 (m, 14H), 1.20–1.05 (m, 2H), 0.86 ppm (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.9, 130.9, 125.0, 60.1, 37.1, 36.9, 34.4, 32.4, 29.8, 29.3, 29.1, 26.9, 25.7, 25.5, 25.0, 19.5, 17.6, 14.2 ppm; elemental analysis calcd (%) for $C_{18}H_{34}O_2$: C 76.54, H 12.13; found: C 76.08, H 12.48.

Data for compound ***6***: Following general procedure A (THF/NMP, 1:2), 2,2-dimethyl-1-trimethylsilanylundec-10-ynenitrile (97 mg, 74% yield) was isolated (R_f=0.50, 5 vol% diethyl ether in pentane) as a clear oil after removing volatile impurities under reduced pressure for 12 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.22 (t, J=7.2 Hz, 2H), 1.60–1.45 (m, 6H), 1.45–1.30 (m, 12H), 0.15 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 125.2, 107.5, 84.3, 41.1, 32.3, 29.4, 28.8, 28.6, 28.5, 26.7, 25.2, 19.8, 0.1 ppm; elemental analysis calcd (%) for $C_{16}H_{29}NSi$: C 72.93, H 11.09; found: C 72.58, H 11.42.

Data for compound ***7***: Following general procedure A (THF/NMP, 1:2), 2,2-dimethyl-9-phenylnonanenitrile (85 mg, 70% yield) was isolated (R_f= 0.50, 5 vol% diethyl ether in pentane) as a clear oil after removing volatile impurities under reduced pressure for 12 h. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.29 (t, J=6.8 Hz 2H), 7.21 (d, J=6.4 Hz, 3H), 2.64 (t, J= 7.6 Hz, 2H), 1.70–1.60 (m, 2H), 1.58–1.45 (m, 4H), 1.40–1.30 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): ?142.8, 128.4, 128.3, 125.6, 125.3, 41.1, 35.9, 32.4, 31.5, 29.5, 29.3, 29.2, 26.7, 25.3 ppm. ^{1}H and ^{13}C NMR spectra have been provided in the Supporting Information to attest purity.

Data for compound ***8***: Following general procedure B (THF/NMP, 2:1), of 1-[(3*S*,7)-dimethyloct-6-enyl]-2-methoxybenzene (107 mg, 87% yield) was isolated (R_f=0.40, 5 vol% diethyl ether in pentane) as a clear viscous oil. $[\alpha]_D^{23}$=+8.55 (c=2.29 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.25–7.15 (m, 2H), 6.93 (t, J=7.6 Hz, 1H), 6.88 (d, J=8.1 Hz, 1H), 5.17 (t, J=6.9 Hz, 1H), 3.87 (s, 3H), 2.72–2.58 (m, 2H), 2.11–1.97 (m, 2H), 1.74 (s, 3H), 1.65–1.40 (m, 7H), 1.30–1.17 (m, 1H), 1.00 ppm (d, J= 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.4, 131.6, 131.0, 129.7, 126.7, 125.1, 120.4, 110.2, 55.3, 37.1, 37.0, 32.5, 27.7, 25.8, 25.5, 19.6, 17.7 ppm; elemental analysis calcd (%) for $C_{17}H_{26}O$: C 82.87, H 10.64; found: C 83.02, H 10.92.

Data for compound ***9***: Following general procedure B (THF/NMP, 1:2), trimethyl-[5-(2,4,6-trimethylphenyl)pent-1-ynyl]silane (115 mg, 89% yield) was isolated (R_f=0.80, pentane) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.88 (s, 2H), 2.80–2.72 (m, 2H), 2.39 (t, J=6.8 Hz, 2H), 2.30 (s, 6H), 2.26 (s, 3H), 1.75–1.66 (m, 2H), 0.22 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.1, 135.6, 135.1, 128.9, 107.3, 85.0, 28.5, 28.1, 20.8, 20.3, 19.7, 0.2 ppm. elemental analysis calcd (%) for $C_{17}H_{26}Si$: C 79.00, H 10.14; found: C 78.69, H 10.42.

Data for compound ***10***: Following general procedure B (THF/NMP, 1:2), [5-(2-methoxyphenyl)pent-1-ynyl]trimethylsilane (113 mg, 92% yield) was isolated (R_f=0.30, 5 vol% diethyl ether in pentane) as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23–7.15 (m, 2H), 6.96–6.85 (m, 2H), 3.84 (s, 3H), 2.74 (t, J=7.5 Hz, 2H), 2.27 (t, J=7.4 Hz, 2H), 1.84 (quint, J=7.7 Hz, 2H), 0.19 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.5, 130.1, 130.0, 127.2, 120.3, 110.2, 107.7, 84.6, 55.2, 29.4, 28.8, 19.6, 0.2 ppm. ^{1}H and ^{13}C NMR spectra have been provided in the Supporting Information to attest purity.

Data for compound ***11***: Following general procedure B (THF/NMP, 1:2), 3-phenyl-1-(4-fluorophenyl)propane (97 mg, 91% yield) was isolated (R_f=0.40, pentane) as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.31 (t, J=8.0 Hz, 2H), 7.22 (t, J=8.0 Hz, 3H), 7.18–7.12 (m, 2H), 6.99 (t, J=8.4 Hz, 2H), 2.66 (q, J=7.6 Hz, 4H), 1.96 ppm (quint, J= 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.2 (^1J(C,F)=242 Hz), 142.1, 137.8 (^4J(C,F)=2 Hz), 129.8 (^3J(C,F)=8 Hz), 128.4, 128.3, 125.8, 115.0 (^2J(C,F)=21 Hz), 35.3, 34.6, 33.1 ppm; ^{1}H and ^{13}C NMR spectra have been provided in the Supporting Information to attest purity.

Data for compound ***12***: Following general procedure C (THF/DMI, 2:1), 6-benzo[1,3]dioxol-5-yl-2,2-dimethylhexanenitrile (99 mg, 81% yield) was isolated (R_f=0.25, 25 vol% diethyl ether in pentane) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.74 (d, J=8.0 Hz, 1H), 6.69 (s, 1H), 6.63 (d, J=8.0 Hz, 1H), 5.94 (s, 2H), 2.58 (t, J=7.6 Hz, 2H), 1.67–1.59 (m, 2H), 1.57–1.50 (m, 4H), 1.35 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=147.5, 145.6, 136.0, 125.2, 121.0, 108.7, 108.1, 100.7, 40.9, 35.4, 32.4, 31.7, 26.7, 24.8 ppm; ^{1}H and ^{13}C NMR spectra have been provided in the Supporting Information to attest purity.

Data for compound ***13***: Following general procedure C (THF/DMI, 2:1), 6-pyridine-2-yl-hexanoic acid ethyl ester (108 mg, 98% yield) was isolated (R_f=0.10, 30 vol% diethyl ether in pentane) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.50 (dd, J=4.2, 0.6 Hz, 1H), 7.56 (dt, J=7.2, 1.8 Hz, 1H), 7.14–7.03 (m, 2H), 4.10 (q, J=7.2 Hz, 2H), 2.77 (t, J= 7.5 Hz, 2H), 2.28 (t, J=7.5 Hz, 2H), 1.82–1.60 (m, 4H), 1.48–1.30 (m, 2H), 1.21 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 173.7, 162.1, 149.2, 136.2, 122.7, 120.9, 60.1, 38.2, 34.2, 29.5, 28.8, 24.8, 14.2 ppm. elemental analysis calcd (%) for $C_{13}H_{19}NO_2$: C 70.56, H 8.65; found: C 70.67, H 8.95.

Data for compound ***14***: Following general procedure C (THF/DMI, 2:1), 1-(4-fluorophenyl)-(4*S*,8)-dimethylnon-7-en-1-one (114 mg, 87% yield) was isolated (R_f=0.40, 3 vol% diethyl ether in pentane) as a clear viscous oil. $[\alpha]_D^{23}$=+1.07 (c=1.68 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.01 (m, 2H), 7.14 (t, J=8.6 Hz, 2H), 5.11 (t, J=5.9 Hz, 1H), 3.00–2.87 (m, 2H), 2.07–1.95 (m, 2H), 1.90–1.65 (m, 4H), 1.60–1.48 (m, 5H), 1.47–1.30 (m, 1H), 1.25–1.13 (m, 1H), 0.95 ppm (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=199.1, 167.2 (^1J(C,F)=337 Hz), 133.4, 131.3, 130.7 (^3J(C,F)=12.2 Hz), 124.6, 115.5 (^2J(C,F)=27.8 Hz), 36.8, 36.2, 32.2, 31.3, 25.7, 25.5, 19.4, 17.6 ppm. elemental analysis calcd (%) for $C_{17}H_{23}FO$: C 77.82, H 8.84; found: C 78.07, H 9.05.

Data for compound ***15***: Following general procedure C (THF/DMI, 2:1), 6-(*N*-boc-indol-5-yl)hexanoic acid ethyl ester (149 mg, 83% yield) was isolated (R_f=0.15, 3 vol% diethyl ether in pentane) as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (d, J=8.1 Hz, 1H), 7.60 (d, J= 3.4 Hz, 1H), 7.38 (s, 1H), 7.16 (d, J=8.5 Hz, 1H), 6.54 (d, J=3.4 Hz, 1H), 4.15 (q, J=7.2 Hz, 2H), 2.73 (t, J=7.5 Hz, 2H), 2.32 (t, J=7.5 Hz, 2H), 1.75–1.65 (m, 13H), 1.44–1.35 (m, 2H), 1.28 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.8, 149.8, 136.9, 133.6, 130.8, 125.9, 125.0, 120.3, 114.9, 107.2, 83.4, 60.2, 35.6, 34.3, 31.6, 28.7, 28.2, 24.9, 14.3 ppm; elemental analysis calcd (%) for $C_{21}H_{29}NO_4$: C 70.17, H 8.13; found: C 70.49, H 8.39.

Data for compound ***16***: This reaction was carried out at 60°C. Following general procedure D (THF/NMP, 1:1), 2,4,6-triisopropyl-2′-methylbiphenyl (133 mg, 90% yield) was isolated (R_f=0.50, hexanes) as a white solid (m.p. 94–95°C). The melting point, ^{1}H and ^{13}C NMR spectra were identical to those previously described.[24]

Data for compound ***17***: The organozinc reagent was prepared through directed ortholithiation followed by transmetalation to $ZnCl_2$ following a literature procedure.[8f] The cross coupling was carried out at 60°C. Following general procedure D (THF/NMP, 1:2), of 2,6-dimethoxy-2′,6′-di-

methylbiphenyl (108 mg, 89% yield) was isolated (R_f = 0.15, 3 vol% diethyl ether in pentane) as a white solid (m.p. 104–105 °C) after removing volatile impurities under reduced pressure for 12 h. The melting point, ^{1}H and ^{13}C NMR spectra were identical to those previously described.[24]

Data for compound ***18***: Following general procedure D (THF/NMP, 1:1), 3-phenyl-6-thiophen-2-ylpyridazine (114 mg, 96% yield) was isolated (R_f = 0.48, 33 vol% ethyl acetate in hexanes) as pale yellow crystals (m.p. 161–162 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (dd, J = 3.9, 1.5 Hz, 2H), 7.87 (q, J = 4.8 Hz, 2H), 7.76–7.70 (m, 1H), 7.58–7.47 (m, 4H), 7.24–7.15 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 153.5, 140.7, 136.0, 130.0, 129.2, 129.0, 128.1, 126.7, 126.1, 124.0, 122.6 ppm. Spectral data is provided as it is more detailed with respect to the literature values.[25]

Data for compound ***19***: Following general procedure D (THF/NMP, 1:1), 1-mesitylnaphthalene (118 mg, 96% yield) was isolated (R_f = 0.65, pentane) as a colorless, viscous oil. The ^{1}H and ^{13}C NMR spectra were identical to those previously described.[26]

Data for compound ***20***: Following general procedure D (THF/NMP, 2:1), 5-(2,4,6-trimethylphenyl)benzo[1,2,5]thiadiazole (114 mg, 90% yield) was isolated (R_f = 0.26, 2 vol% diethyl ether in pentane) as yellow crystals (m.p. 54–55 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, J = 9.0 Hz, 1H), 7.81 (s, 1H), 7.42 (dd, J = 4.5, 1.5 Hz, 1H), 7.02 (s, 2H), 2.39 (s, 3H), 2.08 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 154.0, 142.8, 137.5, 137.3, 135.7, 132.4, 128.4, 121.2, 21.1, 20.8 ppm (one carbon signal missing); elemental analysis calcd (%) for $C_{15}H_{14}N_2S$: C 70.83, H 5.55, N 11.01; found: C 70.61, H 5.92, N 11.06.

Data for compound ***21***: Following general procedure D (THF/NMP, 2:1), 5-(4-fluorophenyl)benzo[1,3]dioxole (106 mg, 98% yield) was isolated (R_f = 0.60, 5 vol% diethyl ether in pentane) as a white solid (m.p. 42–43 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 2H), 7.13 (t, J = 9.2 Hz 2H), 7.01 (d, J = 9.2 Hz, 2H), 6.90 (d, J = 8.0 Hz, 1H), 6.03 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2 (^1J(C,F) = 245 Hz), 148.2, 147.1, 137.1, 134.6, 128.4, 120.5, 115.6 (^2J(C,F) = 21 Hz), 108.6, 107.6, 101.2 ppm. ^{1}H and ^{13}C NMR spectra have been provided in the Supporting Information to attest purity.

Data for compound ***22***: Following general procedure D (THF/NMP, 1:2), 2-cyano-6-(2-methoxyphenyl)pyridine (95 mg, 90% yield) was isolated (R_f = 0.30, 50 vol% diethyl ether in pentane) as white crystals (m.p. 109–110 °C). The melting point, ^{1}H and ^{13}C NMR spectra were identical to those previously described.[27]

Acknowledgement

We wish to thank the ORDCF (Ontario) and NSERC (Canada) for financial support.

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[16] a) Preceeding paper in this issue: C. J. O'Brien, E. A. B. Kantchev, N. Hadei, C. Valente, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743; b) detailed in the above paper are comparisons between the in situ protocol (see ref. [8d]) and the preformed precatalyst **1** (PEPPSI-IPr, see ref. [16a]). These studies showed that the reaction depicted in Scheme 2 yielded 75% after 6 h when employing the in situ protocol (at 4 mol% loading), which compared to 93% in 15 minutes with precatalyst **1** (PEPPSI-IPr, at 1 mol% loading). Furthermore, the apparent turnover number (TON) h^{-1} for the in situ process (4 mol% loading) was 7.5, whereas it was 300 when utilizing **1** (PEPPSI-IPr at 0.1 mol% loading). These results clearly demonstrate the superiority of the preformed precatalyst **1** over in situ methodology.
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Received: February 14, 2006
Published online: March 28, 2006

