The Cobalt-Catalyzed Cross-Coupling Reaction of Alkyl Halides with Alkyl Grignard Reagents: A New Route to Constructing Quaternary Carbon Centers

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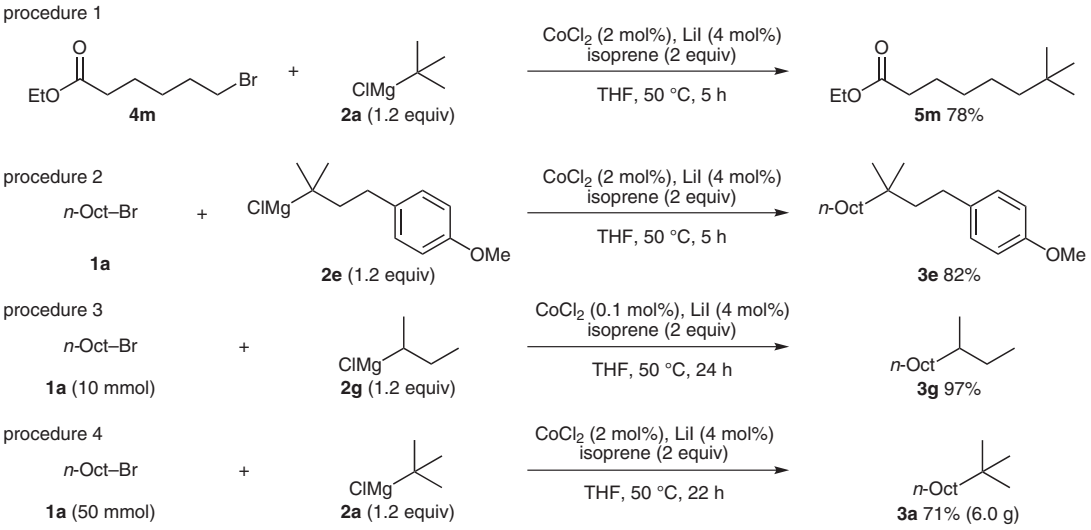
Abstract: The cross-coupling of alkyl (pseudo)halides with alkyl Grignard reagents is catalyzed efficiently by a cobalt(II) chloride–lithium iodide–1,3-diene catalytic system, which provides a new synthetic tool for constructing sp^3 carbon chains. This system is particularly useful for creating quaternary carbon centers via the use of tertiary alkyl Grignard reagents. Various functional groups including esters, amides and carbamates are well tolerated.

Key words: cobalt, cross-coupling, Grignard reagents, alkyl halides, quaternary carbon



Scheme 1 General procedures for the cobalt-catalyzed cross-coupling reaction of alkyl halides with alkyl Grignard reagents (Procedures 1 and 2), a reaction using 0.1 mol% of catalyst (Procedure 3) and a large-scale reaction (Procedure 4)

Introduction

Transition-metal-catalyzed alkyl–alkyl coupling reactions represent one of the simplest and most practical techniques for the construction of saturated hydrocarbon frameworks.[1] The use of tertiary alkylmetal reagents in cross-coupling would permit quaternary carbon centers to be produced, however, such attempts have often proved unsuccessful due to the facile β-hydrogen elimination and/or isomerization of tertiary alkylmetal intermediates resulting in the production of a mixture of coupling products.[2] Therefore, only a unique combination of copper catalysts and a *tert*-butylmagnesium halide (*t*-BuMgX) reagent have been reported as successful examples of alkyl–alkyl cross-coupling reactions in which tertiary alkyl Grignard reagents are employed.[3] During the course our studies on transition-metal-catalyzed cross-couplings using unsaturated hydrocarbon additives,[3d,e,4] we found that cobalt salts, with the aid of lithium iodide (LiI) and conjugated diene additives such as 1,3-butadiene or isoprene, catalyze successfully cross-coupling reactions of alkyl (pseudo)halides with tertiary alkyl Grignard reagents giving rise to the formation of quaternary carbon centers, where esters, amides, carbamates and acetal functional groups were well tolerated.[5–7] It was also possible to couple primary and secondary alkyl Grignard reagents with alkyl halides using this catalyst system. The reactions

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took place exclusively at the primary alkyl C–Br bonds, even in the presence of C–Cl, secondary alkyl C–Br and aromatic C–Br bonds. The reaction proceeded efficiently using only 0.1 mol% of cobalt(II) chloride ($CoCl_2$) and could be easily scaled up to afford the expected product on gram-scale. Herein, we report on the details of the procedures employed in these cobalt-catalyzed alkyl–alkyl cross-coupling reactions (Scheme 1).[5]

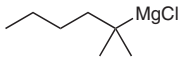
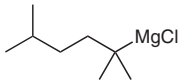
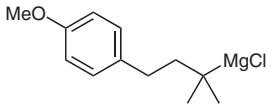
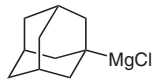
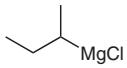
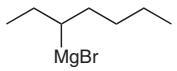
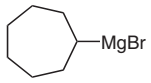
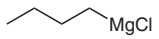
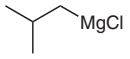
Scope and Limitations

n-Octyl bromide (*n*-OctBr) (**1a**) reacted with *tert*-butylmagnesium chloride (*t*-BuMgCl), within five hours in tetrahydrofuran at 50 °C in the presence of cobalt(II) chloride (2 mol%), lithium iodide (4 mol%) and 1,3-butadiene (2 equiv), to give the desired coupling product in 84% yield. The possible isomerized coupling product, *n*-Oct–*i*-Bu, was not observed on GC analysis, and only trace amounts of octane and octenes (1% or less) were formed (Table 1, entry 1). The presence of lithium iodide and a 1,3-diene were essential for achieving an efficient coupling reaction. When lithium chloride (LiCl), lithium bromide (LiBr), sodium iodide (NaI), potassium iodide (KI) or magnesium iodide (MgI_2) were used instead of lithium iodide, the expected product was obtained, but in lower yields (27%, 31%, 70%, 73% and 60%, respectively). Interestingly, the combined use of cobalt(II) iodide (CoI_2) and lithium chloride gave the cross-coupling product in 76% yield, being comparable to that found in the case of Table 1, entry 1, employing cobalt(II) chloride and lithium iodide. The use of isoprene as the 1,3-diene improved the yield to 92% (Table 1, entry 2).

Cross-couplings using various Grignard reagents were performed under the optimized conditions with isoprene as the additive (Table 1, entry 2), and the results are summarized in Table 1. Acyclic tertiary alkyl Grignard reagents participated in the cross-coupling reaction, giving good to excellent yields (Table 1, entries 3–6); however, the desired product was not obtained when the adamantyl Grignard reagent was used (Table 1, entry 7). Primary and secondary alkyl Grignard reagents also proved to be suitable coupling partners. For example, both acyclic and cyclic secondary alkyl Grignard reagents underwent coupling with *n*-octyl bromide to furnish branched carbon skeletons (Table 1, entries 8–10). No evidence for isomerization of the alkyl groups of the alkyl Grignard reagents was detected in any of the cases examined. Primary alkyl Grignard reagents gave the corresponding coupling products in good yields (Table 1, entries 11 and 12), but methylmagnesium chloride (MeMgCl) and phenylmagnesium bromide (PhMgBr) reacted sluggishly, due to difficulties in generating the active catalytic species (Table 1, entries 13 and 14).[5] The relative reactivity of *n*-, *sec*- and *tert*-butyl Grignard reagents was estimated to be roughly 1:4:0.6, by competitive experiments.

Due to the labile nature of the alkylmetal complexes arising mainly from β-hydrogen elimination, relatively larger quantities of catalysts (a few mol% loading or higher) are often required to achieve an efficient alkyl–alkyl coupling reaction. We examined the efficiency of the present catalyst system and a high turnover number (TON) of 970 could be achieved with a catalyst loading of only 0.1 mol% (Scheme 2). For example, when the reaction of **1a** with **2g** was carried out on a 10 mmol scale with cobalt(II) chloride (0.01 mmol) in the presence of lithium iodide (0.4 mmol) and isoprene (20 mmol), the coupling reaction proceeded smoothly, with a 68% yield of **3g** being observed after six hours; the reaction reached completion within 24 hours to give **3g** in 97% GC yield.

Table 1 Cross-Coupling of *n*-Octyl Bromide (**1a**) with Grignard Reagents[a,b]

Entry	Grignard reagent		Product	Yield (%)[c]
1[d]	**2a**		**3a**	84
2				92
3[e]	**2b**		**3b**	91
4[e]	**2c**		**3c**	85 (82)
5[e]	**2d**		**3d**	81 (80)
6	**2e**		**3e**	82 (80)
7	**2f**		**3f**	<1
8	**2g**		**3g**	93
9	**2h**		**3h**	89 (83)
10[e]	**2i**		**3i**	90 (86)
11	**2j**		**3j**	92
12[f]	**2k**		**3k**	77
13	**2l**	MeMgCl	**3l**	4
14	**2m**	PhMgBr	**3m**	<1

[a] Reprinted (adapted) with permission from *J. Am. Chem. Soc.* **2013**, *135*, 9604. Copyright 2013 American Chemical Society.
[b] Reaction conditions: $CoCl_2$ (2 mol%), LiI (4 mol%), isoprene (2 equiv), THF, 50 °C, 5 h.
[c] Yields were determined by GC. Yields of isolated products are in parentheses.
[d] 1,3-Butadiene was used instead of isoprene.
[e] *n*-DecBr (**1b**) was used instead of *n*-OctBr.
[f] Reaction time was 20 h.

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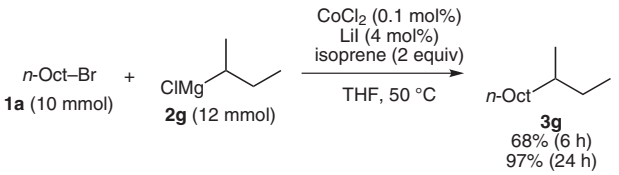


Scheme 2 Coupling reaction using 0.1 mol% of the cobalt catalyst

The scope and limitations of the alkyl (pseudo)halides are summarized in Table 2. An alkyl fluoride underwent coupling with *tert*-butylmagnesium chloride to afford a moderate 62% yield of the expected product (Table 2, entry 1). The reaction of an alkyl chloride was sluggish and only 2% of the coupling product was obtained (Table 2, entry 2). However, an alkyl iodide and alkyl tosylate were found to be suitable alkyl electrophiles (Table 2, entries 3 and 4). Alkenes, alkynes, trifluoromethyl, *tert*-butylsilyl ethers and acetal functionalities were well tolerated (Table 2, entries 6–10). An alkyl bromide having a hydroxy group could be employed as the coupling partner by way of in situ deprotonation with an excess of the Grignard reagent (Table 2, entry 11). Although carbonyl groups are potentially labile toward Grignard reagents, the fact that amides, carbamates and ester functional groups remained intact demonstrates the usefulness of the present catalytic system (Table 2, entries 12–19).

Table 2 Cobalt-Catalyzed Cross-Coupling Reactions[a]

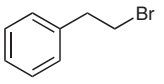
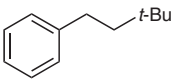
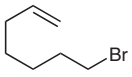
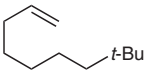
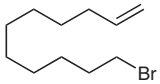
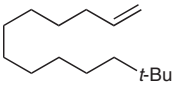
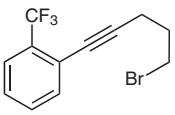
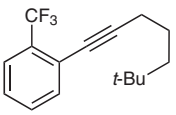
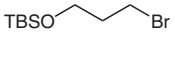
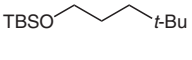
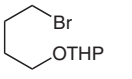
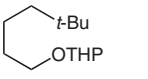
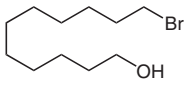
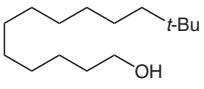
Entry	Alkyl halide		Product		Yield (%)[b]
1[c]	**1c**	*n*-Oct–F	**3a**	*n*-Oct–*t*-Bu	62
2	**1d**	*n*-Oct–Cl	**3a**	*n*-Oct–*t*-Bu	2
3	**1e**	*n*-Oct–I	**3a**	*n*-Oct–*t*-Bu	71
4	**1f**	*n*-Oct–OTs	**3a**	*n*-Oct–*t*-Bu	58
5	**4a**		**5a**		95
6	**4b**		**5b**		86
7	**4c**		**5c**		88 (86)
8	**4d**		**5d**		84 (80)
9	**4e**		**5e**		80 (76)
10	**4f**		**5f**		95 (91)
11[d]	**4g**		**5g**		>99 (88)

Table 2 Cobalt-Catalyzed Cross-Coupling Reactions[a] (continued)

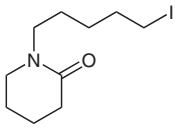
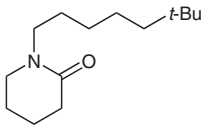
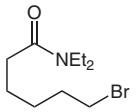
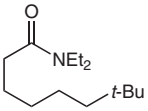
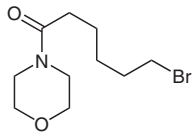
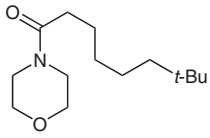
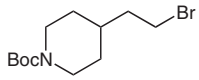
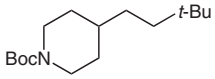
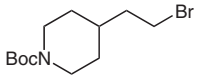
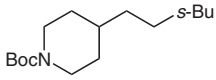
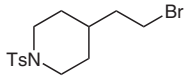
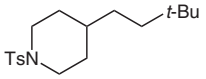
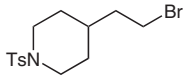
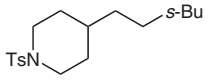
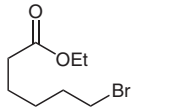
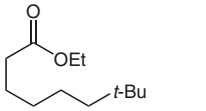
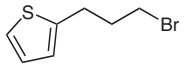
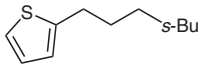
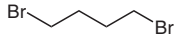
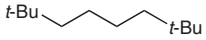
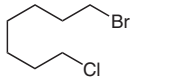
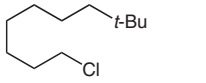
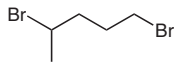
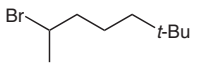
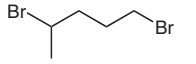
Entry	Alkyl halide		Product		Yield (%)[b]
12	**4h**		**5h**		69 (67)
13	**4i**		**5i**		79 (73)
14	**4j**		**5j**		81 (76)
15	**4k**		**5ka**		61 (60)
16	**4k**		**5kg**		76 (74)
17	**4l**		**5la**		58 (55)
18	**4l**		**5lg**		79 (74)
19	**4m**		**5m**		78 (72)
20	**4n**		**5n**		80 (78)
21[d]	**4o**		**5o**		75
22	**4p**		**5p**		92 (88)
23[e]	**4q**		**5qa**		74 (71)
24[e]	**4q**		**5qg**		86
25	**4r**		**5rg**		71
26	**4r**		**5rj**		94
27	**4s**		**5sa**		81[f] (78)
28	**4s**		**5sg**		88[f] (85)

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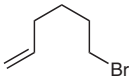
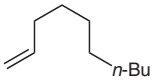
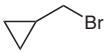
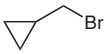
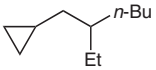
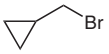
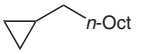
Table 2 Cobalt-Catalyzed Cross-Coupling Reactions[a] (continued)

Entry	Alkyl halide	Product	Yield (%)[b]
29	**4s** 	**5sj** 	89[f]
30	**4t** 	**5td** 	50[g] (49)
31	**4t** 	**5th** 	68[g] (66)
32	**4t** 	**5tn** 	71[g]

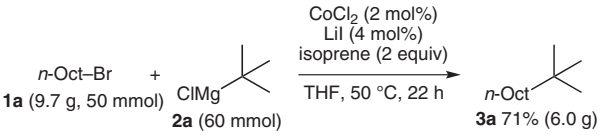
[a] Reprinted (adapted) with permission from *J. Am. Chem. Soc.* **2013**, *135*, 9604. Copyright 2013 American Chemical Society.
[b] Yield was determined by GC. Yields of isolated products are in parentheses.
[c] Reaction time was 24 h.
[d] Excess (2.5 equiv) of the Grignard reagent was used.
[e] Reaction time was 12 h.
[f] Only less than 1% of cyclized coupling product was formed.
[g] Ring-opened coupling product was formed in 2%, <1% and 3% yields for entries 30, 31 and 32, respectively.

An alkyl bromide carrying a thiophene ring underwent the cross-coupling with *sec*-butylmagnesium chloride (*s*-BuMgCl) to give the corresponding product in good yield (Table 2, entry 20), but unfortunately, the similar reaction with *tert*-butylmagnesium chloride resulted in the formation of a complex mixture, probably due to deprotonation of the acidic α-proton of the thiophene ring. 1,4-Dibromobutane (**4o**) underwent cross-coupling at both terminal carbons to install two quaternary carbon centers (Table 2, entry 21). When dihalogenated substrates having different carbon–halogen bonds were employed using the present catalytic system, the coupling reaction was chemoselective, taking place at the primary alkyl bromide moiety and not at primary alkyl chloride, secondary alkyl bromide and aromatic C–Br moieties (Table 2, entries 22–26).

The reactions of 6-bromohex-1-ene (**4s**) with primary, secondary and tertiary alkyl Grignard reagents afforded the corresponding terminal olefins in 81–89% yields as the sole coupling products (Table 2, entries 27–29), suggesting that the free 6-hexenyl radical, which readily undergoes 5-*exo* radical cyclization, was not generated in this catalytic system. In addition, direct cross-coupling products were obtained from (bromomethyl)cyclopropane (**4t**), in moderate yields, without any detectable ring-opened products (Table 2, entries 30–32). These results indicate that no radical intermediates are generated from alkyl halides in the present catalytic system. This is in sharp contrast with previously reported cobalt-catalyzed systems.[6,7]

Unfortunately, no coupling products were produced in the case of secondary alkyl electrophiles. For example, less than 20% yields of the coupled products were obtained, even when highly reactive secondary alkyl bromides possessing a phenyl or alkynyl substituent (benzyl and propargyl bromides) were employed.

The applicability of the present cobalt catalyst system to a large-scale production was demonstrated by the gram-scale (50 mmol) synthesis of **3a** (Scheme 3). The reaction of *n*-octyl bromide (9.7 g, 50 mmol) with *tert*-butylmagnesium chloride (60 mmol) in a modified procedure (see procedure 4 for details) was complete within 22 hours, and the resulting mixture was purified by distillation to give analytically pure product **3a** in 71% yield (6.0 g).



Scheme 3 Gram-scale synthesis of **3a**

Conclusion

In summary, an efficient catalytic system for the cross-coupling of alkyl halides with alkyl Grignard reagents using cobalt(II) chloride along with lithium iodide and 1,3-dienes has been developed. Various polar functional groups as well as 5-hexenyl and cyclopropylmethyl skeletons, which easily undergo radical rearrangement, were well tolerated using the described system. Tertiary alkyl Grignard reagents underwent efficient coupling with alkyl halides to create quaternary carbon centers. The catalyst loading could be reduced to 0.1 mol% without any loss of yield and the reaction could be performed on large scale (50 mmol). The present cross-coupling reaction does not require toxic and expensive phosphine ligands, amines or noble metals.

Experimental Procedures

All reactions were performed under a nitrogen atmosphere using standard Schlenk techniques. Anhydrous THF was purchased from the Kanto Chemical Company and purified by SPS[8] prior to use. THF solutions of *t*-Bu (**2a**), *s*-Bu (**2g**), *n*-Bu (**2j**), *i*-Bu (**2k**), Me (**2l**), Ph (**2m**), and *n*-Oct (**2n**) Grignard reagents were purchased from the Kanto Chemical Company, Aldrich or TCI, and used after titration. Other Grignard reagents were prepared by a standard procedure and were used after titration. All catalytic reactions were performed with highly pure $CoCl_2$ (Aldrich, 99.999% purity) and LiI (Aldrich, 99.999% purity) to avoid contamination by other metals as impurities. 1-(2-Trifluoromethylphenyl)-5-bromopent-1-yne (**4d**) was prepared by the reaction of the corresponding lithiated terminal alkyne with 1,3-dibromopropane. Tetrahydropyranyl (THP) and *tert*-butyldimethylsilyl (TBS) ethers were prepared by standard protection procedures.[9] *N*-(5-iodopentyl)piperidine-2-one (**4h**) was synthesized by coupling piperidine-2-one with diiodopentane under basic conditions (KOH) in THF. Amides **4i** and **4j** were prepared from 6-bromohexanoyl bromide and the corresponding amines. *tert*-Butoxycarbonyl (Boc) or tosyl (Ts)-protected bromoethylpiperidines **4k** and **4l** were synthesized via a protection and bromination sequence from hydroxyethylpiperidine. Thiophene derivative **4n** was synthesized by deprotonation of thiophene with *n*-BuLi and subsequent trapping with 1,3-dibromopropane. All other commercially available reagents were used as received unless otherwise stated. Yields were determined by GC using decane as an internal standard. Yields in parentheses refer to analytically pure isolated

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compounds for which the obtained masses are provided in the analytical data sections. Flash column chromatography was carried out using silica gel (60 mesh spherical) purchased from Kanto Chemical Company. GC was performed on a Shimadzu GC-2014 instrument equipped with a GL Sciences InertCap 5 capillary column (I.D. = 0.25 mm, length = 30 m, df = 0.25 μm) to determine the GC yield. Gel permeation chromatography (GPC) was accomplished using a Japan Analytical Industry Co. Ltd., Model LC-908 instrument equipped with JAIGEL-1 and -2 columns with $CHCl_3$ as the eluent. Melting points were determined on a Stanford Research Systems OptiMelt MPA 100 with a glass capillary. IR spectra were obtained using a JASCO Corporation FT/IR-4200 instrument equipped with ATR PRO450-S. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded at 20 °C on a JEOL JNM-Alice 400. Chemical shifts are given in ppm and spin-spin coupling constants, *J*, are given in Hz. Mass spectra were acquired on a JEOL JMS-700 Mstation spectrometer. HRMS was performed using the same spectrometer.

Coupling of Alkyl Halides with *t*-BuMgCl; Procedure 1 (P1)

An alkyl halide (1.0 mmol), decane (63 mg as an internal standard) and LiI (5.3 mg, 0.04 mmol) were added to a dry, nitrogen-flushed test tube equipped with a rubber septum and a magnetic stir bar. THF (0.8 mL) was added and the solution was cooled to –78 °C using a dry ice/EtOH bath. *t*-BuMgCl (**2a**) (1.5 mL, 0.81 M in THF, 1.2 mmol) was added slowly followed by isoprene (136.2 mg, 2.0 mmol). To this mixture was added $CoCl_2$ [2.6 mg, 0.02 mmol, as a powder or as a THF solution (0.5 mL, 0.04 M)]. (**Note 1**: $CoCl_2$ should be added after isoprene, otherwise the catalytic performance decreases significantly). The cold bath was removed and the mixture was warmed to r.t. (ca. over 10 min), and then heated for 5 h by suspending the reaction vessel in an oil bath kept at 50 °C. (**Note 2**: when the reaction mixture was heated at 30 °C during this stage, unidentified side reactions occurred resulting in low yields of coupling products). The resulting mixture was cooled to 0 °C in an ice bath and the reaction was quenched with aq HCl (5 mL, 1 M). The product was extracted with Et_2O (3 × 20 mL). The combined organic layer dried over Na_2SO_4, concentrated and analyzed by gas chromatography to determine the GC yield. The residue was purified by silica gel column chromatography or by GPC.

Coupling of *n*-OctBr with Alkyl Grignard Reagents; Procedure 2 (P2)

n-OctBr (**1a**) (193 mg, 1.0 mmol), decane (63 mg as an internal standard) and LiI (5.3 mg, 0.04 mmol) were added to a dry, nitrogen-flushed test tube equipped with a rubber septum and a magnetic stir bar. THF (0.8 mL) was added and the solution was cooled to –78 °C using a dry ice/EtOH bath. The appropriate Grignard reagent (in THF, 1.2 mmol) was added slowly followed by the addition of isoprene (136.2 mg, 2.0 mmol). To this mixture was added $CoCl_2$ [2.6 mg, 0.02 mmol, as powder or as a THF solution (0.5 mL, 0.04 M)] (see **Note 1** above). The process was continued and the reaction mixture was worked up following procedure 1 (P1) as described above.

Coupling of *n*-OctBr with *s*-BuMgCl Using 0.1 mol% of $CoCl_2$; Procedure 3 (P3)

In a glove box, LiI (53.5 mg, 0.4 mmol) was added to a 100 mL test tube equipped with a rubber septum and a magnetic stir bar. The test tube was removed from the glove box and THF (1.0 mL), *n*-OctBr (**1a**) (1.94 g, 10.0 mmol) and decane (0.35 g as an internal standard) were added. The solution was cooled to –78 °C using a dry ice/EtOH bath. *s*-BuMgCl (**2g**) (18.5 mL, 0.65 M in THF, 12.0 mmol) was added slowly followed by isoprene (2.0 mL, 20.0 mmol) and $CoCl_2$ (powdered, 1.3 mg, 0.01 mmol) (see **Note 1** above). The cold bath was removed and the mixture was stirred, warmed to r.t. (ca. over 10 min), and then heated at 50 °C by suspending in a preheated oil bath (see **Note 2** above). The progress of the reaction was monitored by GC. The product yield reached 68% and 97% after 6 h and 24 h, respectively.

Large-Scale Coupling of *n*-OctBr with *t*-BuMgCl; Procedure 4 (P4)

To a dry, nitrogen-flushed 300 mL three-necked flask, equipped with a rubber septum and a magnetic stir bar, were added LiI (268 mg, 2 mmol), pentadecane (0.8 g as an internal standard) and THF (40 mL) via a syringe and the solution was cooled to –78 °C using a dry ice/EtOH bath. *t*-BuMgCl (**2a**) (58.0 mL, 1.03 M in THF, 60 mmol), isoprene (6.8 g, 100.0 mmol) and $CoCl_2$ (25 mL, 0.04 M in THF, 1 mmol) were added (see **Note 1** above). The cold bath was removed and the reaction mixture was stirred and warmed to r.t. (ca. over 30 min), and then suspended in an oil bath and heated to 50 °C. After reaching 50 °C, *n*-OctBr (**1a**) (9.66 g, 50 mmol) was added. (**Note**: when *n*-OctBr was added at the beginning, as in P1–3, the yield of the desired coupling product dropped to ca. 50% due to the formation of unidentified side products, which may have been produced during the course of heating to 50 °C. The addition of alkyl halides after the formation of the active catalytic species was found to be effective in preventing side reactions in large-scale reactions, see also **Note 2** above). The reaction progress was monitored by GC, which, after stirring for 22 h at 50 °C, indicated that the *n*-OctBr had been consumed. The mixture was cooled to 0 °C in an ice bath and carefully quenched with aq HCl (1 M) to give a clear bilayer solution. The product was extracted with Et_2O (3 × 100 mL), and the combined organic layer dried over Na_2SO_4, concentrated and purified by distillation (bp 87 °C at 2.1 kPa) to give 2,2-dimethyldecane (**3a**) as a colorless liquid (5.99 g, 71%).

2,2-Dimethyldecane (3a)

According to P1, *n*-OctBr (**1a**) (193 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. See also P4 for a large-scale synthesis.

Yield: 94% (determined by GC using decane as an internal standard).

IR (Zn/Se-ATR, neat): 2951, 2924, 2855, 1465, 1364, 954, 890, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 9 H), 0.88 (t, *J* = 6.4 Hz, 3 H), 1.16 (br s, 2 H), 1.27 (br s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 24.6, 29.38, 29.42, 29.7, 30.3, 30.7, 31.9, 44.3.

3,3-Dimethyltridecane (3b)

According to P2, *n*-DecBr (**1b**) (221 mg, 1.0 mmol) and 2-methyl-2-butylmagnesium chloride (**2b**) (0.60 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 91% (determined by GC using decane as an internal standard).

5,5-Dimethylpentadecane (3c)

According to P2, *n*-DecBr (**1b**) (221 mg, 1.0 mmol) and 2-methyl-2-hexylmagnesium chloride (**2c**) (0.65 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 173 mg (82%); colorless oil.

IR (Zn/Se-ATR, neat): 2956, 2925, 2855, 1469, 949 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.74 (s, 6 H), 0.81 (t, *J* = 6.9 Hz, 3 H), 0.82 (t, *J* = 7.4 Hz, 3 H), 1.08–1.19 (br m, 24 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.2, 22.7, 23.7, 24.0, 26.3, 27.3, 29.4, 29.68, 29.74, 29.76, 30.7, 31.9, 32.5, 41.8, 42.0.

MS (EI): *m*/*z* (%) = 240 (57) $[M]^+$, 225 (11), 183 (14), 168 (7), 141 (8).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{36}$: 240.2817; found: 240.2816.

2,5,5-Trimethylpentadecane (3d)

According to P2, *n*-DecBr (**1b**) (221 mg, 1.0 mmol) and 2,5-dimethyl-2-hexylmagnesium chloride (**2d**) (0.65 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, pu-

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rification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 181 mg (80%); pale yellow oil.

IR (Zn/Se-ATR, neat): 2955, 2925, 2854, 1469, 948 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.73–0.83 (br m, 15 H), 0.98–1.19 (br m, 22 H), 1.36 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 22.8, 24.0, 27.3, 28.8, 29.4, 29.67, 29.73, 29.8, 30.9, 31.9, 32.4, 33.1, 39.5, 41.9.

MS (CI): *m*/*z* (%) = 253 (51) $[M – H]^+$, 238 (15), 197 (18), 183 (31), 169 (9), 155 (8), 141 (6).

HRMS (CI): *m*/*z* $[M – H]^+$ calcd for $C_{18}H_{37}$: 253.2895; found: 253.2893.

1-(3,3-Dimethylundecyl)-4-methoxybenzene (3e)
According to P2, *n*-OctBr (**1a**) (193 mg, 1.0 mmol) and 4-(4-methoxyphenyl)-2-methyl-2-butylmagnesium chloride (**2e**) (0.70 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 232 mg (80%); colorless oil.

IR (Zn/Se-ATR, neat): 2954, 2926, 2855, 1512, 1467, 1247, 1177, 1041, 822 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H), 0.90 (s, 6 H), 1.20–1.35 (br m, 14 H), 1.44 (t, *J* = 8.7 Hz, 2 H), 2.47 (t, *J* = 8.7 Hz, 2 H), 3.78 (s, 3 H), 6.82 (d, *J* = 8.2 Hz, 2 H), 7.09 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 24.0, 27.3, 29.4, 29.7, 29.8, 30.6, 31.9, 32.8, 41.9, 44.5, 55.2, 113.7, 129.1, 135.7, 157.5.

MS (EI): *m*/*z* (%) = 290 (32) $[M]^+$, 275 (20), 261 (8), 249 (7), 233 (13), 219 (6).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{34}O$: 290.2609; found: 290.2608.

3-Methylundecane (3g)
According to P2, *n*-OctBr (**1a**) (193 mg, 1.0 mmol) and *s*-BuMgCl (**2g**) (0.76 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 93% (determined by GC using decane as an internal standard).

See also P3 for the reaction using 0.1 mol% of $CoCl_2$. Yields were determined by GC analysis (using decane as an internal standard) to be 68% and 97% after 6 h and 24 h, respectively.

5-Ethyltridecane (3h)
According to P2, *n*-OctBr (**1a**) (193 mg, 1.0 mmol) and 3-heptylmagnesium bromide (**2h**) (1.0 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 177 mg (83%); colorless oil.

IR (Zn/Se-ATR, neat): 2958, 2924, 2856, 1467, 953 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.81–0.91 (br m, 9 H), 1.16–1.34 (br d, 23 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9, 14.1, 14.2, 22.7, 23.2, 25.9, 26.7, 29.0, 29.4, 29.7, 30.2, 31.9, 32.9, 33.2, 38.8.

MS (EI): *m*/*z* (%) = 212 (46) $[M]^+$, 197 (11), 185 (26), 147 (15), 133 (9).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{32}$: 212.2504; found: 212.2499.

Decylcycloheptane (3i)
According to P2, *n*-DecBr (**1b**) (221 mg, 1.0 mmol) and cycloheptylmagnesium bromide (**2i**) (1.0 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 205 mg (86%); colorless oil.

IR (Zn/Se-ATR, neat): 2922, 2852, 1461, 952, 762 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 6.4 Hz, 3 H), 1.02–1.61 (br m, 31 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 26.6, 27.5, 28.6, 29.4, 29.67, 29.71, 29.8, 30.0, 31.9, 34.7, 38.3, 39.3.

MS (EI): *m*/*z* (%) = 290 (49) $[M]^+$, 275 (18), 261 (7), 233 (11), 219 (5).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{34}$: 238.2660; found: 238.2660.

Dodecane (3j)
According to P2, *n*-OctBr (**1a**) (193 mg, 1.0 mmol) and *n*-BuMgCl (**2j**) (1.0 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 92% (determined by GC using decane as an internal standard).

2-Methylundecane (3k)
According to P2, *n*-OctBr (**1a**) (193 mg, 1.0 mmol) and *i*-BuMgCl (**2k**) (1.9 M in THF, 1.2 mmol) were reacted under standard conditions for 20 h.

Yield: 77% (determined by GC using decane as an internal standard).

(3,3-Dimethylbutyl)benzene (5a)
According to P1, (2-bromoethyl)benzene (**4a**) (185 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 95% (determined by GC using decane as an internal standard).

8,8-Dimethylnon-1-ene (5b)
According to P1, 7-bromohept-1-ene (**4b**) (177 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 86% (determined by GC using decane as an internal standard).

12,12-Dimethyltridec-1-ene (5c)
According to P1, 11-bromoundec-1-ene (**4c**) (233 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 181 mg (86%); colorless oil.

IR (Zn/Se-ATR, neat): 2926, 2855, 1468, 1364, 990, 909 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 9 H), 1.14–1.39 (br m, 16 H), 2.04 (m, 2 H), 4.93 (d, *J* = 10.5 Hz, 1 H), 4.99 (d, *J* = 17.4 Hz, 1 H), 5.81 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 29.0, 29.2, 29.4, 29.5, 29.6, 29.7, 30.3, 30.6, 33.8, 44.3, 114.1, 139.3.

MS (EI): *m*/*z* (%) = 210 (18) $[M]^+$, 195 (16), 180 (13), 153 (53), 139 (15).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{30}$: 210.2348; found: 210.2345.

1-(6,6-Dimethylhept-1-yn-1-yl)-2-(trifluoromethyl)benzene (5d)
According to P1, 1-(2-trifluoromethylphenyl)-5-bromopent-1-yne (**4d**) (291 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 215 mg (80%); orange oil.

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IR (Zn/Se-ATR, neat): 2954, 1491, 1451, 1318, 1160, 1138, 1113, 1063, 1034, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (s, 9 H), 1.35 (m, 2 H), 1.58 (m, 2 H), 2.42 (t, *J* = 6.9 Hz, 2 H), 7.34 (t, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.3 Hz, 1 H), 7.52 (d, *J* = 7.3 Hz, 1 H), 7.61 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 23.7, 29.3, 30.2, 43.3, 76.7, 96.8, 122.3, 125.0, 125.6, 127.1, 131.2, 131.3, 133.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.4.

MS (EI): *m*/*z* (%) = 268 (27) $[M]^+$, 253 (21), 211 (46), 202 (10), 197 (8), 187 (21).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{19}F_3$: 268.1439; found: 268.1437.

1-[(*tert*-Butyldimethylsilyl)oxy]-4,4-dimethylpentane (5e)
According to P1, 1-bromo-3-[(*tert*-butyldimethylsilyl)oxy]propane (**4e**) (253 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 174 mg (76%); yellow oil.

IR (Zn/Se-ATR, neat): 2953, 2893, 2858, 1471, 1253, 1100, 1006, 940, 834, 814, 773 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 6 H), 0.92 (s, 9 H), 0.94 (s, 9 H), 1.21 (m, 2 H), 1.53 (m, 2 H), 3.62 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.2, 18.4, 26.0, 28.2, 29.4, 30.0, 39.9, 64.2.

MS (EI): *m*/*z* (%) = 230 (11) $[M]^+$, 215 (42), 200 (36), 185 (35), 173 (84), 170 (19), 158 (9), 116 (21).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{30}OSi$: 230.2066; found: 230.2066.

2-[(5,5-Dimethylhexyl)oxy]tetrahydro-2*H*-pyran (5f)
According to P1, 2-(4-bromobutoxy)tetrahydro-2*H*-pyran (**4f**) (237 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 196 mg (91%); colorless oil.

IR (Zn/Se-ATR, neat): 2941, 2868, 1475, 1137, 1120, 1078, 1036, 988, 906, 870, 816 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 9 H), 1.17–1.23 (m, 2 H), 1.27–1.37 (m, 2 H), 1.49–1.62 (m, 5 H), 1.67–1.77 (m, 1 H), 1.79–1.87 (m, 1 H), 3.39 (dd, *J* = 16.5, 6.8 Hz, 1 H), 3.47–3.54 (m, 1 H), 3.75 (dd, *J* = 16.5, 6.8 Hz, 1 H), 3.84–3.93 (m, 1 H), 4.58 (t, *J* = 7.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 21.2, 25.5, 29.4, 30.3, 30.6, 30.8, 44.0, 62.3, 67.7, 98.8.

MS (CI): *m*/*z* (%) = 215 (21) $[M + H]^+$, 200 (15), 158 (71), 144 (10), 130 (6).

HRMS (CI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{27}O_2$: 215.2011; found: 215.2015.

12,12-Dimethyltridecan-1-ol (5g)
According to P1, 11-bromoundecan-1-ol (**4g**) (251 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (1.04 M in THF, 2.5 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane then Et_2O) afforded the title compound.

Yield: 201 mg (88%); colorless oil.

IR (Zn/Se-ATR, neat): 3400, 2925, 2854, 1466, 1363, 1056 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 9 H), 1.14–1.31 (m, 18 H), 1.57 (quin, *J* = 7.2 Hz, 2 H), 3.64 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 25.7, 29.4, 29.6, 29.7, 30.2, 30.6, 32.7, 44.2, 63.0.

MS (CI): *m*/*z* (%) = 227 (31) $[M–H]^+$, 211 (100), 171 (6), 155 (13), 141 (14), 127 (16), 113 (14).

HRMS (CI): *m*/*z* $[M–H]^+$ calcd for $C_{15}H_{31}O$: 227.2375; found: 227.2373.

***N*-(6,6-Dimethylheptyl)piperidin-2-one (5h)**
According to P1, *N*-(5-iodopentyl)piperidin-2-one (**4h**) (295 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane–EtOAc, 20:1) afforded the title compound.

Yield: 151 mg (67%); yellow oil.

IR (Zn/Se-ATR, neat): 2933, 2861, 1644, 1494, 1468, 1448, 1418, 1353, 1329, 1301, 1176, 972 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 9 H), 1.17–1.28 (br m, 6 H), 1.54 (m, 2 H), 1.73–1.85 (br m, 4 H), 2.37 (t, *J* = 6.4 Hz, 2 H), 3.27 (t, *J* = 6.2 Hz, 2 H), 3.34 (t, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 23.2, 24.3, 27.1, 27.8, 29.3, 30.2, 32.3, 44.1, 47.2, 47.8, 169.5.

MS (EI): *m*/*z* (%) = 225 (16) $[M]^+$, 220 (15), 205 (7), 167 (59), 153 (18), 139 (8).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{27}NO$: 225.2093; found: 225.2091.

***N*,*N*-Diethyl-7,7-dimethyloctanamide (5i)**
According to P1, 6-bromo-*N*,*N*-diethylhexanamide (**4i**) (250 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane–EtOAc, 20:1) afforded the title compound.

Yield: 167 mg (73%); yellow oil.

IR (Zn/Se-ATR, neat): 2934, 2866, 1648, 1465, 1428, 1363, 1260, 1143, 1081, 946 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 9 H), 1.11 (t, *J* = 7.4 Hz, 3 H), 1.17 (t, *J* = 7.4 Hz, 3 H), 1.17–1.28 (m, 6 H), 1.65 (m, 2 H), 2.28 (t, *J* = 7.8 Hz, 2 H), 3.30 (q, *J* = 7.4 Hz, 2 H), 3.37 (q, *J* = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 14.4, 24.4, 25.5, 29.4, 30.2, 30.4, 33.1, 40.0, 41.9, 44.0, 172.3.

MS (EI): *m*/*z* (%) = 227 (18) $[M]^+$, 212 (14), 198 (10), 170 (62), 169 (7), 155 (11).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{29}NO$: 227.2249; found: 227.2242.

***N*-(7,7-Dimethyloctanoyl)morpholine (5j)**
According to P1, *N*-(6-bromohexanoyl)morpholine (**4j**) (264 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane–EtOAc, 15:1) afforded the title compound.

Yield: 183 mg (76%); pale yellow oil.

IR (Zn/Se-ATR, neat): 2953, 2860, 1651, 1461, 1430, 1272, 1242, 1119, 1035, 962, 851 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 9 H), 1.16–1.30 (br m, 6 H), 1.66 (m, 2 H), 2.31 (t, *J* = 7.8 Hz, 2 H), 3.46–3.76 (br m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 25.3, 29.4, 30.2, 30.4, 33.1, 41.8, 44.0, 46.0, 66.7, 66.9, 171.9.

MS (EI): *m*/*z* (%) = 241 (20) $[M]^+$, 226 (13), 184 (65), 170 (9), 155 (9).

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HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{27}NO_2$: 241.2042; found: 241.2041.

1-*tert*-Butoxycarbonyl-4-(3,3-dimethylbutyl)piperidine (5ka)
According to P1, 4-(2-bromoethyl)-1-(*tert*-butoxycarbonyl)piperidine (**4k**) (292 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane–EtOAc, 10:1) afforded the title compound.

Yield: 162 mg (60%); pale yellow oil.

IR (Zn/Se-ATR, neat): 2926, 2855, 1698, 1475, 1422, 1365, 1279, 1250, 1232, 1163, 1116, 965, 869 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 9 H), 1.06–1.28 (br m, 7 H), 1.45 (s, 9 H), 1.65 (m, 2 H), 2.66 (m, 2 H), 4.06 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 29.3, 30.1, 31.3, 32.3, 36.8, 41.0, 79.1, 154.9.

MS (EI): *m*/*z* (%) = 269 (9) [M]$^+$, 254 (35), 239 (19), 224 (8), 212 (81), 197 (8), 196 (6), 182 (7), 155 (17).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{31}NO_2$: 269.2355; found: 269.2356.

1-*tert*-Butoxycarbonyl-4-(3-methylpentyl)piperidine (5kg)
According to P1, 4-(2-bromoethyl)-1-(*tert*-butoxycarbonyl)piperidine (**4k**) (292 mg, 1.0 mmol) and *s*-BuMgCl (**2g**) (0.76 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane–EtOAc, 10:1) afforded the title compound.

Yield: 200 mg (74%); pale yellow oil.

IR (Zn/Se-ATR, neat): 2962, 2924, 2852, 1698, 1455, 1422, 1365, 1278, 1246, 1175, 1155, 964 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (m, 6 H), 0.97–1.27 (br m, 10 H), 1.38 (s, 9 H), 1.58 (m, 2 H), 2.59 (m, 2 H), 3.99 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 19.2, 28.5, 29.4, 32.2, 33.5, 33.9, 34.5, 36.3, 79.1, 154.9.

MS (EI): *m*/*z* (%) = 269 (15) [M]$^+$, 254 (10), 240 (12), 239 (8), 212 (14), 197 (10), 196 (9), 182 (6), 155 (10).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{31}NO_2$: 269.2355; found: 269.2352.

4-(3,3-Dimethylbutyl)-1-tosylpiperidine (5la)
According to P1, 4-(2-bromoethyl)-1-tosylpiperidine (**4l**) (346 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane–EtOAc, 10:1) afforded the title compound.

Yield: 178 mg (55%); white solid; mp 143–144 °C.

IR (Zn/Se-ATR, neat): 2945, 2844, 1336, 1160, 1093, 1046, 928, 919, 811, 727, 651, 608 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (s, 9 H), 1.07–1.32 (br m, 7 H), 1.71 (m, 2 H), 2.19 (m, 2 H), 2.43 (s, 3 H), 3.75 (m, 2 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 7.64 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 29.3, 30.1, 30.9, 31.6, 36.0, 41.0, 46.6, 127.7, 129.5, 133.2, 143.3.

MS (EI): *m*/*z* (%) = 323 (12) [M]$^+$, 308 (12), 293 (9), 266 (46), 238 (11), 232 (9).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{29}NO_2S$: 323.1919; found: 323.1921.

4-(3-Methylpentyl)-1-tosylpiperidine (5lg)
According to P1, 4-(2-bromoethyl)-1-tosylpiperidine (**4l**) (346 mg, 1.0 mmol) and *s*-BuMgCl (**2g**) (0.76 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane–EtOAc, 10:1) afforded the title compound.

Yield: 240 mg (74%); white solid; mp 88–89 °C.

IR (Zn/Se-ATR, neat): 2925, 2851, 1336, 1166, 1089, 1043, 927, 917, 809, 726, 650, 607 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.4 Hz, 3 H), 0.82 (t, *J* = 6.9 Hz, 3 H), 1.01–1.29 (m, 10 H), 1.70 (d, *J* = 11.4 Hz, 2 H), 2.19 (t, *J* = 9.2 Hz, 2 H), 2.43 (s, 3 H), 3.75 (d, *J* = 11.4 Hz, 2 H), 7.31 (d, *J* = 8.7 Hz, 2 H), 7.64 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 19.1, 21.5, 29.4, 31.5, 31.7, 33.4, 34.4, 35.5, 46.6, 127.7, 129.5, 133.2, 142.3.

MS (EI): *m*/*z* (%) = 323 (28) [M]$^+$, 308 (13), 294 (11), 293 (6), 266 (11), 238 (9), 232 (10).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{29}NO_2S$: 323.1919; found: 323.1915.

Ethyl 7,7-Dimethyloctanoate (5m)
According to P1, ethyl 6-bromohexanoate (**4m**) (223 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane–EtOAc, 10:1) afforded the title compound.

Yield: 145 mg (72%); colorless oil.

IR (Zn/Se-ATR, neat): 2952, 2865, 1739, 1468, 1382, 1365, 1241, 1182, 1127, 1084, 1036, 935 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 9 H), 1.13–1.17 (m, 2 H), 1.23–1.28 (m, 7 H), 1.63 (quin, *J* = 7.3 Hz, 2 H), 2.29 (t, *J* = 7.3 Hz, 2 H), 4.12 (q, *J* = 6.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 24.2, 25.0, 29.4, 30.1, 30.2, 34.4, 44.0, 60.1, 174.0.

MS (EI): *m*/*z* (%) = 200 (21) [M]$^+$, 185 (14), 171 (11), 170 (7), 155 (4), 143 (51), 114 (3).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{24}O_2$: 200.1776; found: 200.1773.

2-(4-Methylhexyl)thiophene (5n)
According to P1, 2-(3-bromopropyl)thiophene (**4n**) (205 mg, 1.0 mmol) and *s*-BuMgCl (**2g**) (0.76 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by flash column chromatography (hexane) afforded the title compound.

Yield: 146 mg (78%); colorless oil.

IR (Zn/Se-ATR, neat): 2959, 2930, 2872, 1461, 1440, 1377, 850, 819, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.8 Hz, 3 H), 0.86 (d, *J* = 5.7 Hz, 3 H), 1.10–1.22 (m, 2 H), 1.29–1.42 (m, 3 H), 1.60–1.75 (m, 2 H), 2.80 (t, *J* = 7.3 Hz, 2 H), 6.78 (d, *J* = 2.8 Hz, 1 H), 6.91 (dd, *J* = 4.8, 2.8 Hz, 1 H), 7.10 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 19.1, 29.4, 30.2, 34.2, 36.0, 122.7, 123.9, 126.6, 145.9.

MS (EI): *m*/*z* (%) = 182 (36) [M]$^+$, 111 (12), 98 (40), 97 (100).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{18}S$: 182.1129; found: 182.1130.

2,2,7,7-Tetramethyloctane (5o)
According to P1, 1,4-dibromobutane (**4o**) (217 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 2.5 mmol) were reacted under standard conditions.

Yield: 75% (determined by GC using decane as an internal standard).

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1-Chloro-8,8-dimethylnonane (5p)
According to P1, 1-bromo-7-chloroheptane (**4p**) (214 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 168 mg (88%); pale yellow oil.

IR (Zn/Se-ATR, neat): 2953, 2931, 2860, 1469, 1393, 1363, 951, 761, 727 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 9 H), 1.14–1.30 (br m, 8 H), 1.40 (m, 2 H), 1.75 (quin, *J* = 6.9 Hz, 2 H), 3.51 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 26.9, 29.0, 29.4, 30.4, 32.7, 44.2, 45.2.

MS (EI): *m*/*z* (%) = 192 (4) $[M(^{37}Cl)]^+$, 190 (11) $[M(^{35}Cl)]^+$, 177 (3), 175 (9), 135 (13), 133 (41).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{23}{}^{35}Cl$: 190.1488; found: 190.1489.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{23}{}^{37}Cl$: 192.1459; found: 192.1459.

6-Bromo-2,2-dimethylheptane (5qa)
According to P1, 1,4-dibromopentane (**4q**) (230 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 147 mg (71%); pale yellow oil.

IR (Zn/Se-ATR, neat): 2953, 2867, 1474, 1393, 1379, 1364, 1247, 1211, 961, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (s, 9 H), 1.10 (m, 2 H), 1.35 (m, 2 H), 1.63–1.76 (br m, 5 H), 1.64 (d, *J* = 6.7 Hz, 3 H), 4.08 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 26.5, 29.4, 30.3, 42.0, 43.4, 52.0.

MS (EI): *m*/*z* (%) = 208 (16) $[M(^{81}Br)]^+$, 206 (17) $[M(^{79}Br)]^+$, 193 (11), 191 (12), 178 (5), 176 (5), 151 (49), 149 (52).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_{19}{}^{79}Br$: 206.0670; found: 206.0670.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_{19}{}^{81}Br$: 208.0650; found: 208.0649.

2-Bromo-6-methyloctane (5qg)
According to P1, 1,4-dibromopentane (**4q**) (264 mg, 1.0 mmol) and *s*-BuMgCl (**2g**) (0.76 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 86% (determined by GC using decane as an internal standard).

1-Bromo-4-(3-methylpentyl)benzene (5rg)
According to P1, 1-bromo-4-(2-bromoethyl)benzene (**4r**) (230 mg, 1.0 mmol) and *s*-BuMgCl (**2g**) (0.76 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 71% (determined by GC using decane as an internal standard).

1-Bromo-4-hexylbenzene (5rj)
According to P1, 1-bromo-4-(2-bromoethyl)benzene (**4r**) (230 mg, 1.0 mmol) and *n*-BuMgCl (**2j**) (1.0 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 94% (determined by GC using decane as an internal standard).

7,7-Dimethyloct-1-ene (5sa)
According to P1, 6-bromohex-1-ene (**4s**) (163 mg, 1.0 mmol) and *t*-BuMgCl (**2a**) (0.81 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 110 mg (78%); pale yellow oil.

IR (Zn/Se-ATR, neat): 2954, 2931, 2864, 1641, 1474, 1364, 990, 969, 910 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 9 H), 1.15–1.37 (br m, 6 H), 2.06 (q, *J* = 6.8 Hz, 2 H), 4.93 (d, *J* = 9.2 Hz, 1 H), 4.99 (d, *J* = 17.0 Hz, 1 H), 5.82 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 29.4, 29.9, 30.3, 33.9, 44.1, 114.1, 139.2.

MS (EI): *m*/*z* (%) = 140 (19) $[M]^+$, 125 (12), 110 (5), 83 (53).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{20}$: 140.1565; found: 140.1561.

7-Methylnon-1-ene (5sg)
According to P1, 6-bromohex-1-ene (**4s**) (163 mg, 1.0 mmol) and *s*-BuMgCl (**2g**) (0.76 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 120 mg (85%); pale yellow oil.

IR (Zn/Se-ATR, neat): 2961, 2927, 2857, 1641, 1463, 1378, 991, 910 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.4 Hz, 3 H), 0.78 (t, *J* = 7.4 Hz, 3 H), 1.01–1.07 (br m, 2 H), 1.22–1.29 (br m, 7 H), 1.97 (m, 2 H), 4.88 (dt, *J* = 10.1, 1.4 Hz, 1 H), 4.92 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.74 (ddt, *J* = 17.2, 10.1, 6.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 19.2, 26.6, 29.3, 29.5, 33.9, 34.3, 36.4, 114.1, 139.2.

MS (EI): *m*/*z* (%) = 140 (39) $[M]^+$, 125 (8), 111 (19).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{20}$: 140.1565; found: 140.1561.

Dec-1-ene (5sj)
According to P1, 6-bromohex-1-ene (**4s**) (163 mg, 1.0 mmol) and *n*-BuMgCl (**2j**) (1.0 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 89% (determined by GC using decane as an internal standard).

(2,2,5-Trimethylhexyl)cyclopropane (5td)
According to P1, (bromomethyl)cyclopropane (**4t**) (135 mg, 1.0 mmol) and 2,5-dimethyl-2-hexylmagnesium chloride (**2d**) (0.65 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

Yield: 83 mg (49%); pale yellow oil.

IR (Zn/Se-ATR, neat): 2955, 2928, 2871, 1469, 1385, 1366, 1016, 974, 822 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = –0.01 (m, 2 H), 0.42 (m, 2 H), 0.63 (m, 1 H), 0.89 (m, 12 H), 1.22 (m, 6 H), 1.44 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.7, 6.5, 22.8, 27.5, 28.9, 33.1, 33.9, 39.9, 46.9.

MS (EI): *m*/*z* (%) = 168 (28) $[M]^+$, 153 (16), 125 (20), 97 (9).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{24}$: 168.1878; found: 168.1873.

(2-Ethylhexyl)cyclopropane (5th)
According to P1, (bromomethyl)cyclopropane (**4t**) (135 mg, 1.0 mmol) and 3-heptylmagnesium bromide (**2h**) (1.0 M in THF, 1.2 mmol) were reacted under standard conditions. After aqueous work-up, purification by GPC (with $CHCl_3$ as the eluent) afforded the title compound.

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Yield: 101 mg (66%); colorless oil.

IR (Zn/Se-ATR, neat): 2959, 2925, 2860, 1463, 1042, 1015, 942, 821 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = –0.01 (m, 2 H), 0.40 (m, 2 H), 0.67 (m, 1 H), 0.85 (t, *J* = 6.9 Hz, 3 H), 0.90 (t, *J* = 7.3 Hz, 3 H), 1.14–1.36 (br m, 11 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.6, 4.7, 8.8, 10.9, 14.2, 23.2, 25.9, 29.0, 32.8, 38.5, 39.9.

MS (EI): *m*/*z* (%) = 154 (39) $[M]^+$, 125 (20), 111 (9), 97 (11).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{22}$: 154.1721; found: 154.1721.

Nonylcyclopropane (5tn)
According to P1, (bromomethyl)cyclopropane (**4t**) (135 mg, 1.0 mmol) and *n*-octylmagnesium chloride (**2n**) (1.8 M in THF, 1.2 mmol) were reacted under standard conditions.

Yield: 71% (determined by GC using decane as an internal standard).

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References

(1) For representative reviews, see: (a) Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384. (b) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (c) Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674. (d) Kambe, N.; Iwasaki, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937. (e) Hu, X. L. *Chem. Sci.* **2011**, *2*, 1867.

(2) (a) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268. (b) Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973**, *50*, C12. (c) Hayashi, T.; Konishi, M.; Yokota, K.-i.; Kumada, M. *Chem. Lett.* **1980**, 767.

(3) (a) Burns, D. H.; Miller, J. D.; Chan, H.-K.; Delaney, M. O. *J. Am. Chem. Soc.* **1997**, *119*, 2125. (b) Donkervoort, J. G.; Vicario, J. L.; Jastrzebski, J. T. B. H.; Gossage, R. A.; Cahiez, G.; van Koten, G. *J. Organomet. Chem.* **1998**, *558*, 61. (c) Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733. (d) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646. (e) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 2086. (f) Cahiez, G.; Gager, O.; Buendia, J. *Synlett* **2010**, 299. (g) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124. (h) Ren, P.; Stern, L.-A.; Hu, X. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 9110.

(4) (a) Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 663. (b) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545. (c) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (d) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2003**, *32*, 890. (e) Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 6180. (f) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Commun.* **2007**, 825. (g) Singh, S. P.; Terao, J.; Kambe, N. *Tetrahedron Lett.* **2009**, *50*, 5644. (h) Singh, S. P.; Iwasaki, T.; Terao, J.; Kambe, N. *Tetrahedron Lett.* **2011**, *52*, 774. (i) Iwasaki, T.; Tsumura, A.; Omori, T.; Kuniyasu, H.; Terao, J.; Kambe, N. *Chem. Lett.* **2011**, *40*, 1024. (j) Shen, R.; Iwasaki, T.; Terao, J.; Kambe, N. *Chem. Commun.* **2012**, *48*, 9313. (k) Iwasaki, T.; Higashikawa, K.; Reddy, V. P.; Ho, W. W. S.; Fujimoto, Y.; Fukase, K.; Terao, J.; Kuniyasu, H.; Kambe, N. *Chem. Eur. J.* **2013**, *19*, 2956. (l) For the alkylation of 2-methylthiobenzothiazoles, see: Ghaderi, A.; Iwasaki, T.; Fukuoka, A.; Terao, J.; Kambe, N. *Chem. Eur. J.* **2013**, *19*, 2951.

(5) Iwasaki, T.; Takagawa, H.; Singh, S. P.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2013**, *135*, 9604.

(6) For reviews on Co-catalyzed C–C bond forming reactions, see: (a) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081. (b) Yorimitsu, H.; Oshima, K. *Pure Appl. Chem.* **2006**, *78*, 441. (c) Gosmini, C.; Bégouin, J.-M.; Moncomble, A. *Chem. Commun.* **2008**, 3221. (d) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435.

(7) For Co-catalyzed C–C bond formation between sp^3 carbon centers, see: (a) Cahiez, G.; Chaboche, C.; Duplais, C.; Giulliani, A.; Moyeux, A. *Adv. Synth. Catal.* **2008**, *350*, 1484. (b) Zhou, W.; Napoline, J. W.; Thomas, C. M. *Eur. J. Inorg. Chem.* **2011**, 2029. For examples with allylic and benzylic nucleophiles, see: (c) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4137. (d) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2004**, *10*, 5640. (e) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1565. (f) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2007**, *63*, 8609.

(8) Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

(9) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley: New York, **2006**.

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