Homogeneous Catalysis

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Cobalt-Catalyzed Alkenylzincation of Unfunctionalized Alkynes

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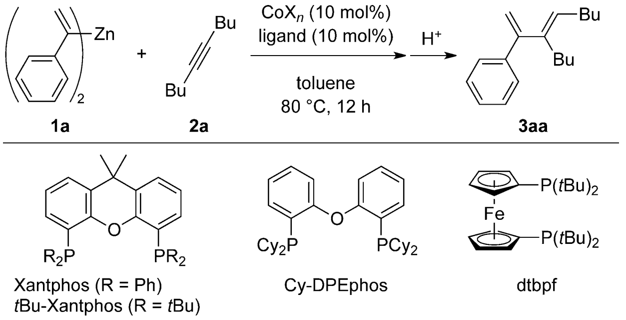
Abstract: *While transition metal catalyzed addition reactions of arylmetal reagents to unfunctionalized alkynes have been extensively developed in the last decade, analogous reactions using alkenylmetal reagents remain rare regardless of their potential utility for the synthesis of unsymmetrical 1,3-dienes. Reported herein is the development of a cobalt/diphosphine catalyst which promotes efficient and stereoselective addition of alkenylzinc reagents to unfunctionalized internal alkynes. The resulting dienylzinc species serve as versatile intermediates for further synthetic transformations.*

The addition of organometallic reagents to alkynes, combined with electrophilic trapping of the resulting alkenylmetal species, offers a useful method for the stereocontrolled synthesis of multisubstituted alkenes.[1] Among such carbometalation reactions, the reaction of arylmetal reagents with unfunctionalized alkynes has gained particular attention as a fundamentally challenging transformation, as well as an attractive route to pharmaceutically relevant olefins such as tamoxifen and its analogues.[2,3] Over the last decades, nickel,[2a–c,4] manganese,[5] iron,[6] chromium,[7] and cobalt[8] catalysts have been developed for arylmetalation of alkynes, including dialkylacetylenes, using arylmagnesium, arylzinc, or aryllithium reagents.[9] The success of these reactions may be partly attributed to the reluctance of the product, that is, alkenylmetal species, to undergo further addition to the alkyne, and in turn implies a difficulty in achieving efficient addition of preformed alkenylmetal reagents to unfunctionalized alkynes. The difficulty of alkenylmetalation is also expected from the apparent similarity of the starting alkenylmetal reagent and the resulting dienylmetal species, which potentially causes oligomerization reactions. In fact, the addition of alkenylmetal reagents to unfunctionalized alkynes has rarely been achieved[6c,10–12] regardless of its potential utility for the regio- and stereoselective synthesis of multisubstituted 1,3-dienes. Herein we report that such alkenylmetalation can be achieved by the combination of a cobalt/diphosphine catalyst and an alkenylzinc reagent. The reaction allows facile preparation of synthetically versatile unsymmetrical 1,3-diene building blocks.[13]

Recently, our group developed cobalt/diphosphine-catalyzed addition reactions of arylzinc reagents to unfunctionalized internal alkynes and norbornene derivatives involving 1,4-cobalt migration.[14] These previous studies prompted us to explore the ability of a cobalt/diphosphine complex to catalyze the addition of alkenylzinc reagents to alkynes as well as to participate in 1,4-cobalt migration in such systems. The exploration commenced with a screening of cobalt sources and ligands for the addition of the di(α-styryl)zinc reagent **1a** (prepared from 1.2 equiv of $ZnCl_2$·TMEDA and 2.4 equiv of α-styrylmagnesium bromide) to 5-decyne (**2a**) in toluene at 80 °C (Table 1). When using $CoCl_2$ (10 mol%) alone, the reaction afforded, upon protonation, the desired 1,3-diene **3aa** in a modest yield of 30% (entry 1). Whereas the addition of Xantphos as a supporting ligand did not have an apparent effect on the catalytic activity (entry 2), a bulky and electron-rich analogue of Xantphos, *t*Bu-Xantphos, gave rise to a noticeable improvement in the yield of **3aa** (entry 3). Other diphosphine ligands bearing bulky dialkylphosphino groups did not show positive effects (entries 4 and 5), and typical N-heterocyclic carbene ligands (e.g., IMes, IPr) were much less effective (< 10% yield; data not shown). Subsequent screening using *t*Bu-Xantphos as the ligand revealed

Table 1: Addition of the α-styrylzinc reagent **1a** to 4-cctyne (**2a**).[a]



Entry	CoX_n	Ligand	Yield [%][b]
1	$CoCl_2$	None	30
2	$CoCl_2$	Xantphos	33
3	$CoCl_2$	*t*BuXantphos	43
4	$CoCl_2$	Cy-DPEphos	21
5	$CoCl_2$	dtbpf	27
6	CoF_2	*t*Bu-Xantphos	83[c]
7	$CoBr_2$	*t*Bu-Xantphos	45
8	CoI_2	*t*Bu-Xantphos	0
9	$Co(OAc)_2$	*t*Bu-Xantphos	71
10	CoF_2	none	50
11[d]	CoF_2	*t*BuXantphos	19

[a] Unless otherwise noted, the reaction was performed using **1a** (prepared from 0.3 mmol of $ZnCl_2$·TMEDA and 0.6 mmol of α-styrylmagnesium bromide, 1.2 equiv), **2a** (0.25 mmol), CoX_n (10 mol%), ligand (10 mol%) in toluene. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Yield of isolated product. [d] THF was used as the solvent. THF = tetrahyrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

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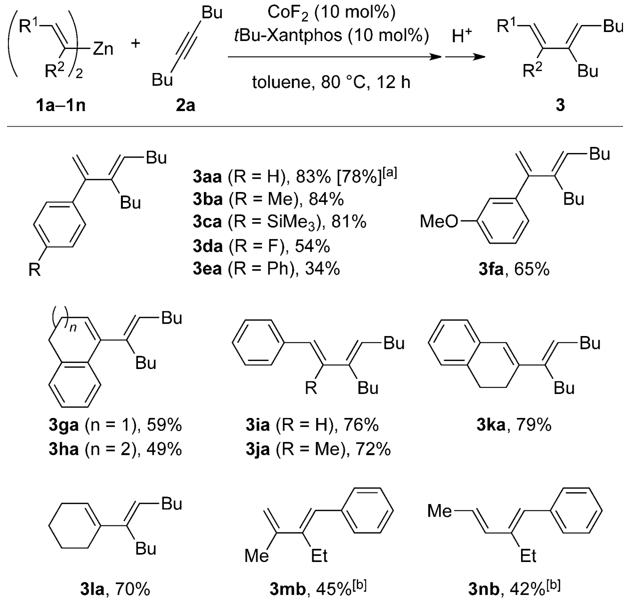
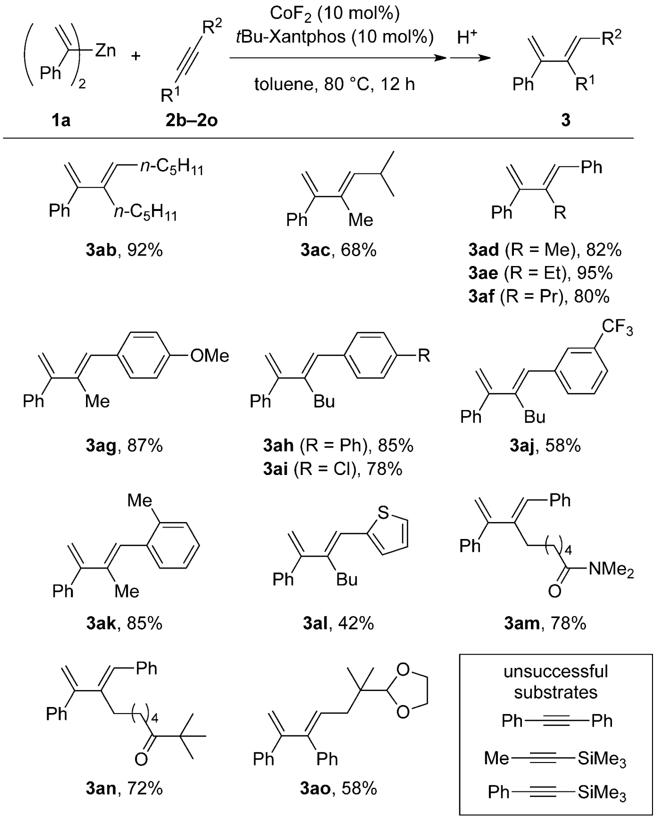
a significant influence of the cobalt precatalyst on the catalytic activity (entries 6–9). The use of CoF_2 instead of $CoCl_2$ improved the yield of **3aa** to 83 % (entry 6), while the reaction was completely shut down using CoI_2 as the precatalyst (entry 8). A control experiment using CoF_2 alone also showed the superiority of CoF_2 over $CoCl_2$ (entry 1 versus entry 10), as well as the positive influence of *t*Bu-Xantphos (entry 6 versus entry 10). The use of THF as the solvent resulted in a drastic decrease in the yield of **3aa** (entry 11). Note that the reaction using a mono(α-styryl)zinc reagent or α-styrylmagnesium bromide instead of **1a** did not give any trace of **3aa**.[15]

With the CoF_2/*t*Bu-Xantphos catalyst system in hand, we explored the reaction of various alkenylzinc reagents with **2a** (Scheme 1). α-Styrylzinc reagents bearing various *para* and *meta* substituents afforded the desired 1,3-dienes **3aa–fa** in moderate to good yields with exclusive *syn* stereoselectivity, while the one bearing an *ortho*-methyl group failed to undergo the addition reaction. The reaction of **1a** and **2a** could be performed on a 5 mmol scale without significant decrease in the yield of **3aa**. β-Substituted α-styrylzinc reagents such as (3,4-dihydronaphthalen-1-yl)zinc and (6,7-dihydro-5*H*-benzo[7]annulen-9-yl)zinc reagents participated in the reaction to afford the 1,2,3,4-tetrasubstituted 1,3-dienes **3ga** and **3ha**, respectively, in moderate yields. The cobalt catalyst also promoted the addition of β-styrylzinc reagents to **2a**, thus affording the desired tri- or tetrasubstituted dienes **3ia–ka** in good yields. Alkenylzinc reagents without aryl groups, such as cyclohexen-1-ylzinc, propen-2-ylzinc, and propen-1-ylzinc reagents, were also amenable to the present carbozincation reaction (**3la**, **3mb**, and **3nb**).



Scheme 1. Scope with respect to the alkenylzinc reagents. The reaction was performed according to the reaction conditions detailed in entry 6 of Table 1, using an alkenylzinc reagent prepared from a 1:2 mixture of $ZnCl_2$·TMEDA and the corresponding alkenylmagnesium bromide. [a] Yield for a 5 mmol reaction is shown in the brackets. [b] 1-Phenyl-1-butyne was used as the alkyne.

We next explored the reactivity of a series of unfunctionalized internal alkynes using **1a** as the reaction partner (Scheme 2). Not unexpectedly, **1a** and 6-dodecyne (**2b**) reacted smoothly to afford the desired product **3ab** in a good yield. The reaction of **1a** with an unsymmetrical dialkylalkyne, 4-methylpent-2-yne (**2c**), afforded the 1,3-diene **3ac** as a single regio- and stereoisomer, wherein the C–C bond formation took place at the less hindered acetylenic carbon atom. This result is in a sharp contrast to the poor regioselectivities in the cobalt-catalyzed addition of arylzinc reagents to **2c**,[8b,14a] whereas the same sense of regioselectivity was observed in a few examples of other transition metal catalyzed arylmetalations.[6c,7] We speculate that the steric hindrance around the α-carbon atom of **1a** outweighed the hindrance around the cobalt center, thus resulting in the observed regioselectivity. Besides the dialkylalkynes, a variety of aryl(alkyl)alkynes participated in the reaction with **1a** to regio- and stereoselectively afford the products **3ad–ao** in moderate to good yields with a tolerance for functional groups such as chloro (**3ai**), amide (**3am**), and ketone (**3an**) moieties. Following the typical regioselectivity in carbometalation of aryl(alkyl)alkynes,[1] these reactions resulted in C–C bond formation at the acetylenic carbon atom bonded to the alkyl group, except that an acetal-appended C3 alkyl chain caused the opposite regioselectivity, presumably through coordination of the oxygen atom to the cobalt center

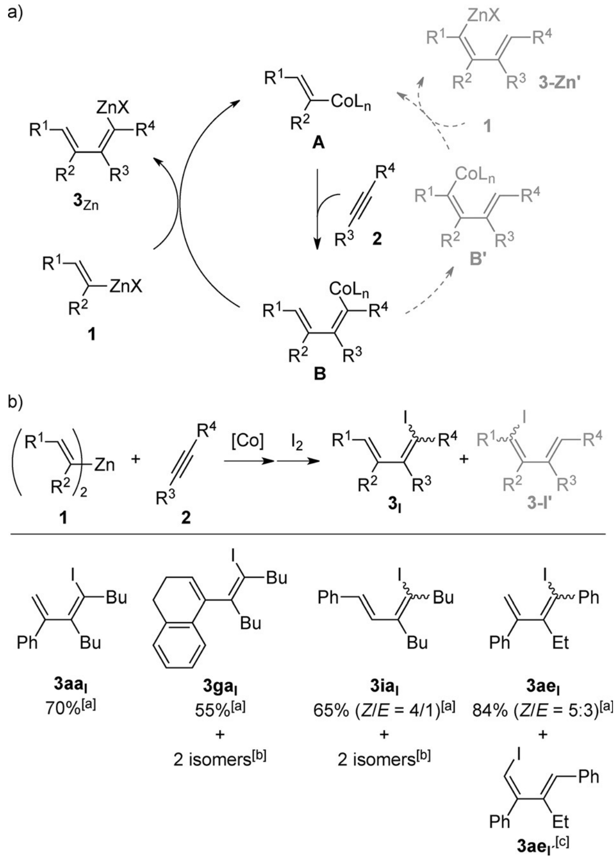


Scheme 2. Scope with respect to the alkynes. The reaction was performed according to the reaction conditions detailed in entry 6 of Table 1.

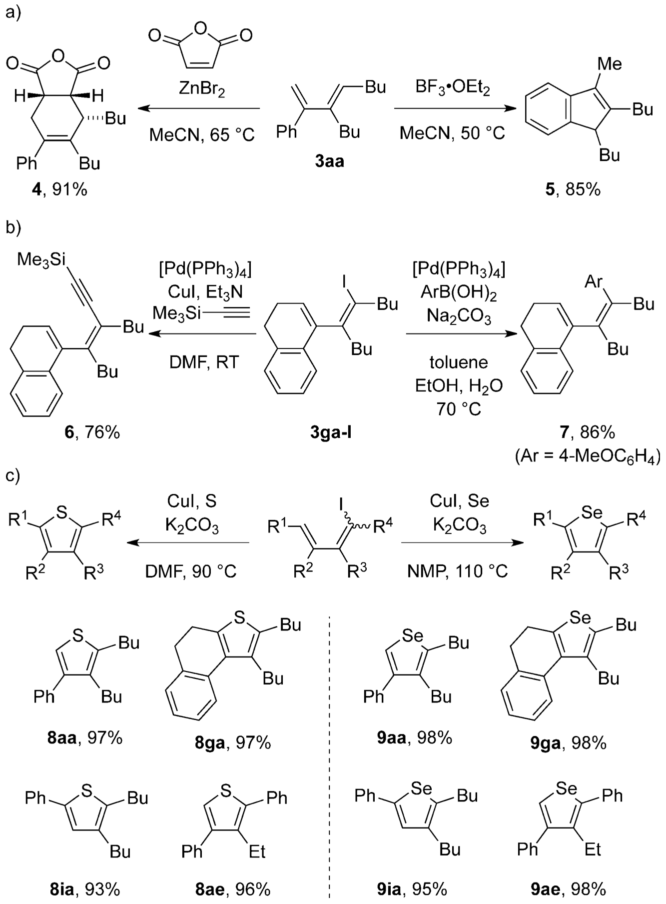
(see **3ao**).[16] Unfortunately, the present catalytic system was not effective for some nonpolar alkynes such as diphenylacetylene (< 10% GC yield), 1-trimethylsilylprop-1-yne (no adduct detected), and 1-trimethylsilyl-2-phenylacetylene (< 15% GC yield, mixture of regio/stereoisomers). Also, terminal alkynes such as phenylacetylene and 1-octyne failed to give the desired adducts.

The present addition reaction is considered to proceed through insertion of the alkyne into an alkenylcobalt species **A** followed by transmetalation of the resulting dienylcobalt species **B** and the alkenylzinc reagent **1** to afford a dienylzinc species $\mathbf{3_{Zn}}$ while regenerating the alkenylcobalt species **A** (Scheme 3a). Given our previous studies on arylzincation involving 1,4-cobalt migration,[14] the dienylcobalt species **B** may potentially rearrange to a regioisomeric dienylcobalt species **B′**, thus giving rise to a regioisomeric dienylzinc species $\mathbf{3_{Zn'}}$. To confirm the formation of $\mathbf{3_{Zn}}$ as well as to probe the possibility of 1,4-cobalt migration, we performed iodinative quenching of the reactions of selected alkenylzinc reagents and alkynes (Scheme 3b). The reaction of **1a** with **2a**, upon quenching with I_2, afforded the regio- and stereochemically pure 1-iodo-1,3-diene $\mathbf{3aa_I}$ in 70% yield without detectable amounts of other isomers. In contrast, the reaction of the (3,4-dihydronaphthalen-1-yl)zinc reagent **1g** and **2a** produced three isomers in a ratio of 100:16:6 (judged from GCMS analysis of the crude reaction mixture), where the major isomer was isolated and identified as the expected iododiene $\mathbf{3ga_I}$. Likewise, β-styrylzinc reagent **1i** and **2a** gave rise to four isomers (ratio = 100:39:4:3), among which the two major isomers were isolated and identified as *Z*/*E* isomers (4:1) of the expected iododiene $\mathbf{3ia_I}$. We speculate that some of the unknown minor isomer(s) detected in these reactions correspond to regioisomeric iododienes such $\mathbf{3_{I'}}$ arising from 1,4-cobalt migration. However, further characterization was not possible because of their limited quantities. The reaction of **1a** and 1-phenyl-1-butyne (**2e**) afforded three isomers (ratio = 100:66:24), where the two major isomers were isolated and identified as *Z*/*E* isomers (5:3) of the expected iododiene $\mathbf{3ae_I}$. ^{1}H NMR spectra of $\mathbf{3ae_I}$ and the original product mixture suggested that the minor isomer corresponds to a regioisomeric iododiene $\mathbf{3ae_{I'}}$. Collectively, these iodination experiments show that dienylcobalt species may undergo 1,4-cobalt migration depending on the substituents, but only to a small extent. Note also that the alkenylzincation/iodination reactions could be performed on 5 mmol scale in comparable yields (see the Supporting Information), thus readily providing sufficient amounts of the iododienes for further transformations (see below).

1,3-Dienes and 1-iodo-1,3-dienes prepared by the present alkenylzincation reaction serve as versatile starting materials for further synthetic transformations (Scheme 4). Diels–Alder reaction of **3aa** with maleic anhydride proceeded



Scheme 3. a) Proposed catalytic cycle. b) Alkenylzincation quenched with I_2. [a] Yield and/or stereoselectivity of the isolated products (0.25 mmol scale). [b] Detected by GCMS analysis. [c] Detected and assigned by GCMS and ^{1}H NMR analysis.



Scheme 4. Transformations of 1,3-dienes and 1-iodo-1,3-dienes. DMF = N,N-dimethylformamide, NMP = *N*-methylpyrrolidone.

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smoothly in the presence of catalytic $ZnBr_2$ (20 mol%) to afford a bicyclic product **4** in a good yield, while exposure of **3aa** alone to $BF_3{\cdot}OEt_2$ (20 mol%) caused intramolecular Friedel–Crafts reaction to furnish an indene derivative **5** (Scheme 4a). Besides standard palladium-catalyzed cross-coupling reactions such as Sonogashira and Suzuki–Miyaura couplings (Scheme 4b), 1-iodo-1,3-dienes proved to be applicable to copper-catalyzed chalcogenative cyclization with either elemental sulfur or selenium,[17] thus affording the corresponding thiophenes **8** and selenophenes **9**, respectively, in excellent yields (Scheme 4c). It is worth noting that even the stereochemically impure iododienes **3ia**$_{\mathbf{I}}$ and **3ae**$_{\mathbf{I}}$ (see Scheme 3) were near quantitatively converted into the corresponding chalcogenophene products.

In summary, we have developed a CoF_2/*t*Bu-Xantphos catalytic system for the addition reaction of an alkenylzinc reagent to an unactivated internal alkyne. The reaction allows regio- and stereocontrolled synthesis of unsymmetrical multisubstituted 1,3-dienes, which may be used as versatile synthetic intermediates. Further synthetic exploration of the present alkenylzincation is currently underway. Mechanistic aspects of the reaction, including the positive influence of the CoF_2 precatalyst,[18] also deserve further investigation.

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