The Ruthenium Acetylide Catalyzed Cross-Coupling Reaction of Terminal and Internal Alkynes: Isolation of a Catalytically Active β-Agostic Intermediate Species

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*Summary: The in situ generated ruthenium acetylide complex $C_5Me_5(PPh_3)RuC{\equiv}CPh$ (**1**) was found to catalyze the cross-coupling reaction of terminal and internal alkynes to yield functionalized enynes. An intermediate β-agostic species was isolated from the reaction of $C_5Me_5(PPh_3)(Cl)Ru{=}C{=}CHBu\text{-}t$ (**2b**) with 2-butyne in the presence of NaOMe.*

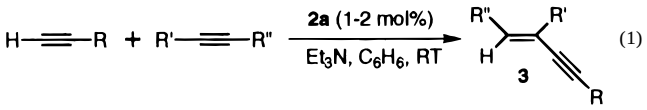
Transition-metal-catalyzed cross-coupling reactions of alkynes constitute an effective method for forming synthetically useful enynes.[1] In contrast to *intramolecular* alkyne coupling reactions, however, metal-catalyzed *intermolecular* alkyne coupling reactions have not been extensively utilized in organic synthesis because these are usually considered to give a mixture of products.[1c] Trost and co-workers recently reported a remarkably selective palladium-mediated regiospecific cross-coupling reaction of terminal and activated internal alkynes.[2] Transition-metal-mediated selective intermolecular [2+ 2+ 2] cyclotrimerization of enynes and diynes[3] and [2 + 2 + 1] cycloaddition reactions of terminal alkynes[4] have also been reported, but the detailed nature of intermediate species for many of these reactions still remain to be elucidated. Previously, we reported the ruthenium-catalyzed linear dimerization of terminal alkynes[5] and showed that the unsaturated ruthenium acetylide species $C_5Me_5Ru(PPh_3)C{\equiv}CPh$ (**1**), generated *in situ* from the reaction of $C_5Me_5(PPh_3)(Cl)Ru{=}C{=}CHPh$ (**2a**) with a base, was the key intermediate species for the dimerization reaction.[5c] Here we report a ruthenium-catalyzed alkyne cross-coupling reaction and the isolation of β-agostic enynyl intermediate species.

Table 1. Ruthenium-Catalyzed Alkyne Coupling Reactions of Terminal and Internal Alkynes[a]

entry no.	R	R′	R″	product	yield (%)[b]
1	*t*-Bu	Ph	Ph	**3a**	78
2	*t*-Bu	CH_3	CH_3	**3b**	87
3	*t*-Bu	*n*-C_3H_7	*n*-C_3H_7	**3c**	76
4	*t*-Bu	CH_3	CO_2Et	**3d**	74
5	*t*-Bu	CO_2Me	CO_2Me	**3e**	76
6	*t*-Bu	CH_2CH_3	COMe	**3f**	77
7	*s*-Bu	CH_3	CO_2Et	**3g**	89
8	*s*-Bu	CO_2Me	CO_2Me	**3h**	75
9	*s*-Bu	CH_2CH_3	COMe	**3i**	58
10	$SiMe_3$	CH_3	CO_2Et	**3j**	85
11	$SiMe_3$	CH_2CH_3	COMe	**3k**	90
12	Ph	CH_2CH_3	COMe	**3l**	44[c]

[a] Reaction conditions: 0.5−2.2 mmol of terminal alkyne and 1.1 equiv of internal alkyne; 1−2 mol % of **2a** and 5 equiv of NEt_3; C_6H_6 (5 mL); room temperature; 12−24 h. [b] The isolated yields. [c] 41% of PhC≡CH homodimer **4** was also formed. See ref 5a for the characterization data of **4**.

The *in situ* generated ruthenium acetylide complex **1** was found to be an effective catalyst for the cross-coupling reaction of terminal and internal alkynes (eq 1). For example, the treatment of $HC{\equiv}CC(CH_3)_3$ (63



(1)

μL, 0.51 mmol) with PhC≡CPh (100 mg, 0.56 mmol) in the presence of 1.5 mol % of **2a** (5 mg, 0.01 mmol) and Et_3N (6 μL, 5 equiv) in C_6H_6 (5 mL) at room temperature for 24 h cleanly yielded **3a** as the sole organic product (Table 1, entry 1). The compound **3a** was isolated in 78% yield (103 mg) after simple column chromatography (silica gel, 3:1 hexanes/Et_2O), and its structure was completely characterized by spectroscopic methods.[6] The cis stereochemistry of **3a** was established from a relatively small coupling constant between the α-acetylenic carbon and the adjacent vinyl proton ($^3J_{CH}$ = 10.1 Hz) in the ^{1}H-undecoupled ^{13}C NMR.[7] Analogous coupling reactions with 2-butyne and 4-octyne yielded the enyne products **3b** and **3c**, respectively (entries 2 and 3). Virtually no homocoupling product was formed in these

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(6) See the Supporting Information for the spectroscopic data of **3** and **7**.

(7) Typical $^3J_{CH}$ values are 9−10 Hz for cis complexes and 15−16 Hz for trans complexes. For a detailed treatment, see: Kalinowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; Wiley: New York, 1988.

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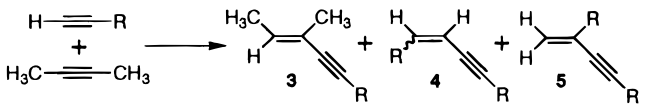
Table 2. Ruthenium-Mediated Coupling Reactions of 2-Butyne with Terminal Alkynes[a]



entry no.	R	product ratio[b] (**3**:**4**[d]:**5**)	yield (%)[c]
1	*t*-Bu	100:0:0	87
2	CH_2Cy	56[e]:20:24	70
3	*n*-Bu	0:59:41	56
4	$SiMe_3$	76[e]:0:24	74
5	Ph	43[e]:57:0	64
6	CO_2Me	0:100:0	80

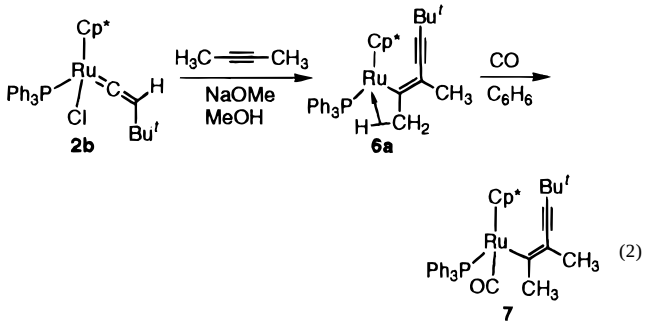
[a] Reaction conditions: 0.5−2.2 mmol of terminal alkyne and 1.1 equiv of internal alkyne; 1−2 mol % of **2a** and 5 equiv of NEt_3; C_6H_6 (5 mL); room temperature; 12−24 h. [b] The product ratio was determined by ^1H NMR. [c] Combined isolated yields for **3**, **4** and **5**. [d] Combined product ratio of **4** for both *cis*- and *trans*-enynes. [e] R = CH_2Cy (**3m**), $SiMe_3$ (**3n**), Ph (**3o**). See the Supporting Information for spectroscopic data of these products.

reactions. To the best of our knowledge, this is the first example of the metal-catalyzed selective cross-coupling reaction of *unactivated* alkyl-substituted alkynes.

The cross-coupling reactions of terminal alkynes with functionalized internal alkynes were examined to establish both the scope and selectivity of the coupling reaction. In general, the ruthenium catalyst **1** was shown to be compatible with a variety of carbonyl compounds, and 1:1 cross-coupling products **3** were isolated in good to high yields, except for phenylacetylene, in which case a mixture of **3** and the homodimer **4** was formed (entry 12). High regio- and stereoselective formation of **3** has been observed for internal alkynes with electron-withdrawing groups (R″ = CO_2Et, COMe), where the acetylide of a terminal alkyne was added β to the electron-withdrawing group of the internal alkyne. Similar regioselectivity has been previously observed in Pd-mediated cross-coupling reactions.[2]

Next, the coupling reactions of terminal alkynes with different substituents were conducted using 2-butyne as an acceptor alkyne to examine the steric and electronic influences of the terminal alkyne on the product formation (Table 2). As before, **3** was formed predominantly for sterically demanding terminal alkynes (entries 1 and 4). In contrast, a mixture of both homocoupling and cross-coupling products was formed for a sterically less demanding alkyne (entry 2) and for phenylacetylene (entry 5), while the homocoupling products **4** and **5** were formed exclusively for both 1-hexyne and methyl propiolate (entries 3 and 6).

The stoichiometric reactions of ruthenium acetylide species with different internal alkynes were explored in hope of generating a stable intermediate species independently. The reaction of *t*-Bu-substituted **2b** (100 mg, 0.16 mmol) with $H_3CC{\equiv}CCH_3$ (127 μL, 1.6 mmol) using NaOMe as a base in MeOH at room temperature rapidly formed a new species, whose spectroscopic data are consistent with the β-agostic enynyl complex **6a** (eq 2).[8] In particular, fluxional behavior of the β-agostic hydrogens was established from the variable-temperature ^1H NMR; a broad α-methyl resonance at δ −1.66 (br s, $w_{1/2}$ = 66 Hz) at 18 °C turned into two distinct set of peaks at δ −8.80 (br d, J_{PH} = 35.0 Hz, Ru−$H_{agostic}$) and 0.82 (br m, Ru−CCH_2H) at −70 °C with a coalescence temperature of −25 °C.



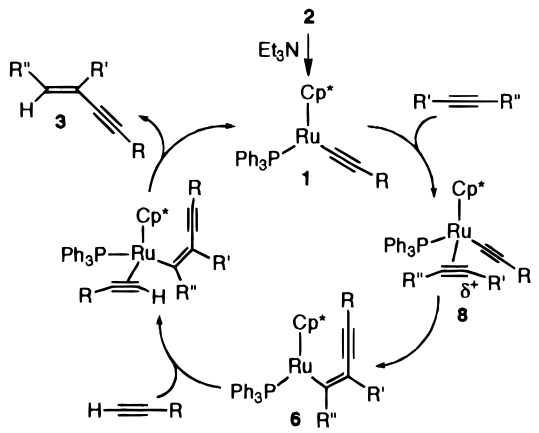
An exposure of the solution containing **6a** with CO (1 atm) cleanly formed the stable adduct **7** (82% yield), the structure of which was unequivocally established by spectroscopic methods.[6] Furthermore, we found that the isolated complex **6a** was an equally effective catalyst for the cross-coupling reaction. For example, the addition of excess 2-butyne and *tert*-butylacetylene to a C_6H_6 solution of **6a** cleanly yielded **3b** at room temperature. Complex **6a** was found to be stable in the solid state for a few weeks at room temperature, but it slowly decomposed in C_6D_6 solution at room temperature ($t_{1/2}$ = 12 h). Though coordinatively unsaturated metal-enynyl species have been proposed in a number of alkyne coupling reactions,[2a,9] complex **6a** represents a rare example of an isolable agostic enynyl intermediate which is catalytically active toward the alkyne cross-coupling reaction.

A plausible mechanism of the reaction is shown in Scheme 1. The key step of alkyne coupling reactions has been commonly proposed to involve the migration of a metal acetylide to a coordinated alkyne.[1,2a] In our case, the acetylide migration to a coordinated alkyne from the intermediate **8** would generate the coordinatively unsaturated enynyl intermediate **6**. As has been demonstrated in eq 2, the enynyl intermediate **6** would be stabilized by having a strong M-to-H_β agostic interaction in the cases of alkyl-substituted alkynes.[10] The β-agostic alkyl complexes have been widely regarded as important intermediate species in a number of metal-mediated reactions.[10,11] For alkynes with electron-withdrawing groups, the acetylide migration is electronically facilitated β to the electron-withdrawing group to generate the σ-enynyl species **6**.[12] The subsequent steps of the reaction, coordination of a terminal

(8) A stronger base such as NaOMe was needed to form the acetylide species for **2b**. Selected spectroscopic and analytical data for **6a**: ^1H NMR (toluene-d_8, 300 MHz, 18 °C) δ 7.6−6.9 (m, Ph), 2.26 (s, =C(CH_3)C≡C), 1.69 (s, C_5Me_5), 1.34 (s, C(CH_3)$_3$), −1.66 (br s, $w_{1/2}$ = 66 Hz, Ru−C(CH_3)=); ^1H NMR (toluene-d_8, 500 MHz, −70 °C) δ 0.82 (br m, Ru−C(CH_2H), 2H), −8.80 (br d, J_{PH} = 35.0 Hz, Ru−$H_{agostic}$, 1H); $^{13}C\{^1H\}$ NMR (C_6D_6, 75 MHz, 18 °C) δ 167.8 (d, J_{PC} = 11.6 Hz, Ru-*C*(CH$_3$)=), 137.9 (=*C*(CH$_3$)C≡C), 137.4 (d, J_{PC} = 41.1 Hz, Ph_{ipso}), 134.1 (d, J_{PC} = 10.4 Hz, Ph_{ortho}), 128.8 (s, Ph_{meta}), 127.4 (d, J_{PC} = 8.9 Hz, Ph_{para}), 108.4 (*C*≡CCMe$_3$), 95.0 (C_5Me_5), 92.7 (C≡*C*CMe$_3$), 32.4 (C*Me*$_3$), 30.1 (*C*(CH$_3$)$_3$), 29.3 (=C(*C*H$_3$)C≡C), 10.5 (C_5*Me*$_5$), 4.5 (Ru−C(*C*H$_3$)=); $^{31}P\{^1H\}$ NMR (C_6D_6, 121.6 MHz) δ 66.5 (PPh_3); FAB-MS *m*/*z* 609 (M^+). Anal. Calcd for $C_{38}H_{45}PRu$: C, 72.01; H, 7.16. Found C, 71.89; H, 7.17.

(9) For examples of metal-enynyl complexes in alkyne coupling reactions, see: (a) Yoshida, M.; Jordan, R. F. *Organometallics* **1997**, *16*, 4508. (b) Bianchini, C.; Innocenti, P.; Peruzzini, M.; Romerosa, A.; Zanobini, F. *Organometallics* **1996**, *15*, 272. (c) Schäfer, M.; Mahr, N.; Wolf, J.; Werner, H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1315. (d) Wakatsuki, Y.; Yamazaki, H.; Kumegawa, N.; Satoh, T.; Satoh, J. Y. *J. Am. Chem. Soc.* **1991**, *113*, 9604. (e) Yasuda, T.; Kai, Y.; Yasuoka, N.; Kasai, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2888.

Scheme 1



alkyne, the σ-bond metathesis of the terminal alkyne, and the reductive elimination, would yield the product **3** and the ruthenium acetylide **1**.

The results from Tables 1 and 2 suggest that both the steric and the electronic nature of terminal alkynes are important in the selective formation of **3**. For example, in the coupling reaction of a sterically demanding terminal alkyne (R = *t*-Bu, *s*-Bu, $SiMe_3$) and an unactivated internal alkyne (R′ = R" = Me, *n*-Pr), the selective formation of **3** may have resulted from the "blocked" formation of the homocoupling products due to unfavorable steric interactions between the acetylide and the terminal alkyne substrate. On the other hand, the predominant formation of the homocoupling products **4** and **5** suggests that the acetylide migration is electronically favored to the terminal alkynes with electron-withdrawing groups (R = Ph, CO_2Me). Similar steric and electronic effects have recently been observed in the palladium-mediated carbostannylation of alkynes.[13] Efforts are currently underway to resolve the detailed steric and electronic effects of alkyne substrates and to determine the role of agostic enynyl species in the catalytic reaction.

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Supporting Information Available: Text giving experimental procedures and characterization data for **3** and **7** (5 pages). Ordering information is given on any current masthead page.

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(10) For recent examples of β-agostic alkyl complexes, see: (a) Brookhart, M.; Green, M. L. H.; Wong, L.-L. *Prog. Inorg. Chem.* **1988**, *36*, 1 and references therein. (b) Brookhart, M.; Volpe, A. F., Jr.; Lincoln, D. M.; Horváth, I. T.; Millar, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 5634. (c) Jordan, R. F.; Bradley, P. K.; Baenziger, N. C.; LaPointe, R. E. *J. Am. Chem. Soc.* **1990**, *112*, 1289. (d) Carmona, E.; Contreras, L.; Poveda, M. L.; Sánchez, L. J. *J. Am. Chem. Soc.* **1991**, *113*, 4322. (e) Lemke, F. R.; Szalda, D. J.; Bullock, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 8466. (f) Brookhart, M.; Hauptman, E.; Lincoln, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 10394. (g) Ogasawara, M.; Saburi, M. *Organometallics* **1994**, *13*, 1911. (h) Tanner, M. J.; Brookhart, M.; DeSimone, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 7617.

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(12) No enynyl intermediates have been detected for reactions of **2b** with internal alkynes having electron-withdrawing groups (R″ = COMe, CO_2Et).

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