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Cp*Li as a base: application to palladium-catalyzed cross-coupling reaction of aryl-X or alkenyl-X (X=I, Br, OTf, ONf) with terminal acetylenes

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Abstract

The reaction of aryl-X or alkenyl-X (X=I, Br, OTf, ONf) with terminal acetylenes in the presence of a catalytic amount of $Pd(OAc)_2$ provided the alkynylated products in good yields by using Cp*Li (Cp*=1,2,3,4,5-pentamethylcyclopentadienyl) as a base.

Keywords: Pentamethylcyclopentadiene; Cross-coupling reaction; Lithium acetylides; Alkynylation

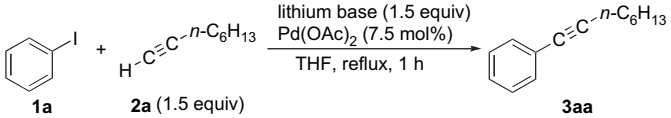
1. Introduction

Pentamethylcyclopentadienide ($Me_5C_5^-$, Cp^{*-}) has been used as a ligand of transition metal complexes for 40 years.[1] Although Cp^{*-} has unique properties, such as six-electron donation and steric bulkiness by the five methyl groups on the five-membered ring, it has not been used for other purposes. Then we have been exploring applications of Cp^{*-} as a reagent in organic synthesis.[2] Now, we have been interested in Cp^{*-} as a base. We expected that its strong basicity and steric bulkiness would exhibit interesting reactivities. We have found that the reaction of aryl-X or alkenyl-X (X=I, Br, OTf, ONf) with terminal acetylenes in the presence of a catalytic amount of palladium provided the alkynylated products in good yields by using Cp*Li as a base.

2. Results and discussions

Treatment of a suspension of Cp*Li in THF with iodobenzene (**1a**), 1-octyne (**2a**), and a catalytic amount of $Pd(OAc)_2$ at reflux for 1 h gave 1-octynylbenzene (**3aa**) in 82% yield (Table 1, entry 7). Other lithium bases, such as *n*-BuLi, lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LHMDS), and lithium cyclopentadienide (CpLi), did not assist the coupling reaction efficiently (entries 1–4). However, lithium indenide resulted in the formation of **3aa** in 24% yield (entry 5). Interestingly, the reaction with lithium

Table 1
Effect of lithium bases on palladium-catalyzed cross-coupling reaction of iodobenzene (**1a**) with 1-octyne (**2a**)



Entry	Lithium base	NMR yield/%
1	*n*-BuLi	3
2	Lithium diisopropylamide (LDA)	3
3	Lithium hexamethyldisilazide (LHMDS)	3
4	Lithium cyclopentadienide (CpLi)	3
5	Lithium indenide[a]	24
6	Lithium tetramethylcyclopentadienide	55
7	Cp*Li	82[b]

[a] Derived from indene and *n*-BuLi.
[b] Isolated yield.

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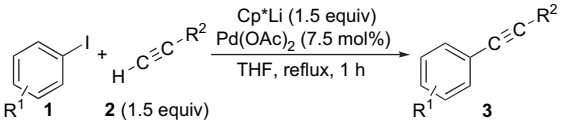
tetramethylcyclopentadienide, which lacks one methyl group compared with Cp*Li, gave **3aa** in lower yield than that with Cp*Li yet in higher yield than that with CpLi (entry 6).

Although many kinds of alkynylmetals have been used for palladium-catalyzed cross-coupling reaction of aryl-X or alkenyl-X, there are no reports on the cross-coupling reaction with lithium acetylides.[3] The coupling reaction with lithium acetylides is difficult because the reaction of a palladium catalyst with an excess amount of lithium acetylides provides lithium palladate **4**, which does not exhibit any catalytic activity (Eq. 1).[4] We thought that gradual formation of lithium acetylides by means of Cp*Li would avoid the formation of **4**.

$$Cl_2Pd(PPh_3)_2 + \underset{\text{(excess)}}{Li{-}C{\equiv}C{-}R} \longrightarrow \underset{\mathbf{4}}{Li_2Pd(C{\equiv}C{-}R)_4} \quad (1)$$

To confirm the gradual generation of lithium acetylides, we carried out the following experiments. Treatment of lithium acetylide **5** with Cp*H for 1 h at reflux followed by an addition of benzaldehyde at 0 °C gave a mixture of octynylated alcohol **6** and pentamethylcyclopentadienylated alcohol **7** (Eq. 2). On the other hand, **7** was obtained selectively by using the reaction mixture of **5** and Cp*H, which was treated for 11 h at reflux. These facts indicate that the pK_a value of Cp*H is smaller than that of **2a** and that a high energy barrier exists between **2a**+Cp*Li and **5**+Cp*H. A similar reaction with cyclopentadiene (CpH), instead of Cp*H, only for 1 h followed by an addition of benzaldehyde did not give **6** but gave Cp adduct-derived compounds such as 6-phenylfulvene. This result means that the energy barrier between **2a**+CpLi and **5**+CpH is lower than that between **2a**+Cp*Li and **5**+Cp*H. Not only the pK_a values of lithium bases but also the high energy barrier is important to promote the cross-coupling reaction. The reaction of a mixture of **2a** and Cp*Li with benzaldehyde at reflux or at 0 °C provided **6** or **7**, respectively (Eq. 3). The results mean that **5** is generated only at reflux. The reason why **7** is not provided at reflux conditions is that nucleophilic addition reaction of Cp*Li to benzaldehyde is thermally reversible and that of **5** to benzaldehyde is irreversible. We are sure that the equilibrium between **2a**+Cp*Li and **5**+Cp*H is mostly biased toward **2a**+Cp*Li and that a modest amount of **5**+Cp*H would be generated at reflux.

Table 2
Reactions of various aryl iodides **1** with terminal acetylenes **2**



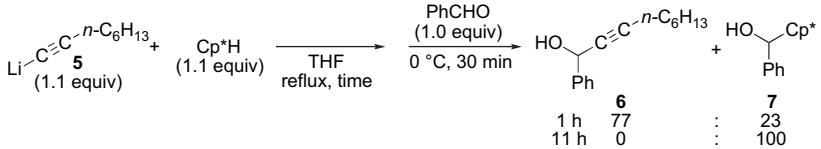
Entry	R^1	R^2	Isolated yield/%
1	H (**1a**)	*n*-C_6H_{13} (**2a**)	82 (**3aa**)
2	**1a**	*c*-C_6H_{11} (**2b**)	85 (**3ab**)
3	**1a**	Ph (**2c**)	93 (**3ac**)[a]
4	**1a**	TES (**2d**)	69 (**3ad**)[b]
5	**1a**	TMS (**2e**)	72 (**3ae**)[a,b]
6	*p*-Me (**1b**)	**2a**	81 (**3ba**)
7	*p*-OMe (**1c**)	**2a**	82 (**3ca**)
8	*p*-CF_3 (**1d**)	**2a**	70 (**3da**)
9	*p*-Cl (**1e**)	**2a**	71 (**3ea**)
10	*p*-COOEt (**1f**)	**2a**	83 (**3fa**)
11	*p*-CN (**1g**)	**2a**	74 (**3ga**)
12	*m*-Me (**1h**)	**2a**	83 (**3ha**)
13	*o*-Me (**1i**)	**2a**	83 (**3ia**)[c]
14	1-Naphthyl iodide (**1j**)	**2a**	67 (**3ja**)

[a] PPh_3 of 15 mol % was added.
[b] The reaction was carried out at 50 °C for 2 h.
[c] The reaction was carried out for 1.5 h.

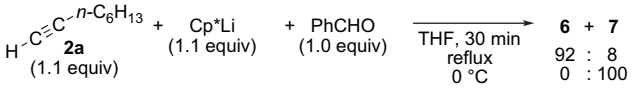
Table 2 summarizes the results obtained by the Cp*Li-mediated reaction of aryl iodides **1** with terminal acetylenes **2**. Aromatic iodide **1** bearing an electron-donating group (Table 2, entry 7) or an electron-withdrawing group (entry 8) afforded **3** in high yields. Surprisingly, ester (entry 10) or cyano moiety (entry 11) on the aromatic ring did not undergo nucleophilic addition reaction of Cp*Li or lithium acetylides during thermal conditions. Reaction of *meta*- or *ortho*-substituted **1** also proceeded smoothly (entries 12 and 13). 1-Naphthyl iodide could be used in this reaction (entry 14). The reaction with phenylacetylene (**2c**) or trimethylsilylacetylene (**2e**) afforded **3** in good yields by using 15 mol % of triphenylphosphine (entries 3 and 5).

Not only aryl iodides but also aryl bromides, triflate, or nonaflate could be also used as substrates in the Cp*-mediated reaction (Table 3). In these cases, triphenylphosphine was essential as a ligand.

By utilizing the advantages of Cp*Li as a base, we find two applications. The reaction of 2-iodobenzoic acid with **2** provided isocoumarin **8** and (*Z*)-3-alkylidenephthalide **9** in good yields (Eq. 4).[5] We also found that Cp*Li can be used as a bulky base to prepare lithium enolates. With this reactivity, we accomplished one-pot synthesis of enynes **12** from ketone **10** via nonaflate **11** in good yields (Eq. 5).

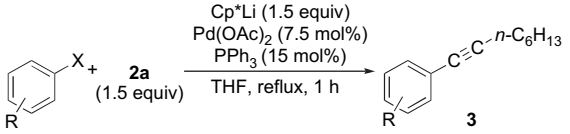


(2)



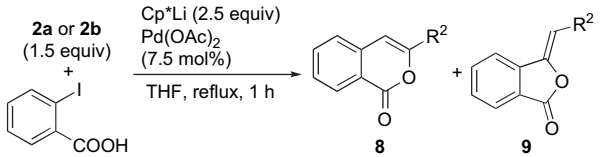
(3)

Table 3
Reactions of various aryl bromides, triflate, or nonaflate with 1-octyne (**2a**)



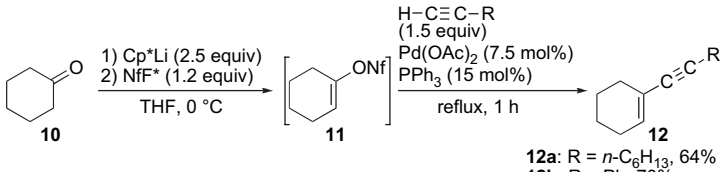
Entry	X	R	Isolated yield/%
1	Br	H	79 (**3aa**)
2	Br	*p*-OMe	74 (**3ca**)[c]
3	Br	*p*-CF_3	79 (**3da**)
4	OTf[a]	H	58 (**3aa**)
5	ONf[b]	H	88 (**3aa**)[c]

[a] Tf=trifluoromethanesulfonyl.
[b] Nf=1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonyl.
[c] The reaction was carried out for 1.5 h.



8a+9a: R^2 = *n*-C_6H_{13}, 70% (68:32)
8b+9b: R^2 = *c*-C_6H_{11}, 78% (63:37)

(4)



12a: R = *n*-C_6H_{13}, 64%
12b: R = Ph, 70%
12c: R = TMS, 69% (50 °C, 2 h)

*NfF = 1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonyl fluoride

(5)

3. Experimental

3.1. Instrumentation and materials

^{1}H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on a Varian UNITY INOVA 500 spectrometer unless otherwise noted. Chemical shifts (δ) are in parts per million relative to chloroform at 7.26 ppm for ^{1}H and at 77.0 ppm for ^{13}C. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Gel permeation chromatography (GPC) was performed by LC-908 (Japan Analytical Industry Ltd., two in-line JAIGEL-2H, toluene, 7.8 mL/min, UV and RI detectors). Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. 1,2,3,4,5-Pentamethyl-1,3-cyclopentadiene was purchased from Kanto Chemical Co. THF (dehydrated, stabilizer free) was purchased from Kanto Chemical Co., stored under nitrogen, and used without distillation. All reactions were carried out under argon atmosphere.

*3.1.1. General procedure for palladium-catalyzed cross-coupling reaction of aryl iodides **1** with terminal acetylenes **2** using Cp*Li*

A solution of *n*-BuLi in hexane (1.60 M, 0.47 mL, 0.75 mmol) was added to a solution of 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (0.13 mL, 0.80 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 10 min at the same temperature. $Pd(OAc)_2$ (8.4 mg, 0.038 mmol), **2a** (82.7 mg, 0.75 mmol) in THF (0.5 mL), and **1a** (102 mg, 0.50 mmol) in THF (0.5 mL) were added to the reaction mixture. The resulting mixture was stirred for 1 h at reflux. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with hexane. The combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil. The oil was purified by chromatography on silica gel (Wakogel C-200, hexane) to afford **3aa** (75.5 mg, 0.41 mmol, 82%).

*3.1.2. General procedure for palladium-catalyzed cross-coupling reaction of aryl bromides, triflate, or nonaflate with 1-octyne (**2a**) using Cp*Li*

A solution of *n*-BuLi in hexane (1.60 M, 0.47 mL, 0.75 mmol) was added to a solution of 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (0.13 mL, 0.80 mmol) in THF (5 mL) at 0 °C. The white suspension was stirred for 10 min at the same temperature. $Pd(OAc)_2$ (8.4 mg, 0.038 mmol), PPh_3 (19.7 mg, 0.075 mmol), 1-octyne (82.7 mg, 0.75 mmol) in THF (0.5 mL), and bromobenzene (78.5 mg, 0.50 mmol) in THF (0.5 mL) were added to the reaction mixture, and the mixture was stirred for 1 h at reflux. The reaction was terminated with saturated aqueous NH_4Cl, and the mixture was extracted with hexane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil. Chromatographic purification on silica gel (Wakogel C-200, hexane) afforded **3aa** (73.4 mg, 0.39 mmol, 79%).

*3.1.3. General procedure for palladium-catalyzed annulation of 2-iodobenzoic acid with terminal acetylenes **2** using Cp*Li*

A solution of *n*-BuLi in hexane (1.60 M, 0.78 mL, 1.25 mmol) was added to a solution of 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (0.20 mL, 1.3 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C. $Pd(OAc)_2$ (8.4 mg, 0.038 mmol), **2a** (82.7 mg, 0.75 mmol) in THF (0.5 mL), and 2-iodobenzoic acid (124 mg, 0.50 mmol) in THF (0.5 mL) were added to the reaction mixture, and the mixture was stirred for 1 h at reflux. After being quenched

with water, the mixture was extracted with ethyl acetate. The combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil. Purification on silica gel (Wakogel C-200, hexane–ethyl acetate=20:1) afforded a mixture of **8a** and **9a** (**8a**–**9a**=68:32, 80.8 mg, 0.35 mmol, 70%).

3.1.4. General procedure for palladium-catalyzed one-pot synthesis of enynes *12* from *10* via *11*

A solution of *n*-BuLi in hexane (1.60 M, 0.78 mL, 1.25 mmol) was added to a solution of 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (0.20 mL, 1.3 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature. Cyclohexanone (49.1 mg, 0.5 mmol) in THF (0.5 mL) was added to the resulting white suspension, and the mixture was stirred for 30 min at 0 °C. 1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonyl fluoride (181 mg, 0.60 mmol) in THF (0.5 mL) was added to the reaction mixture, and the mixture was stirred for 30 min at 0 °C. 1-Octyne (**2a**, 82.7 mg, 0.75 mmol) in THF (0.5 mL), PPh_3 (19.7 mg, 0.075 mmol), and $Pd(OAc)_2$ (8.4 mg, 0.038 mmol) were added to the reaction mixture, and the mixture was stirred for 1 h at reflux. Water was added to quench the reaction, and the mixture was extracted with hexane. The combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil. The oil was purified by chromatography on silica gel (Wakogel C-200, hexane) to afford **12a** (60.3 mg, 0.32 mmol, 64%).

3.1.5. Preparation of phenyl 1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonate

A solution of *n*-BuLi in hexane (1.60 M, 3.44 mL, 5.5 mmol) was added to a solution of phenol (471 mg, 5.0 mmol) in THF (17 mL) at 0 °C. The mixture was stirred for 10 min at the same temperature. 1,1,2,2,3,3,4,4,4-Nonafluoro-1-butanesulfonyl fluoride (1.81 g, 6.0 mmol) in THF (1 mL) was added to the reaction mixture, and the mixture was stirred for 30 min at room temperature. The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude oil. The oil was purified by chromatography on silica gel (Wakogel C-200, hexane–ethyl acetate=40:1) to afford phenyl 1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonate (1.52 g, 4.0 mmol, 81%).

3.2. Characterization data

The compounds **3aa**, **3ac**, and **3ae** are commercially available. The products **3ab**,[6] **3ad**,[7] **3ba**,[8] **3ca**,[8] **3da**,[8] **3ea**,[9] **3ga**,[8] **3ha**,[8] **3ia**,[8] **3ja**,[10] **12a**,[11] **12b**,[12] and **12c**[12] can be found in the literature.

3.2.1. Ethyl 4-(1-octynyl)benzoate (*3fa*)

IR (neat) 2932, 2859, 1720, 1608, 1466, 1367, 1306, 1272, 1175, 1106, 1097, 1021, 857, 770, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J=7.0 Hz, 3H), 1.28–1.64 (m, 8H), 1.39 (t, J=7.0 Hz, 3H), 2.42 (t, J=7.0 Hz, 2H), 4.36 (t, J=7.0 Hz, 2H), 7.41–7.45 (m, 2H), 7.93–7.97 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.04, 14.30, 19.50, 22.53, 28.54, 28.60, 31.33, 61.01, 80.12, 93.90, 128.81, 129.13, 129.33 (×2), 131.39 (×2), 166.20. Found: C, 78.92; H, 8.78%. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58%.

3.2.2. Phenyl 1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonate

IR (neat) 1488, 1427, 1354, 1230, 1204, 1145, 1133, 1036, 891, 772, 686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28–7.31 (m, 2H), 7.37–7.42 (m, 1H), 7.44–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 107.44–118.48 (m, ×4), 121.35 (×2), 128.35, 130.25 (×2), 149.89. Found: C, 31.87; H, 1.50%. Calcd for $C_{10}H_5F_9O_3S$: C, 31.93; H, 1.34%.

3.2.3. 3-Hexylisocoumarin (*8a*) and (Z)-3-heptylidenephthalide (*9a*) (68:32)

IR (neat) 2929, 2857, 1782, 1733, 1658, 1484, 1161, 1024, 983, 759, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J=7.5 Hz, 3H), 1.24–1.74 (m, 8H), 2.47 (dt, J=7.5, 7.5 Hz, 2×0.32H), 2.52 (t, J=7.5 Hz, 2×0.68H), 5.64 (t, J=7.5 Hz, 1×0.32H), 6.25 (s, 1×0.68H), 7.32–8.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.01, 14.05, 22.49, 22.56, 25.81, 26.85, 28.66, 28.96, 29.22, 31.48, 31.60, 33.51, 102.82, 109.76, 119.59, 120.10, 124.43, 124.98, 125.22, 127.49, 129.27, 129.48, 134.17, 134.67, 137.63, 139.58, 145.58, 158.33, 163.11, 167.21. Found: C, 78.13; H, 7.83%. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88%.

3.2.4. 3-Cyclohexylisocoumarin (*8b*) and (Z)-3-cyclohexylmethylenephthalide (*9b*) (63:37)

IR (Nujol) 1776, 1727, 1718, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28–2.08 (m, 10H), 2.41–2.48 (m, 1×0.63H), 2.79–2.88 (m, 1×0.37H), 5.50 (d, J=9.5 Hz, 1×0.37H), 6.23 (s, 1×0.63H), 7.34–8.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 25.63, 25.86 (×3), 25.92 (×2), 30.56 (×2), 32.85 (×2), 35.28, 41.84, 100.85, 115.04, 119.64, 120.26, 124.37, 125.20, 125.22, 127.45, 129.27, 129.42, 134.15, 134.60, 137.74, 139.78, 144.16, 162.35, 163.12, 167.25. Found: C, 79.13; H, 7.20%. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06%. Mp 78.0–79.0 °C.

Acknowledgements

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