Iridium Complex-Catalyzed Cross-Coupling Reaction of Terminal Alkynes with Internal Alkynes *via* C–H Activation of Terminal Alkynes

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Abstract: The cross-dimerization of an electron-rich terminal alkyne with an electron-deficient internal alkyne was promoted by an iridium complex to produce a 1:1 adduct in high regio- and stereoselectivities. This reaction was extended to various combinations of terminal alkynes with internal alkynes such as alkynyl esters and alkynyl aldehydes. The selectivity of the reaction was found to markedly depend on the ligands used. When dppe was used as a ligand, the 1:2 cross-cyclotrimerization reaction took place to form substituted benzene derivatives. A plausible reaction path was suggested based on a labeling experiment. This reaction provides a method for the production of complicated enynes which are difficult to be prepared by conventional methods.

Keywords: alkynes; C–H activation; catalysis; cross-coupling; dimerization; iridium complex

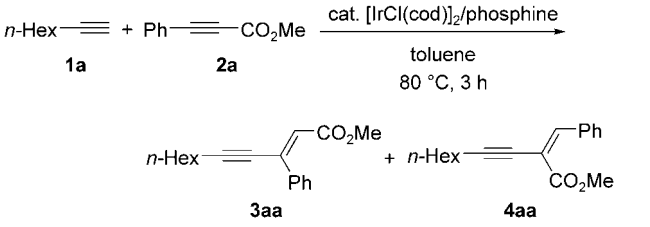
Introduction

The C–C bond-forming reaction is one of the most important reactions in organic synthesis. In particular, the dimerization of alkynes is a very useful method for forming compounds such as enynes from simple alkynes.[1] Transition metal-catalyzed coupling reactions of alkynes constitute an effective method for forming synthetically useful compounds.[2] However, the catalytic intermolecular dimerization of alkynes has not yet been developed,[3] since the homo- and cross-dimerizations of two different alkynes take place simultaneously to result in a complex mixture of products like homodimers,[4] trimers, [5] and oligomers in addition to the desired cross-dimers. Trost et al. have reported the selective cross-addition of terminal alkynes (donor alkynes) to activated internal alkynes (acceptor alkynes) by the use of palladium acetate in the presence of an electron-rich, sterically encumbered ligand like tris(2,6-dimethoxyphenyl)phosphine.[6] Quite recently, Yi and co-worker have reported a similar cross-dimerization of unactivated internal alkynes using a ruthenium-vinylidene complex as the catalyst.[7] Furthermore, there have been several studies on the synthesis of enyne compounds from halogenated alkenes and alkynes catalyzed by a Cu complex and from alkynes and a stoichiometric amount of a Ti complex.[8]

In the course of our studies to develop a new coupling reaction of alkynes using an iridium complex as a catalyst,[9] we have now found that terminal alkynes add selectively to activated internal alkynes in the presence of a catalytic amount of $[IrCl(cod)]_2$ combined with bidentate ligands such as (*rac*)-BINAP, 1,4-bis(diphenylphosphino)butane (dppb) and 1,1′-bis(diphenylphosphino)-ferrocene (dppf).

Results and Discussion

In the first place, we examined the cross-addition of 1-octyne (**1a**) with methyl phenylpropiolate (**2a**) using $[IrCl(cod)]_2$ (cod = cycloocta-1,5-diene) combined with various phosphines [Eq. (1) and Table 1].



(1)

A typical reaction was carried out as follows. To a solution containing $[IrCl(cod)]_2$ (0.035 mmol) and dppb (0.07 mmol) in toluene was added a 1:1 mixture of **1a** (0.5 mmol) and **2a** (0.5 mmol). The reaction was carried

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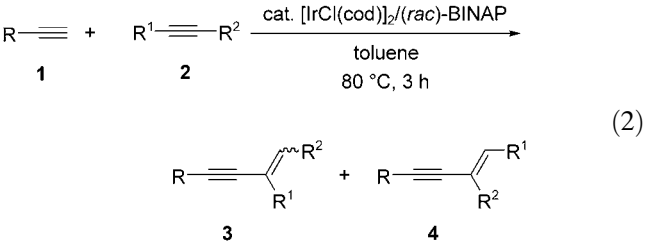
Table 1. The cross-dimerization of **1a** with **2a** catalyzed by $[IrCl(cod)]_2$ under various conditions.[a]

Entry	Ir Complex	Ligand	Conversion [%][b]	Yield [%][c]	
1	$[IrCl(cod)]_2$	dppb	69	35	9
2	$[IrCl(cod)]_2$	none	8	n.d.	n.d.
3	$[IrCl(cod)]_2$	PPh_3	48	<1	2
4	$[IrCl(cod)]_2$	PCy_3	89	n.d.	n.d.
5	$[IrCl(cod)]_2$	$P(OBu\text{-}n)_3$	3	<1	n.d.
6	$[IrCl(cod)]_2$	dppf	>99	62	12
7	$[IrCl(cod)]_2$	(*rac*)-BINAP	>99	83	2
8	$[Ir(cod)_2]^+BF_4^-$	(*rac*)-BINAP	4	n.d.	n.d.
9	$IrCl_3$	(*rac*)-BINAP	No reaction		

[a] Alkyne **1a** (0.5 mmol) was reacted with **2a** (0.5 mmol) in the presence of $[IrCl(cod)]_2$ (0.035 mmol) and ligand (0.07 mmol) in toluene (1 mL) at 80 °C for 3 h.
[b] The conversion was based on **2a**.
[c] The yield was based on **2a** used.

out at 80 °C for 3 h, giving a regioisomeric mixture of cross-addition products, **3aa** (35%) and **4aa** (9%) (Entry 1). In the absence of a ligand, most of **2a** was recovered (Entry 2). Monodentate phosphines, PPh_3 and PCy_3, and phosphite $P(OBu\text{-}n)_3$, resulted in **3aa** in poor yields (Entries 3 to 5), while the reaction using a bidentate phosphine like dppf gave **3aa** in fair yield (62%) (Entry 6). When (*rac*)-BINAP was employed as a ligand, **3aa** was produced in the highest yield (83%) (Entry 7). This is the first successful 1:1 cross-addition of alkynes catalyzed by iridium complexes. The cationic iridium complex $[Ir(cod)_2]^+BF_4^-$ and $IrCl_3$ were inert in this reaction (Entries 8 and 9).

On the basis of these results, the cross-dimerization of various terminal alkynes (**1b**–**f**) with internal alkynes was examined [Eq. (2) and Table 2].



(2)

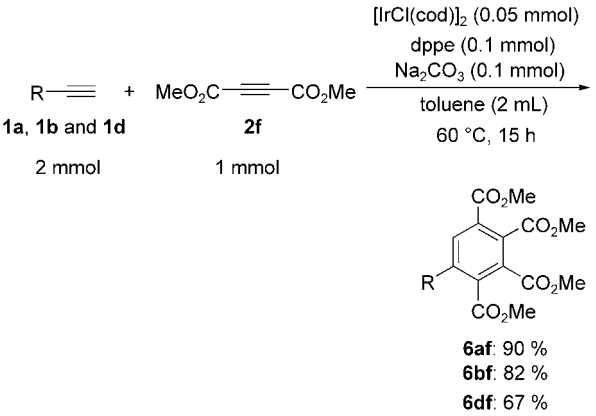
Trimethylsilylacetylene (**1b**), phenylacetylene (**1c**), *tert*-butyl 1-methyl-2-propynyl ether (**1d**) and 1-ethynyl-1-cyclohexanol (**1e**) reacted with **2a** under these conditions to give the corresponding cross-addition products, **3ba**, **3ca**, **3da** and **3ea**, respectively, in fair to good yields (Entries 1 to 4). The reaction of methyl propiolate (**1f**) as the electron-deficient terminal alkyne with **2a** did not form a cross-adduct, but rather afforded small amounts of the cyclotrimerization products of **1f**, trimethyl 1,2,4- and 1,3,5-benzenecarboxylates (**7**) (Entry 5). When **1a** was allowed to react with **2b** under the standard conditions, the desired product (**3ab**) consisting of a 1:1 mixture of *E*- and *Z*-isomers was obtained in 56% yield (Entry 6). The reaction of **1c** with **2b** and **1d** with **2c** provided the corresponding cross-adducts **3cb** (57%) and **3dc** (62%), respectively (Entries 7 and 8). Alyknyl ether **1d** reacted with alkynyl aldehyde (**2d**), giving **3dd** (32%)

Table 2. The cross-dimerization of two different monoynes catalyzed by $[IrCl(cod)]_2$.[a]

Entry	Terminal alkyne R		Internal alkyne R^1	R^2		Product (Yield [%][b])
1	TMS	(**1b**)		**2a**		**3ba** (73 (99 /1)) **4ba** (2)
2	Ph	(**1c**)		**2a**		**3ca** (79 (99 / 1)) **4ca** (2)
3	*t*-BuO	(**1d**)		**2a**		**3da** (73 (99 / 1)) **4da** (1)
4	OH	(**1e**)		**2a**		**3ea** (59 (99 / 1)) **4ea** (6)
5	CO_2Me	(**1f**)		**2a**		**7** (12)
6[c]	**1a**		*n*-Pn	CO_2Me	(**2b**)	**3ab** (56 (50 / 50))
7[c]	**1c**			**2b**		**3cb** (57 (51 / 49))
8[d]	**1d**		*n*-Hex	CO_2Me	(**2c**)	**3dc** (62 (55 / 45))
9[c,e]	**1d**		*n*-Pn	CHO	(**2d**)	**3dd** (32)
10[c]	**1a**		Ph	Ph	(**2e**)	**3ae** (16)
11[f]	**1a**		CO_2Me	CO_2Me	(**2f**)	**6af** (38)

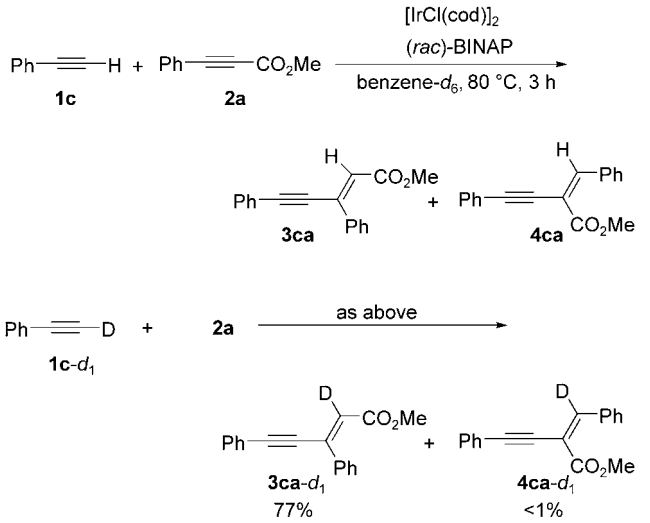
[a] Alkyne **1** (0.5 mmol) was reacted with **2** (0.5 mmol) in the presence of $[IrCl(cod)]_2$ (0.035 mmol) and (*rac*)-BINAP (0.07 mmol) in toluene (1 mL) at 80 °C for 3 h.
[b] The yield was based on **2** used, and the number in parenthesis shows the *E*/*Z* ratio.
[c] Dppf was used instead of (*rac*)-BINAP.
[d] Dppb was used instead of (*rac*)-BINAP.
[e] 3-(3-*tert*-Butoxybut-1-ynyl)-oct-3-enal (**5dd**) was obtained in 22% yield.
[f] See text.

along with 3-(3-*tert*-butoxybut-1-ynyl)-oct-3-enal (**5dd**) (22%) (Entry 9). The reaction of **1a** with diphenylacetylene (**2e**) formed a 1:1 cross-adduct **3ae** in low yield (16%) (Entry 10). However, dimethyl acetylenedicarboxylate (**2f**) reacted with **1a** to give the [2+2+2] cyclotrimerization product (**6af**) of **1a**:**2f**=1:2 in 38% yield, but not the desired product **3af** (Entry 11). Recently, Takeuchi and co-workers have reported the iridium-catalyzed the [2+2+2] cyclotrimerizations of **1c** and **2f**.[10] We found that the cross-cyclotrimerization is also promoted by $[IrCl(cod)]_2$ by the use of dppe as a ligand in the presence of a small amount of Na_2CO_3 under mild conditions [Eq. (3)].



(3)

In order to obtain mechanistic information about the present cross-addition, we attempted the reaction of phenylacetylene-d_1 (**1c**-d_1) with **2a**. The ^{1}H NMR spectrum of the resulting product showed that the reaction cleanly proceeded with almost complete selectivity to form mono-deuterio cross-adduct **3ca**-d_1 [Eq. (4), Figure 1].



(4)

These results suggest that the reaction proceeds *via* the following reaction pathway (Scheme 1). First, the oxidative addition of terminal alkyne **1c**-d_1 to an iridium complex leads to an alkynyl-iridium complex (**A**). The coordination of an internal alkyne (**2a**) to **A** followed by insertion gives a vinyliridium complex (**C**). The oxidative

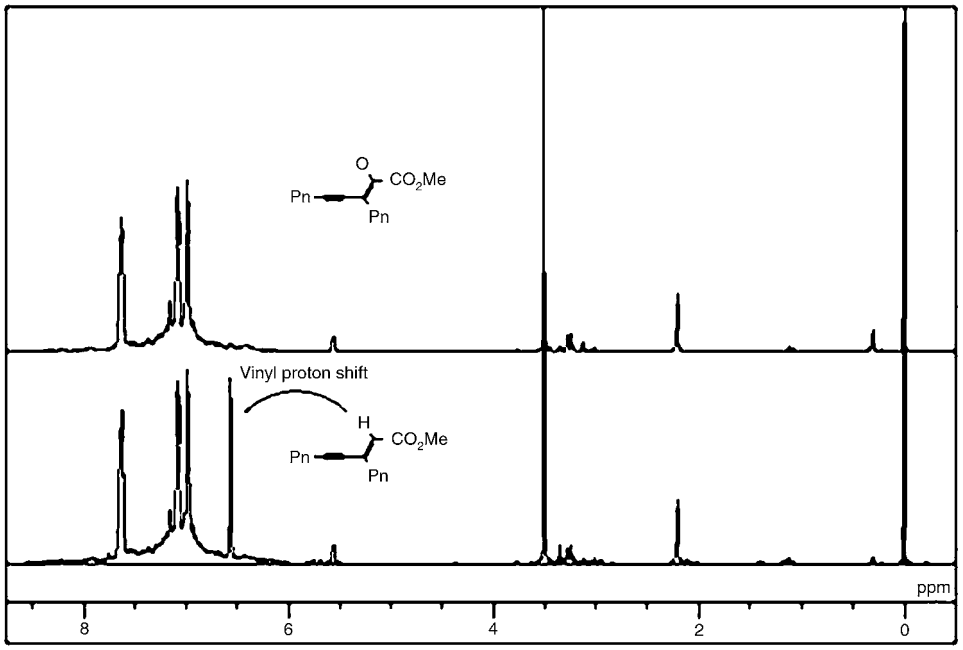
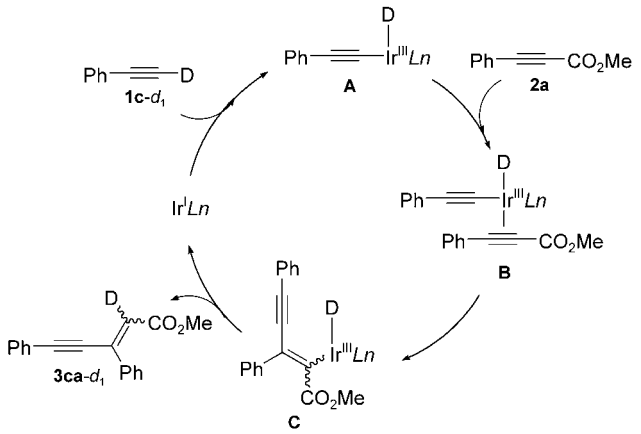


Figure 1. ^{1}H NMR spectrum of the product from the reaction of **1c**-d_1 with **2a**.



Scheme 1. A plausible reaction pathway for the cross-dimerization of alkynes.

addition of alkyne to **C** followed by reductive elimination produces the enyne **3ca**-d_1, and the complex **A** may be regenerated.

Conclusion

We have found a catalytic cross-dimerization between terminal alkynes and internal alkynes, catalyzed by an iridium complex. This reaction provides a method for the production of various complicated enyne compounds.

Experimental Section

General Remarks

^{1}H and ^{13}C NMR were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ with TMS as the internal standard. Infrared (IR) spectra were measured as thin films on NaCl plate or KBr pressed disks. GLC analysis was performed with a flame ionization detector using a 0.2 mm × 25 m capillary column (OV-17). Mass spectra were determined at an ionizing voltage of 70 eV. All starting materials, catalysts, and initiators were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

Typical Procedure for the Cross-Coupling of 1-Octyne (1a) and Methyl Phenylpropiolate (2a)

To a solution containing $[IrCl(cod)]_2$ (0.035 mmol) and dppb (0.07 mmol) in toluene (1 mL) was added a 1:1 mixture of **1a** (0.5 mmol) and **2a** (0.5 mmol). The reaction was carried out at 80 °C for 3 h. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 10/1) to give the corresponding product. The products were characterized by ^{1}H and ^{13}C NMR, IR, and GC-MS, respectively.

Procedure for the Cyclotrimerization of 1a and Methyl Propiolate (2f)

To a solution containing $[IrCl(cod)]_2$ (0.05 mmol), dppe (0.1 mmol) and Na_2CO_3 (0.1 mmol) in toluene (2 mL) was added a 2:1 mixture of **1a** (2 mmol) and **2f** (1 mmol). The reaction was carried out at 60 °C for 15 h. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 9/1) to give the corresponding product. The products were characterized by ^{1}H and ^{13}C NMR, IR, and GC-MS, respectively.

Supporting Information

Characterization data for products **3**.

Acknowledgements

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