Cobalt-catalyzed cross-coupling of alkynyl Grignard reagents with alkenyl triflates†

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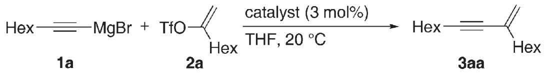
Alkenyl triflates in combination with Co(acac)$_3$ as a catalyst were found to be excellent coupling partners of alkynyl Grignard reagents, where no special additives (even a phosphine ligand) but a common solvent, THF, are required to obtain variously substituted enynes.

Conjugated enynes are important components of natural products and versatile precursors for synthesis of pharmaceuticals.[1] One of the most convenient methods to construct the enyne framework is the transition metal-catalyzed alkynyl–alkenyl coupling forming C(sp)–C(sp^2) bonds.[2] Among these, the coupling of terminal alkynes with alkenyl (pseudo)halides catalyzed by a palladium complex, often in combination with a copper catalyst, is the most widely used.[3] Alkynylmetals also work as coupling partners of alkenyl (pseudo)halides under palladium catalysis.[4] Recently, attempts to promote the coupling with a less expensive catalyst composed of a metal such as Ni[5] or Cu[6,7] also have attracted attention, but the scope of the substrates is rather limited. Here we report a practically useful and widely applicable method for the alkynyl–alkenyl coupling giving enynes, where only a readily available Co(acac)$_3$ and THF respectively as a catalyst and a solvent are required besides the combination of substrates consisting of alkynyl Grignard reagents and alkenyl triflates. This presents the first cobalt-catalyzed sp–sp^2 coupling.[8–10]

Table 1 Comparison of catalysts in the coupling of 1-octyn-1-ylmagnesium bromide with 1-octen-2-yl triflate[a]



Entry	Catalyst	Time/h	Conversion (%)[b]	Yield (%)[c]
1	Co(acac)$_3$	2	>99	98
2	Co(acac)$_2$	2	>99	98
3	Pd(acac)$_2$	2	<5	<5
4	Pd(PPh$_3$)$_4$	2	75	71
5	Pd(PPh$_3$)$_4$	4	>99	97
6	Ni(acac)$_2$	2	19	16
7	NiCl$_2$(PPh$_3$)$_2$	2	47	42
8	NiCl$_2$(PPh$_3$)$_2$	12	65	61
9	Fe(acac)$_3$	2	>99	29
10	Ru(acac)$_3$	2	>99	63

[a] The reaction was carried out in THF (1.0 mL) using **1a** (0.45 mmol) and **2a** (0.25 mmol) in the presence of a catalyst (7.5 μmol). [b] Estimated by ^{1}H NMR spectroscopy of the crude product. [c] Isolated yield based on **2a**.

The reaction of 1-octyn-1-ylmagnesium bromide (**1a**: 1.8 equiv.), generated *in situ* from 1-octyne and ethylmagnesium bromide, with 1-octen-2-yl triflate (**2a**: 1.0 equiv.) in the presence of Co(acac)$_3$ (3 mol%) in THF at 20 °C for 2 h gave 2-hexyl-1-decen-3-yne (**3aa**) in 98% yield (entry 1 of Table 1).[11] The corresponding cobalt(II) complex, Co(acac)$_2$, was equally effective (entry 2). Enyne **3aa** was not obtained at all with Pd(acac)$_2$ under the same conditions, whereas Pd(PPh$_3$)$_4$, which is a palladium–phosphine catalyst of common use for this type of coupling reaction, catalyzed the coupling, though in a reduced rate than Co(acac)$_3$ (entries 3–5).[12] In contrast, nickel complexes were not so effective, even with a phosphine ligand, giving **3aa** in only moderate yields (entries 6–8).[5b] The reaction with an acetylacetonate salt of iron or ruthenium gave **3aa** in a moderate yield (entries 9 and 10).

Co(acac)$_3$ as a catalyst was found to be applicable to various combinations of alkynylmagnesium bromides and alkenyl triflates (Table 2).‡ Besides α-substituted vinyl triflate **2a**, β-substituted **2b** coupled with octynyl Grignard reagent **1a** to give enyne **3ab** in a good yield (entries 1 and 2). Less reactive cyclic alkenyl triflates **2c**–**2g** with a 5- to 7-membered ring also underwent the coupling within 2 h by raising the temperature to 40 °C (entries 3–7). Even sterically demanding trisubstituted vinyl triflate **2h** participated in the coupling, albeit with a moderate yield (entry 8). Carbamate and alkene functionalities are compatible with the coupling (entries 9 and 10). Instead of volatile vinyl triflate, the corresponding nonaflate was used for vinylation of alkynyl Grignard reagent **1b** to give monosubstituted enyne **3bk** in a high yield (entry 11). The present coupling also shows a wide scope on alkynyl Grignard reagents. The reaction of non-substituted ethynylmagnesium bromide (**1c**) gave enyne **3cg** in a high yield despite **3cg** having a reactive acetylenic methyne proton (entry 12). Ethynyl Grignard reagents with a bulky aliphatic group (**1d**), an aryl group (**1e**) or a silyl group (**1f**) underwent the coupling in high yields (entries 13–17). The simplicity of the catalyst system, which does not even require ligands, enables us to conduct the coupling on a gram-scale with no problems. Thus, 1.0 g of triflate **2g** coupled with silylethynyl Grignard reagent **1f** in the presence of a reduced amount (1 mol%) of Co(acac)$_3$ to give enyne **3fg** in 95% yield (Scheme 1).

A marked preference of the catalyst system for alkenyl triflates was revealed by some competitive reactions with other electrophiles (Scheme 2). Thus, treatment of a 1 : 1 mixture of alkenyl triflate **2a** and 2-propenyl bromide with 1 equivalent of octynyl Grignard reagent **1a** gave predominantly the triflate-derived coupling product (**3aa**) in 89% selectivity. Strong preference for

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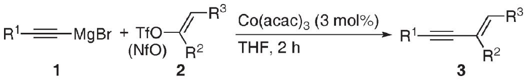
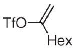
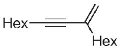
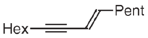
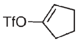
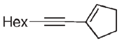
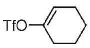
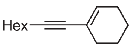
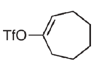
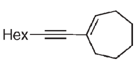
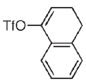
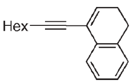
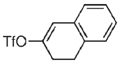
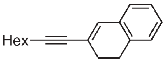
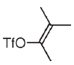
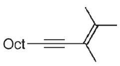
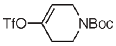
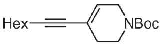
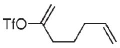
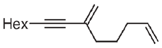
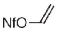
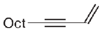
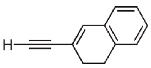
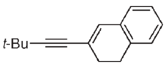
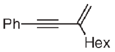
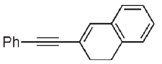
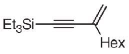
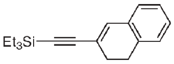
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b711884h

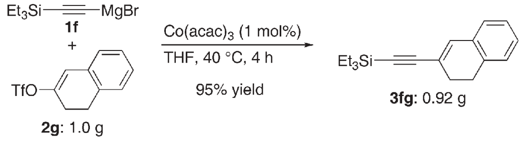
Table 2 Cobalt-catalyzed coupling of alkynyl Grignard reagents with alkenyl triflates[a]



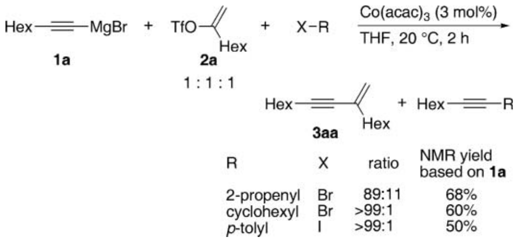
Entry	R^1	**2**		T/°C	Product **3**		Yield (%)[b]
1	Hex (**1a**)	**2a**		20	**3aa**		98
2	Hex (**1a**)	**2b**		20	**3ab**		81
3	Hex (**1a**)	**2c**		40	**3ac**		85
4	Hex (**1a**)	**2d**		40	**3ad**		64
5	Hex (**1a**)	**2e**		40	**3ae**		97
6	Hex (**1a**)	**2f**		40	**3af**		94
7	Hex (**1a**)	**2g**		40	**3ag**		92
8[c]	Oct (**1b**)	**2h**		60	**3bh**		52
9	Hex (**1a**)	**2i**		40	**3ai**		69
10	Hex (**1a**)	**2j**		20	**3aj**		73
11	Oct (**1b**)	**2k**		20	**3bk**		88
12	H (**1c**)	**2g**		40	**3cg**		86
13	*t*-Bu (**1d**)	**2g**		40	**3dg**		85
14	Ph (**1e**)	**2a**		20	**3ea**		82
15	Ph (**1e**)	**2g**		40	**3eg**		98
16	Et_3Si (**1f**)	**2a**		20	**3fa**		95
17	Et_3Si (**1f**)	**2g**		40	**3fg**		93

[a] The reaction was carried out in THF (1.0 mL) using an alkynylmagnesium bromide (**1**: 0.45 mmol) and an alkenyl triflate (**2**: 0.25 mmol) in the presence of $Co(acac)_3$ (7.5 μmol). [b] Isolated yield based on **2**. [c] Reaction time = 6 h.

alkenyl triflates was observed also in the competitive reaction with cyclohexyl bromide or *p*-tolyl iodide, where the halide-derived coupling product was not detected at all. The much higher reactivity of the triflate than the alkyl bromide observed here is worthy of note as secondary alkyl bromides are known to be excellent electrophiles in cobalt-catalyzed cross-coupling reactions.[8d,f,10b–d,f–h] The preference of the $Co(acac)_3$ catalyst was utilized for a sequential coupling of alkenyl triflate and aryl bromide moieties in **2l** with alkynyl nucleophiles (Scheme 3). Thus, the cobalt-catalyzed coupling of alkynyl Grignard reagent **1a** with the alkenyl triflate gave enyne **3al** with the intact aryl bromide moiety, which underwent the Sonogashira coupling catalyzed by palladium–copper to give bisalkynylated product **4**.

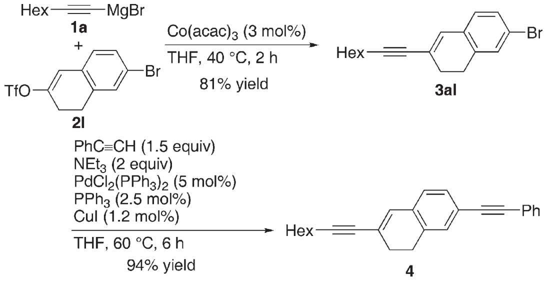


Scheme 1



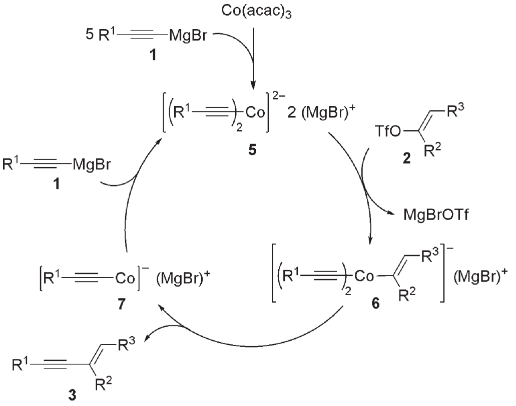
R	X	ratio	NMR yield based on **1a**
2-propenyl	Br	89:11	68%
cyclohexyl	Br	>99:1	60%
p-tolyl	I	>99:1	50%

Scheme 2

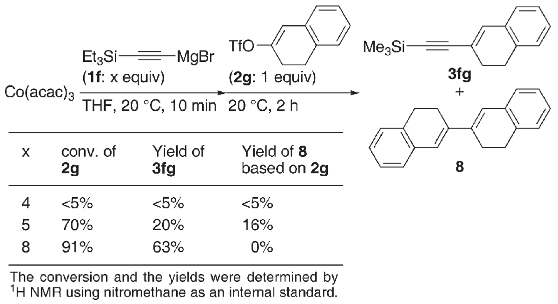


Scheme 3

A plausible catalytic cycle based on that proposed by Oshima and co-workers for the cobalt-catalyzed cyclization–cross-coupling reaction of aryl Grignard reagents with haloalkenes is shown in Scheme 4.[10b,h] $Co(acac)_3$ is first reduced to a cobalt(0) complex by 3 equivalents of alkynyl Grignard reagent **1**, which further accepts the attack of 2 equivalents of **1** to form bisalkynyl di-ate complex **5**. Oxidative addition of alkenyl triflate **2** to **5** gives mono-ate cobalt(II) complex **6**, which undergoes reductive elimination to give enyne **3** and monoalkynyl ate complex **7**. Finally, the reaction of **7** with **1** regenerates di-ate complex **5**. Stoichiometric reactions



Scheme 4



x	conv. of **2g**	Yield of **3fg**	Yield of **8** based on **2g**
4	<5%	<5%	<5%
5	70%	20%	16%
8	91%	63%	0%

The conversion and the yields were determined by ^{1}H NMR using nitromethane as an internal standard.

Scheme 5

shown in Scheme 5 similar to those conducted by Oshima and co-workers gave a result consistent with the plausible catalytic cycle.[10b,h] Thus, alkenyl triflate **2g** was not consumed at all on treatment with 1 equivalent of the cobalt complex generated from Co(acac)$_3$ and 4 equivalents of triethylsilylethynylmagnesium bromide (**1f**).[13] In contrast, 70% of **2g** was consumed with the use of one more equivalent (total 5 equiv.) of **1f**, giving a considerable amount of the corresponding cross-coupling product (**3fg**) and the reductive homocoupling product (**8**) of triflate **2g**. Coproduction of **8** was completely suppressed by use of an excess amount (8 equiv.) of **1f**. The observation that 4 equivalents of **1f** was consumed to transform the precursor to some complex, which is not yet reactive towards **2g**, and that the addition of another equivalent of **1f** converted it into an active species that reacts with **2g** implies that Grignard reagents first get into the catalytic cycle and then alkenyl triflates follow as shown in Scheme 4. There is some possibility that oxidative addition of **2** to **5** proceeds through two successive single electron transfers, as in the case with alkyl halides,[10b,h] but Oshima and co-workers proposed a non-radical oxidative addition mechanism for alkenyl iodides in the cobalt-catalyzed coupling with trimethylsilylmethylmagnesium chloride.[8d]

In conclusion, we have developed a simple, inexpensive and widely applicable catalyst system for alkynyl–alkenyl coupling, where alkynyl Grignard reagents undergo coupling with alkenyl triflates in the presence of a catalytic amount of Co(acac)$_3$ in THF.

Notes and references

‡ General procedure for the cobalt-catalyzed coupling of alkynylmagnesium bromides with alkenyl triflates: to an alkyne (0.50 mmol) placed in a 20 mL Schlenk tube was added ethylmagnesium bromide (*ca.* 1.0 M THF solution, 0.45 mmol) at room temperature, and it was stirred for 30 min. To the mixture was added THF (0.50 mL), Co(acac)$_3$ (2.7 mg, 7.5 μmol) and an alkenyl triflate (0.25 mmol). After stirring at the temperature for the time both specified in Table 2, a 0.1 M HCl aqueous solution (10 mL) was added and the resulting mixture was extracted with diethyl ether (10 mL × 3). The combined organic layer was washed with brine (10 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by purification with PTLC or column chromatography (SiO$_2$) gave the corresponding enyne.

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7 Terminal alkynes couple with alkenyl iodides in the presence of a Ni–Cu catalyst. See: (*a*) L. Wang, P. Li and Y. Zhang, *Chem. Commun.*, 2004, 514–515; (*b*) M. Wang, P. Li and L. Wang, *Synth. Commun.*, 2004, **34**, 2803–2812.

8 For examples of the use of alkenyl halides in cobalt-catalyzed cross-coupling reactions, see: (*a*) G. Cahiez and H. Avedissian, *Tetrahedron Lett.*, 1998, **39**, 6159–6162; (*b*) H. Avedissian, L. Bérillon, G. Cahiez and P. Knochel, *Tetrahedron Lett.*, 1998, **39**, 6163–6166; (*c*) T. Kamachi, A. Kuno, C. Matsuno and S. Okamoto, *Tetrahedron Lett.*, 2004, **45**, 4677–4679; (*d*) W. Affo, H. Ohmiya, T. Fujioka, Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, Y. Imamura, T. Mizuta and K. Miyoshi, *J. Am. Chem. Soc.*, 2006, **128**, 8068–8077. For examples of the use of alkynyl Grignard reagents in cobalt-catalyzed cross-coupling reactions, see: (*e*) A. Kuno, N. Saino, T. Kamachi and S. Okamoto, *Tetrahedron Lett.*, 2006, **47**, 2591–2594; (*f*) H. Ohmiya, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2006, **8**, 3093–3096.

9 Electrophiles with an oxygen leaving group are used in cobalt-catalyzed cross-coupling reactions. For allyl methoxides, see: (*a*) K. Mizutani, H. Yorimitsu and K. Oshima, *Chem. Lett.*, 2004, **33**, 832–833; (*b*) H. Yasui, K. Mizutani, H. Yorimitsu and K. Oshima, *Tetrahedron*, 2006, **62**, 1410–1415. For *ortho*-acylphenyl tosylates, see: (*c*) T. J. Korn, M. A. Schade, S. Wirth and P. Knochel, *Org. Lett.*, 2006, **8**, 725–728.

10 Recently the cobalt-catalyzed cross-coupling reaction of Grignard reagents has been extensively investigated, in particular, by Oshima and co-workers. For examples not cited in ref. 8 and 9, see: (*a*) Y. Nishii, K. Wakasugi and Y. Tanabe, *Synlett*, 1998, 67–69; (*b*) K. Wakabayashi, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2001, **123**, 5374–5375; (*c*) T. Tsuji, H. Yorimitsu and K. Oshima, *Angew. Chem.*, 2002, **114**, 4311–4313, (*Angew. Chem., Int. Ed.*, 2002, **41**, 4137–4139); (*d*) K. Mizutani, H. Shinokubo and K. Oshima, *Org. Lett.*, 2003, **5**, 3959–3961; (*e*) T. J. Korn, G. Cahiez and P. Knochel, *Synlett*, 2003, 1892–1894; (*f*) H. Ohmiya, T. Tsuji, H. Yorimitsu and K. Oshima, *Chem.–Eur. J.*, 2004, **10**, 5640–5648; (*g*) H. Ohmiya, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2006, **128**, 1886–1889; (*h*) H. Ohmiya, K. Wakabayashi, H. Yorimitsu and K. Oshima, *Tetrahedron*, 2006, **62**, 2207–2213.

11 In this coupling reaction, an excess amount of alkynyl Grignard reagent is required for complete consumption of alkenyl triflates. A considerable amount of RC≡CMgBr was found to be transformed to RC≡CC≡CR as well as some oligomers and polymers. For details, see ESI.†

12 H. P. Dang and G. Linstrumelle, *Tetrahedron Lett.*, 1978, **19**, 191–194. See also ref. 2.

13 In the ^{1}H NMR spectrum of each entry of Scheme 5, small peaks of 1,4-bis(triethylsilyl)-1,3-butadiyne were observed amongst a much higher amount of broadened peaks corresponding to the Et$_3$Si groups of some polymeric compounds. It is likely that the diyne was produced during the reduction of the cobalt(III) complex but was too unstable under the reaction conditions to undergo polymerization.