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Cobalt-Catalyzed Arylzincation of Alkynes

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ABSTRACT

Cobalt(II) bromide catalyzes arylzincation of alkynes with arylzinc iodide•lithium chloride complexes in acetonitrile. The scope of the arylzincation is wide enough to use unfunctionalized alkynes, such as 6-dodecyne, as well as arylacetylenes. The inherent functional group compatibility of arylzinc reagents allows preparation of various functionalized styrene derivatives. The reaction is applicable to the efficient and stereoselective synthesis of a synthetic estrogen and its derivative.

Carbometalation of alkynes is a useful reaction to synthesize multisubstituted alkenes.[1] In particular, carbozincation is one of the most important reactions due to the high functional group compatibility of organozinc reagents. Although there are several reports on transition metal-catalyzed carbozincation of propynoate derivatives,[2] alkynyl sulfoxide,[3] phenylacetylenes,[4] or ynamides,[5] carbozincation of unfunctionalized alkynes such as dialkylacetylene remains an important challenge.[6] Here we wish to report that simple cobalt salts[7] can catalyze arylzincation of a wide range of alkynes including unfunctionalized ones.[8] In addition, the reaction offers a new route to the key structure of various synthetic estrogen derivatives.

Our investigation began with treatment of 6-dodecyne (**1a**) with 4-methylphenylzinc iodide•lithium chloride complex (1 M in THF)[9] in toluene at 100 °C in the presence of cobalt bromide for 1 h. However, the reaction did not proceed (Table 1, entry 1). Interestingly, the addition of acetonitrile promoted the reaction to provide (*E*)-6-(4-methylphenyl)-6-

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(3) (a) Sklute, G.; Bolm, C.; Marek, I. *Org. Lett.* **2007**, *9*, 1259–1261. (b) Maezaki, N.; Sawamoto, H.; Yoshigami, R.; Suzuki, T.; Tanaka, T. *Org. Lett.* **2003**, *5*, 1345–1347.

(4) (a) Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299–1316. (b) Yasui, H.; Nishikawa, T.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1271–1274. The cobalt-catalyzed allylzincation reaction of 6-dodecyne afforded only an 18% yield of the corresponding allylated product.

(5) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802–3803.

(6) There are few examples of carbometalation of dialkylacetylenes. Carbomagnesiation: (a) Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 17164–17165. (b) Murakami, K.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1569–1571. Carboboration: (c) Suginome, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc.* **2006**, *128*, 14438–14439. (d) Daini, M.; Suginome, M. *Chem. Commun.* **2008**, 5224–5226. Carbostannylation: (e) Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221–10222.

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(8) Cobalt-catalyzed hydroarylation of alkynes with arylboronic acid was reported. Most of alkynes used were propynoate esters and alkynes having a directing group. The addition to 3-hexyne was found to afford a 1:1 mixture of stereoisomers. Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chem.−Eur. J.* **2008**, *14*, 11296–11299.

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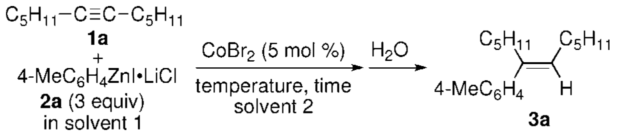
10.1021/ol900883j CCC: $40.75

Table 1. Optimization of the Arylzincation of 6-Dodecyne



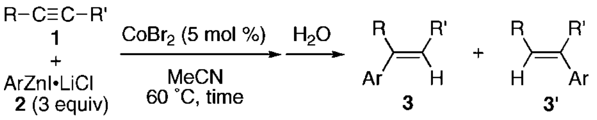
entry	solvent 1	solvent 2	temp (° C), time (h)	yield(%)[a]
1	THF	toluene	100, 1	–
2	THF	toluene/MeCN (3/1)	100, 1	22
3	MeCN	–	60, 4	55
4	EtCN	–	60, 4	32
5	^{i}PrCN	–	60, 4	–
6	MeCO$_2$Et	–	60, 4	–
7[b]	MeCN	–	60, 4	64[c]

[a] Yields were determined by ^{1}H NMR. [b] P^{t}Bu$_3$ (10 mol %) was added. [c] Isolated yield.

dodecene (**3a**) stereoselectively in 22% yield (Table 1, entry 2). Hence we replaced THF and toluene with acetonitrile as the next trial. Gratifyingly, the reaction proceeded smoothly to provide **3a** in 55% yield (Table 1, entry 3).[10] The addition of propionitrile was less effective, and isobutyronitrile completely suppressed the reaction (Table 1, entries 4 and 5). Other polar solvents such as ethyl acetate are also ineffective (Table 1, entry 6). Further investigation revealed that the addition of P^{t}Bu$_3$ improved the efficiency of the reaction and afforded **3a** in 64% yield (Table 1, entry 7).[11,12]

The scope of arylzinc reagents and alkynes was studied, and the results are summarized in Table 2. The reactions with phenyl- and 3-methylphenylzinc reagents proceeded smoothly to afford the corresponding products in high yields (entries 1 and 2). However, sterically hindered 2-methylphenylzinc reagent **2d** failed to react (entry 3). Arylzinc reagents bearing bromo and ethoxycarbonyl group were also applicable and provided the corresponding arylated products in 64% and 72% yields, respectively (entries 4 and 5). Whereas an arylzinc reagent having an electron-donating methoxy group reacted smoothly, a trifluoromethyl-substituted arylzinc reagent was less reactive (entries 6 and 7). Attempts to alkylate **1a** with hexylzinc iodide•lithium chloride under cobalt catalysis afforded (*Z*)-6-dodecene in less than 20% yields, and none of the corresponding hexylated product was observed.

Table 2. Scope of Arylzinc Reagents and Alkynes[a]



1b : R = Me, R' = C$_5$H$_{11}$
1c : R = Me, R' = Ph
1d : R = Me, R' = 2-MeOC$_6$H$_4$
1e : R = C$_6$H$_{13}$, R ' = ^{i}Pr
1f : R = EtO$_2$C(CH$_2$)$_4$, R' = 2-MeOC$_6$H$_4$
1g : R = C$_4$H$_9$, R' = 2-thienyl
1h : R = Ph, R' = P(O)(OEt)$_2$

2b : Ph
2c : 3-MeC$_6$H$_4$
2d : 2-MeC$_6$H$_4$
2e : 4-BrC$_6$H$_4$
2f : 4-EtO$_2$CC$_6$H$_4$
2g : 3-MeOC$_6$H$_4$
2h : 3-CF$_3$C$_6$H$_4$

entry	1	2	time (h)	3	yield (%)[b]	3:3'[c]
1[d]	**1a**	**2b**	2 (4)[e]	**3b**	82 (77)[e]	–
2	**1a**	**2c**	3	**3c**	71	–
3	**1a**	**2d**	6	**3d**	trace	–
4	**1a**	**2e**	2	**3e**	64	–
5	**1a**	**2f**	6	**3f**	72	–
6	**1a**	**2g**	3	**3g**	74	–
7	**1a**	**2h**	5	**3h**	53	–
8	**1b**	**2b**	2	**3i**	64	55:45
9	**1c**	**2b**	3	**3j**	89	90:10
10[d]	**1d**	**2b**	1.5	**3k**	86	>99:1
11	**1e**	**2b**	1.5	**3l**	trace	–
12[d]	**1f**	**2b**	2	**3m**	86	>99:1
13[d]	**1g**	**2b**	2	**3n**	91	98:2
14[d,f]	**1h**	**2b**	2	**3o**	80	>99:1

[a] Reaction was performed on a 0.3 mmol scale. [b] Isolated yield. [c] Ratio of regioisomers was determined by ^{1}H NMR. [d] P^{t}Bu$_3$ (10 mol %) was added. [e] Reaction was performed on a 5 mmol scale. [f] Reaction was performed at room temperature.

The reaction of 2-octyne (**1b)** provided a 55:45 mixture of regioisomers (entry 8). 1-Phenyl-1-propyne reacted smoothly with high regioselectivity (entry 9). The phenylzincation of phenylacetylene having a methoxy group at the ortho position exhibited perfect regioselectivity to yield phenylation product **3k** (entry 10). Unfortunately, 2-methyl-3-decyne (**1e**) failed to react because of its steric hindrance (entry 11). Acetylene having an ester group reacted without any observable side reactions (entry 12). The reaction proceeded efficiently with heteroaryl-substituted alkyne **1g** (entry 13). The reaction of alkynyl phosphonate **1h** gave the corresponding product **3o** regioselectively (entry 14). Bulky triethylsilyl-substituted alkyne was inert under the reaction conditions, and the reaction of diyne **1i** gave **3p** selectively (eq 1). Attempts to

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(10) Preparation of acetonitrile solutions of arylzinc reagents: Arylzinc reagents in THF were prepared from zinc powder (Wako Pure Chemical Industries, Ltd.), lithium chloride (Wako Pure Chemical Industries, Ltd.), and the corresponding aryl iodides in THF.[9] An arylzinc iodide•lithium chloride complex in THF (1.0 M, 0.9 mmol, 0.9 mL) was placed in a 50-mL round-bottomed flask under argon. The THF solvent was evaporated in vacuo. Then, acetonitrile (0.5 mL) was added to the flask to afford an acetonitrile solution of an arylzinc reagent. The solutions were prepared immediately prior to use.

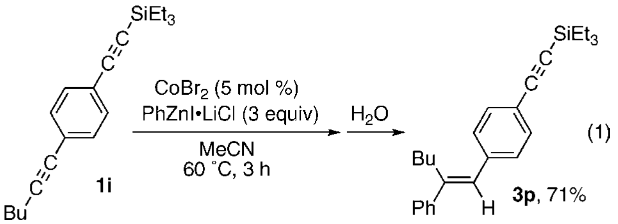
(11) Typical procedure for cobalt-catalyzed reactions: The reaction of 6-dodecyne with 4-methylphenylzinc iodide•lithium chloride complex is representative. CoBr$_2$ (3.3 mg, 0.015 mmol) was placed in a 20-mL reaction flask under argon. 6-Dodecyne (50 mg, 0.30 mmol) and P^{t}Bu$_3$ (1.0 M hexane solution, 0.030 mL, 0.030 mmol) were added. Then, 4-methylphenylzinc iodide•lithium chloride complex in acetonitrile (0.90 mmol) was added. The mixture was stirred at 60 °C for 4 h. A saturated aqueous solution of NH$_4$Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na$_2$SO$_4$ and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent afforded (*E*)-6-(4-methylphenyl)-6-dodecene (47 mg, 0.19 mmol) in 64% yield.

(12) The necessity of P^{t}Bu$_3$ as an additive heavily depended on alkynes and arylzinc reagents used. The addition of P^{t}Bu$_3$ often retarded the reaction. The exact role of P^{t}Bu$_3$ is not clear.

(13) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340–348.

(14) *meso*-Hexestrol is an effective inhibitor of microtubule assembly of proteins. Thus, its derivatives have also been extensively studied. However, it is difficult to synthesize asymmetrical *meso*-hexestrol derivatives diastereoselectively. (a) Wilson, J. W.; Burger, A.; Turnbull, L. B.; Peters, M.; Milnes, F. *J. Org. Chem.* **1953**, *18*, 96–105. (b) Angelis, M. D.; Katzenellenbogen, J. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5835–5839.

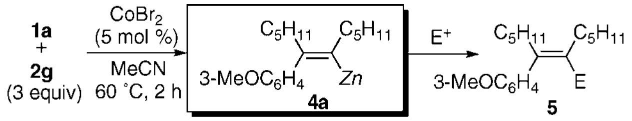
use terminal alkynes resulted in low yields (less than 20%) as well as formation of 1:1 mixtures of regioisomers.



With the reliable arylzincation reaction in hand, we investigated the utility of the intermediary alkenylzinc compounds. Intermediate **4a** reacted with various electrophiles, such as deuterium oxide, iodine, and allyl bromide, to give the corresponding tetrasubstituted alkenes stereoselectively. As for trapping **4a** with allyl bromide, the addition of a catalytic amount of CuCN•2LiCl improved the yield of the corresponding product **5c**. Alkenylzinc intermediate **4a** participated in Negishi coupling reactions.[13] The reactions with iodobenzene and 4-iodobenzonitrile afforded the corresponding diarylethene derivatives **5d** and **5e** stereoselectively.

Finally, we attempted to synthesize a synthetic estrogen, *meso*-hexestrol, and its derivative.[14] Treatment of 3-hexyne (**1j**) with 4-benzyloxyphenylzinc reagent **2i** yielded alkenylzinc intermediate **4b**. Negishi coupling reactions of **4b** proceeded smoothly to yield *cis*-stilbestrol derivatives **6a** and **6b**. Reduction of **6a** and **6b** under hydrogen in the presence of $Pd(OH)_2$/C afforded *meso*-hexestrol (**7a**)[15] and its derivative **7b**, respectively.

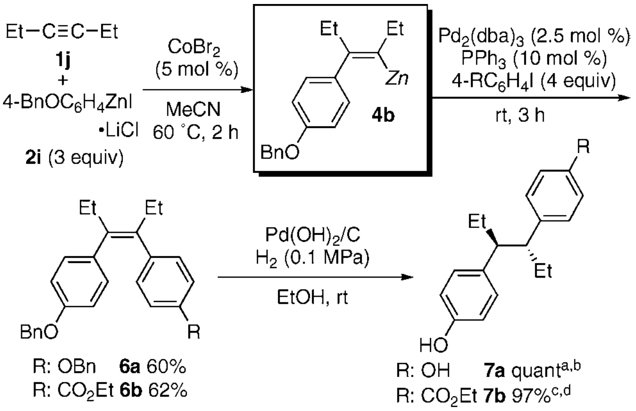
Scheme 1. Reactions of Alkenylzinc Intermediate **4a** with Various Electrophiles



D_2O	: **5a** 77%	(*E*/*Z* > 99/1) 92%D
I_2	: **5b** 60%	(*E*/*Z* < 1/99)
$CH_2{=}CHCH_2Br$	: **5c** 65%[a]	(*E*/*Z* < 1/99)
PhI	: **5d** 68%[b]	(*E*/*Z* < 1/99)
$4\text{-}IC_6H_4CN$	: **5e** 53%[b]	(*E*/*Z* < 1/99)

[a] 20 mol % of CuCN•2LiCl was added. [b] 2.5 mol % of $Pd_2(dba)_3$ and 10 mol % of P(*o*-tol)$_3$ were added.

Scheme 2. Diastereoselective Synthesis of *meso*-Hexestrol and Its Derivative



[a] Reaction was performed in the presence of 10 mol % of $Pd(OH)_2$/C for 4 h. [b] Contained 4% of diastereomer. [c] Reaction was performed in the presence of 100 mol % of $Pd(OH)_2$/C for 0.5 h. [d] Contained 5% of diastereomer.

In summary, the protocol described here provides a mild and efficient method for the preparation of multisubstituted alkenes. The application to the synthesis of *meso*-hexestrol and its derivative highlights the synthetic potential of this reaction.

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Supporting Information Available: Experimental details, characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Synthesis of *meso*-hexestrol: $CoBr_2$ (3.3 mg, 0.015 mmol) was placed in a 20-mL reaction flask under argon. 3-Hexyne (25 mg, 0.30 mmol) was added. Then, 4-benzyloxyphenylzinc iodide•lithium chloride complex in acetonitrile (0.90 mmol) was added. The mixture was stirred at 60 °C for 2 h. The mixture was cooled to 0 °C. A THF solution of 1-benzyloxy-4-iodobenzene (372 mg, 1.2 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), and PPh_3 (7.9 mg, 0.030 mmol) was added to the solution. The mixture was warmed to 25 °C and stirred for 3 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane/ethyl acetate (20/1) as an eluent afforded (*Z*)-3,4-bis(4-benzyloxyphenyl)-3-hexene contaminated with 4,4′-dibenzyloxybiphenyl. Further purification by GPC afforded pure (*Z*)-3,4-bis(4-benzyloxyphenyl)-3-hexene (81 mg, 0.18 mmol) in 60% yield. (*Z*)-3,4-Bis(4-benzyloxyphenyl)-3-hexene (111 mg, 0.25 mmol) was reduced under hydrogen (0.1 MPa) in the presence of $Pd(OH)_2$/C (20 wt % of Pd, 13 mg, 0.025 mmol) in ethanol (10 mL). The mixture was filtrated through a pad of Celite, and the filtrate was concentrated in vacuo. Chromatographic purification on silica gel by using hexane/ethyl acetate (5/1) as an eluent afforded *meso*-hexestrol (68 mg, 0.25 mmol) in quantitive yield (including 4% of diastereomer).