Cobalt-catalyzed regio- and stereoselective intermolecular enyne coupling: an efficient route to 1,3-diene derivatives†

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The reaction of alkynes with vinyl arenes or vinyl trimethyl silane in the presence of a cobalt(II) complex, Zn and ZnI_2 in CH_2Cl_2 at rt to 50 °C provides 1,3-dienes in good to excellent yields.

Transition metal-catalyzed coupling of alkenes and alkynes has become a prevailing method for the construction of C–C bonds in organic synthesis. These enyne coupling reactions provide an efficient way of synthesizing substituted alkenes[1] and dienes[2] in a highly regio- and stereoselective manner. Of these coupling reactions, the ene type coupling can give either 1,3- or 1,4-dienes depending on the substrates and the catalytic conditions used.[2] Despite various transition metal complexes, including Ru, Rh, Pd, Co, Ni–Cr, Ti and Ir, being known to catalyze the intramolecular ene type reactions,[2,3] only few of them have been used in the intermolecular version. In 1991, Mitsudo *et al.* reported a ruthenium-catalyzed intermolecular co-dimerization of electron-rich alkynes with α,β-unsaturated alkenes to give 1,3-dienes.[4] Trost's group studied extensively the intermolecular Alder-ene reaction of alkynes with alkenes for the synthesis of 1,4-dienes using ruthenium complexes as catalysts.[5] Later, Ito and his co-workers reported a ruthenium-catalyzed 1,3-diene synthesis from terminal alkynes and alkenes *via* mechanistically different vinylidene ruthenium complexes as the intermediates.[6] Recently Hilt and Treutwein demonstrated a cobalt-catalyzed intermolecular Alder-ene type reaction of alkynes with unactivated terminal alkenes with allylic hydrogen atoms to afford 1,4-dienes,[7] while Tanaka *et al.* reported a rhodium-catalyzed coupling of electron-deficient alkynes and α,β-unsaturated alkenes to give 1,3-dienes.[8]

We have been involved in the coupling reactions of two different π-components,[1,9] particularly using cobalt complexes as the catalysts.[1c] In view of the catalytic ability of cobalt complexes in the reaction of alkynes with α,β-unsaturated alkenes to give reductive coupling products by us[1d,e] and with unactivated terminal alkenes with allylic hydrogen atoms to afford 1,4-dienes by Hilt and Treutwein,[7] it should be interesting to explore the possibility of a cobalt-catalyzed enyne coupling that can give 1,3-dienes. Herein, we wish to report that cobalt complexes regio- and stereoselectively catalyze the intermolecular coupling of alkynes with styrenes to afford substituted 1,3-dienes.[10] It is known that 1,3-dienes are valuable intermediates in organic synthesis,[11] most notably in Diels–Alder reactions.

On treatment of styrene **2a** with diphenylacetylene **1a** in the presence of CoI_2 (5 mol%), dppp (5 mol%), Zn (20 mol%) and ZnI_2 (20 mol%) in dichloromethane (DCM) as solvent at rt for 24 h, enyne coupling product **3a** was obtained in 97% yield. Control experiments revealed that the reaction did not proceed in the absence of either CoI_2/dppp or Zn and ZnI_2.[12] The 1,3-diene product **3a** was obtained highly stereo- and regioselectively, with the two phenyl groups of the diphenylacetylene moiety *cis* to each other and the double bond attaching to the styryl group exclusively in the *E* form. Moreover, the carbon–carbon bond formed in the product is between the methylene carbon of styrene and an alkyne carbon. Solvents play a major role in this reaction: CH_3CN, DMF and THF were totally inactive whereas toluene, DCE and DCM were effective, affording product **3a** in 18, 73 and 97% yields, respectively. Based on these solvent studies, it appears that the reaction requires a polar but less coordinating solvent which can dissolve the cobalt complex and ZnI_2 but which does not compete strongly with **1a** and **2a** for coordination to the cobalt metal center.[13]

To explore the scope of the reaction, the coupling of various substituted styrenes with diphenylacetylene **1a** was investigated. Thus, treating 4-bromo- and 3-chloro-substituted styrenes, **2b–c** with **1a** under the standard conditions (see Table 1, footnote a) furnished **3b–c** in 92 and 94% yields, respectively (entries 2 and 3). The reaction of vinyl silane **2d** with **1a** gave **3d** in 64% yield (entry 4). The extension of enyne coupling to 3-methoxy and 3-formyl substituted styrenes, **2e–f**, with **1a** were also successful, affording products **3e–f** in 88 and 85% yields, respectively (entries 5 and 6).

The present catalytic reaction can also be applied to a variety of unsymmetrical internal alkynes. When methylphenylacetylene **1b** was treated with styrene (**2a**), two regioisomeric dienes **3g/3g′** were obtained with a regioisomeric ratio of 90 : 10 in 91% combined yield (entry 7). Similarly, the reaction of **1b** with 4-bromostyrene (**2b**) afforded **3h/3h′** also with a regioisomeric ratio of 90 : 10 in 95% combined yield (entry 8). Likewise, ethyl- and *n*-butylphenylacetylene, **1c** and **1d**, respectively, coupled with **2a** to provide products **3i** and **3j** in 90 and 97% yield (entries 9 and 10). Arylhexyne, **1e**, with an electron withdrawing 4-acetyl substituent also underwent coupling reaction with **2a** to give **3k** in 90% yield (entry 11). It should be noted that products **3i** and **3k** were obtained in a completely regioselective fashion but the *E* : *Z* ratios of the styrene double bond were 91 : 9 and 88 : 12, respectively, whereas complete regio- and stereoselectivity was found for product **3j**. Heteroaromatic unsymmetrical alkyne, 3-(1-pentynyl)-thiophene (**1f**) also successfully participated in the coupling with **2a** to afford **3l** in 75% yield (entry 12). In addition, alkyne

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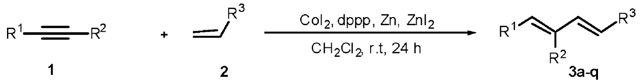
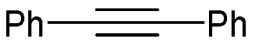
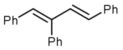
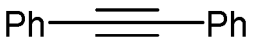
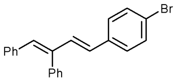
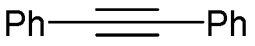
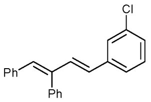
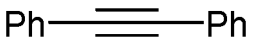
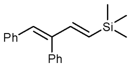
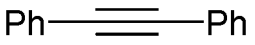
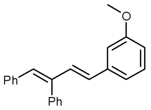
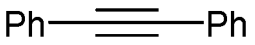
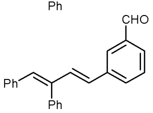
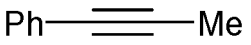
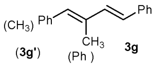
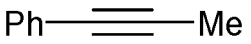
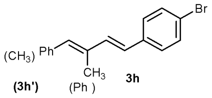
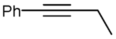
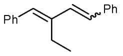
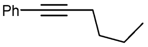
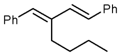
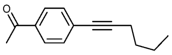
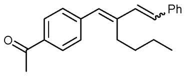
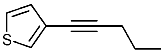
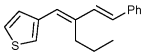
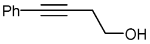
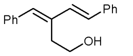
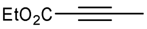
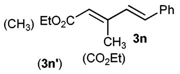
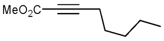
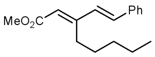
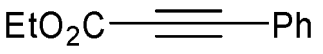
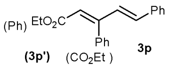
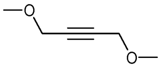
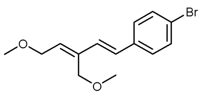
† Electronic supplementary information (ESI) available: General experimental procedure, spectral data (^{1}H, ^{13}C NMR and HRMS) and copies of ^{1}H and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/b920071a

Table 1 Results of the coupling of alkynes **1** and alkenes **2**[a]

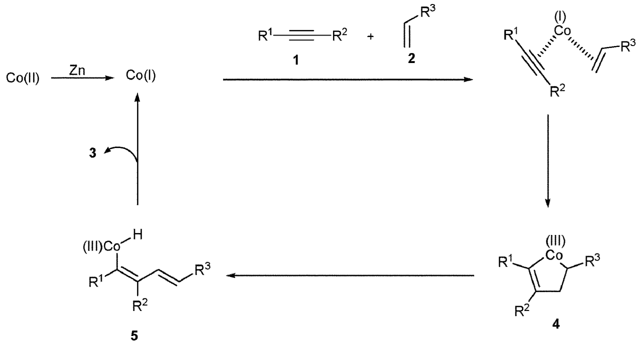


1a: $R^1 = R^2 = Ph$
1b: $R^1 = Ph, R^2 = CH_3$
1c: $R^1 = Ph, R^2 = C_2H_5$
1d: $R^1 = Ph, R^2 = -(CH_2)_3CH_3$
1e: $R^1 = 4\text{-}CH_3COC_6H_5$ $R^2 = -(CH_2)_3CH_3$
1f: $R^1 = 3\text{-thienyl}, R^2 = -(CH_2)_2CH_3$
1g: $R^1 = Ph, R^2 = (CH_2)_2OH$
1h: $R^1 = CO_2Et, R^2 = CH_3$
1i: $R^1 = CO_2Me, R^2 = -(CH_2)_4CH_3$
1j: $R^1 = CO_2Et, R^2 = Ph$
1k: $R^1 = R^2 = CH_2OCH_3$

2a: $R^3 = C_6H_5$
2b: $R^3 = 4\text{-Br-}C_6H_5$
2c: $R^3 = 3\text{-Cl-}C_6H_5$
2d: $R^3 = \text{-Si(Me)}_3$
2e: $R^3 = 3\text{-OMe-}C_6H_5$
2f: $R^3 = 3\text{-CHO-}C_6H_5$

Entry	1		2	Product 3		Yield (%)[b]
1		**1a**	**2a**		**3a**	97 (99)
2		**1a**	**2b**		**3b**	92
3		**1a**	**2c**		**3c**	94
4		**1a**	**2d**		**3d**	64[c]
5		**1a**	**2e**		**3e**	88
6		**1a**	**2f**		**3f**	85
7		**1b**	**2a**		**3g (3g′)**	91 (90 : 10)[d]
8		**1b**	**2b**		**3h (3h′)**	95 (90 : 10)[d]
9		**1c**	**2a**		**3i**	90 (91 : 9)[e]
10		**1d**	**2a**		**3j**	97
11		**1e**	**2a**		**3k**	90[f] (88 : 12)[e]
12		**1f**	**2a**		**3l**	75[g]
13		**1g**	**2a**		**3m**	91[g]
14		**1h**	**2a**		**3n (3n′)**	78[h] (>95 : 5)[d]
15		**1i**	**2a**		**3o**	84[h]
16		**1j**	**2a**		**3p (3p′)**	82[h] (2 : 1)[d]
17		**1k**	**2b**		**3q**	38[i]

[a] Unless otherwise stated, the reaction conditions are alkyne **1** (1.0 mmol), alkene **2** (1.2 mmol), CoI_2 (5 mol%), dppp (5 mol%), Zn (20 mol%) and ZnI_2 (20 mol%) and DCM (1.5 mL) at rt for 24 h. [b] Isolated yields; yield in parentheses was determined by an ^1H NMR integration method using mesitylene as an internal standard. [c] Reaction time was 36 h. [d] Regioisomeric ratio. [e] *E* : *Z* ratio of the styrene double bond. [f] $Co(dppe)Br_2$ (5 mol%) in DCE at 80 °C for 20 h. [g] $Co(dppe)Br_2$ (5 mol%) for 36 h. [h] $Co(dppe)Br_2$ (5 mol%)/2,2′-bipyridine (5 mol%) at 50 °C. [i] $Co(dppe)Cl_2$ (5 mol%)/$P(2\text{-furyl})_3$ (5 mol%) 50 °C for 36 h.



Scheme 1

1g containing a hydroxy functional group underwent coupling with **2a** to give product **3m** in 91% yield (entry 13).

The standard reaction conditions were also employed for the coupling of electron deficient alkyne **1h** with **2a**, but no corresponding diene product was observed. We then carried out the reaction using Co(dppe)Br_2, Zn and ZnI_2 as the catalyst system.[7] Again, we did not get the expected coupling product **3n**. However, when we added electron donating bidentate nitrogen ligand 2,2′-bipyridine to the reaction system, the catalytic reaction proceeded to provide product **3n/3n′** in 30% combined yield with complete stereoselectivity with a regioisomeric ratio of >95 : 5. The reaction yield was improved up to 78% by increasing the reaction temperature to 50 °C (entry 14). Similarly, methyl oct-2-ynoate (**1i**) reacted with **2a** under the same conditions to give the expected product **3o** in 84% yield with complete regio- and stereoselectivity (entry 15). For ethyl 3-phenylpropiolate (**1j**), regioisomeric products **3p/3p′** were obtained in a ratio of 2 : 1 in 82% combined yield (entry 16). Symmetrical dimethoxybutyne **1k** also underwent coupling reaction with **2b** to afford product **3q** in 38% yield (entry 17). In this case, the reaction was carried out in the presence of Co(dppe)Cl_2 and 1 equiv. of electron-withdrawing ligand P(2-furyl)$_3$.[11] Other cobalt catalyst systems used in Table 1 are not suitable for this coupling reaction. It is noteworthy that for the reaction of styrene **2a** with electron deficient alkynes, **1h–j** and the reaction of **2b** with aliphatic alkyne **1k**, a high reaction temperature is crucial to obtain high product yields. We should also mention here that the present enyne coupling reaction is not suitable for terminal alkynes leading to a facile homocyclotrimerization of the alkynes under the standard reaction conditions.

A possible reaction mechanism for the enyne coupling is shown in Scheme 1. Reduction of Co^{II} to Co^{I} by zinc powder initiates the catalytic reaction. Highly chemoselective coordination of an alkyne **1** and an alkene **2** to the Co^{I} center[2a] followed by regioselective oxidative cyclometalation yields cobaltacyclopentene intermediate **4**. Subsequent β-hydride elimination of intermediate **4** gives **5** and reductive elimination affords the 1,3-diene **3** and Co^{I} which can be further used for the catalytic cycle.

In conclusion, we have demonstrated that cobalt complexes efficiently catalyze the intermolecular enyne coupling reaction to give 1,3-dienes in good to excellent yields. The results considerably extend the scope of the catalytic ability of cobalt complexes in the enyne coupling reaction. This coupling reaction proceeds with high regio- and stereoselectivity and is also compatible with both electron-rich and electron-deficient substituents attached to alkynes, unlike the reactions catalyzed by ruthenium[4] and rhodium complexes.[8]

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Notes and references

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