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Ni-Catalyzed Ketene Cycloaddition: A System That Resists the Formation of Decarbonylation Side Products

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Supporting Information

ABSTRACT: Ni−phosphine complexes were used as catalysts for the cycloaddition of various ketenes and diynes. In general, 2,4-cyclohexadienones were formed instead of products arising from decarbonylation of the ketenes.

Almost every possible unsaturated starting material (alkynes, alkenes, dienes, CO_2, nitriles, isocyanates, carbonyls, etc.) has been employed as a substrate in transition-metal-catalyzed cycloadditions.[1,2] Despite this rich history of cycloaddition chemistry, ketene substrates are notoriously absent.[3] Insufficient reactivity between potential transition-metal catalysts and ketenes is not the problem. Ketenes easily form η^2 complexes with various metals (Ni, Pd, Pt, Co, Rh, Ir, etc.).[4,5] Furthermore, two modes of coordination, C−O or C−C binding, are available to ketenes (Figure 1). The inability of these η^2 complexes to undergo further reactions with other unsaturated coupling partners lies in their propensity to undergo decarbonylation and form stable, unreactive M−CO complexes (Scheme 1).[4−6] In addition, ketenes often undergo homodimerization under thermal conditions.[7] In view of these pitfalls, we were surprised and delighted to discover that Ni−phosphine catalysts mediate the cycloaddition of ketenes and diynes to afford cyclohexadienones in good yields.[8,9] Herein, we report these results.

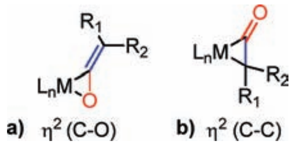
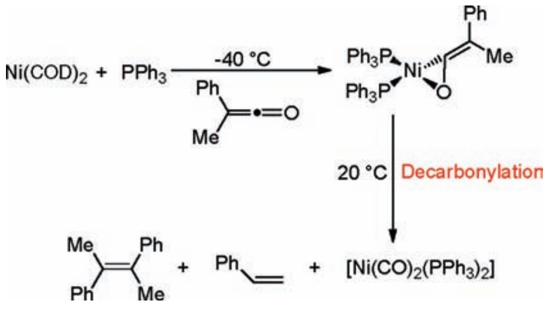
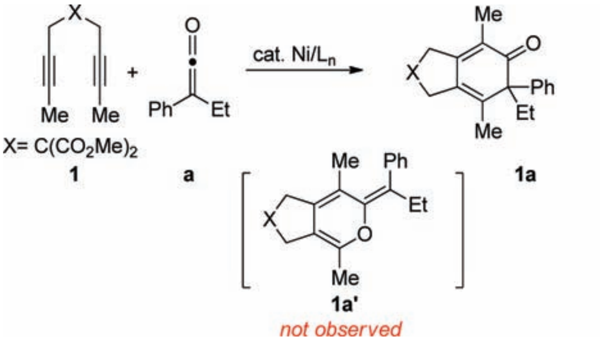


Figure 1. Modes of ketene coordination.

Scheme 1



We initially discovered that the combination of 10 mol % $Ni(COD)_2$ and 10 mol % DPPF successfully catalyzed the cycloaddition of diyne **1** and phenyl ethyl ketene **a** (eq 1). The cycloaddition afforded a carbocyclic product (**1a**) resulting from the coupling of the C−C bond of ketene **a** rather than the pyran (**1a′**) that would have resulted from the coupling of the C−O bond.[2j,k] Other ligands and conditions were evaluated in an effort to optimize the reaction conditions (Table 1). In most cases, byproducts arising from dimerization of the diyne and ketene were observed (entries 1−8). However, we found that high yields were obtained when either DPPF or DPPB was employed as the ligand. Ultimately, the following optimized conditions were employed: 5 mol % catalyst loading [$Ni(COD)_2$ and DPPB in 1:1 ratio] at a 0.1 M reaction concentration in toluene at 60 °C.[10]



(1)

Importantly, we found that ketenes other than **a** could be used as substrates in the cycloaddition reaction and that a variety of cyclohexadienones could be prepared under these optimized reaction conditions (Table 2). For example, diyne **1** not only reacted with ketene **a** but also with diaryl ketene **b** as well as ketene **c** with increased steric hindrance (entries 1−3). Diynes that are prone to cyclotrimerization side reactions,[11] such as phenyl-substituted diyne **2** and terminal diynes **3** and **4**, were also successfully converted to their respective cyclohexadienone products in moderate yields (entries 4−6). In addition, cycloaddition products could be prepared from sulfonamide diynes and diyne−ethers (entries 7−9).

Diynes separated by a four-atom linker instead of a three-atom linker afforded cyclohexadienones in higher yields (entries 10−18). For example, the reaction between diyne 7 and ketene **a** afforded the product in 91% yield (entry 10) versus 82% with diyne **1** (entry 1). We found that a ketene bearing an electron-withdrawing group at the para position (−F; entry 13) enhanced the formation of the carbocyclic product, whereas ketenes

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Table 1. Ni-Catalyzed Cycloaddition of Diynes and Ketenes[a]

Entry	Ligand (L_n)	Ni:L_n	**1** % Conv.[b]	**1a** % Yield[b]
1	IPr[c]	1:2	100	12
2	SIPr[c]	1:2	63	3
3	PPh_3	1:2	100	39
4	PCy_3	1:2	100	20
5	$MePPh_2$	1:2	100	54
6	$CyPPh_2$	1:2	100	31
7	DPPE	1:1	32	2
8	DCPE	1:1	22	–
9	DPPF	1:1	100	>99 (86)[d]
10	DPPB	1:1	100	86 (86)[d]

[a] Reaction conditions: Ni catalyst (5 mol %), diyne (1 equiv, 0.05 M), and ketene (1.2 equiv) in benzene at 60 °C for 12 h. [b] Analyzed by GC using decane as an internal standard. [c] The catalyst solutions were equilibrated for at least 6 h before use. [d] The values in parentheses are isolated yields.

bearing an electron-donating group at the para position (−OMe, −Me; entries 11 and 12) had the opposite effect. Interestingly, the cycloaddition of diyne **7** and trimethylsilyl ketene **i** gave a phenolic product resulting from a facile 1,3-silyl migration (Figure 2).[12] The reaction of ketene **j** afforded a spirobicyclic product in good yield (entry 17). Again, terminal diynes **8** and **9** were also found to afford carbocyclic products, as evidenced by the formation of **8a** and **9a** (entries 18 and 19 respectively).[13]

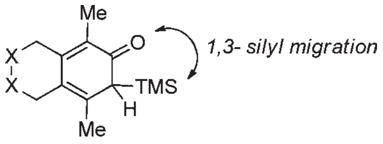
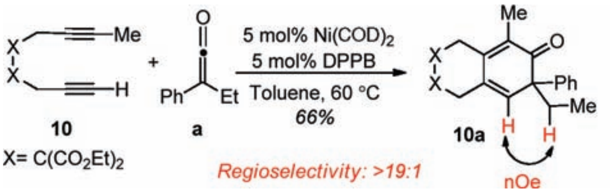
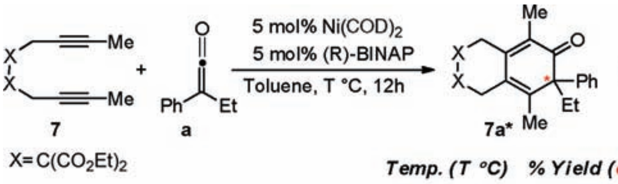


Figure 2. Proposed intermediate.

The standard reaction conditions were applied to unsymmetrical diyne **10**. We were delighted to obtain regioisomer **10a** selectively in 66% yield (eq 2). The regiochemistry of **10a** was determined by one-dimensional nuclear Overhauser effect (nOe) spectroscopy.



(2)

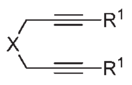
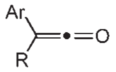
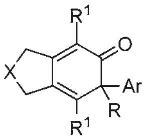
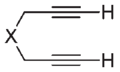
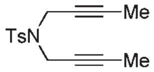
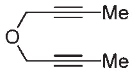
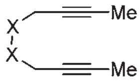
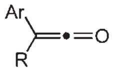
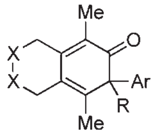
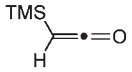
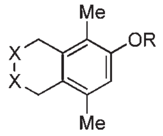
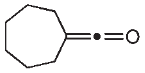
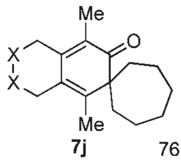
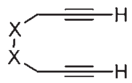
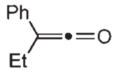
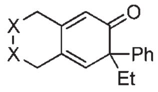


(3)

Temp. (T °C)	% Yield (ee)
60 °C	No reaction
80 °C	38 (99%)
100 °C	58 (95%)

The asymmetric formation of quaternary stereocenters remains a formidable challenge for organic chemists.[14] With this in mind, we also investigated the development of an asymmetric version of the cycloaddition reaction. Initial investigations employing (*R*)-BINAP as the ligand gave dismal results. That is, no

Table 2. Ni-Catalyzed Cycloaddition of Diynes and Ketenes[a]

Entry	Diyne	Ketene		Product	Yield[b,c]
	 X=C(CO_2Me)$_2$				
1	**1** (R^1=Me)	**a**	Ar= Ph, R=Et	**1a**	82%
2	**1**	**b**	Ar= Ph, R=Ph	**1b**	46%
3	**1**	**c**	Ar= Ph, R=*i*-Pr	**1c**	50%
4	**2** (R^1=Ph)	**a**	Ar= Ph, R=Et	**2a**	65%
					
5	**3** (X=C(CO_2Et)$_2$)	**a**	Ar= Ph, R=Et	**3a**	54%
6	**4** (X=CH_2)	**a**	Ar= Ph, R=Et	**4a**	35%
					
7	**5**	**a**	Ar= Ph, R=Et	**5a**	50%
8	**5**	**d**	Ar= Ph, R=*n*-Pr	**5d**	55%
					
9	**6**	**a**	Ar= Ph, R=Et	**6a**	33%
	 X=C(CO_2Et)$_2$				
10	**7**	**a**	Ar= Ph, R=Et	**7a**	91%
11	**7**	**e**	Ar= *p*-OMe-Ph, R=Et	**7e**	81%
12	**7**	**f**	Ar= *p*-Me-Ph, R=Et	**7f**	80%
13	**7**	**g**	Ar= *p*-F-Ph, R=Et	**7g**	>99%[d]
14	**7**	**h**	Ar= Ph, R=Me	**7h**	65%
15	**7**	**d**	Ar= Ph, R=*n*-Pr	**7d**	76%
					
16	**7**	**i**		**7i-i'** R=TMS:H = 63:19	82%
					
17	**7**	**j**		**7j**	76%
					
18	**8** (X=C(CO_2Et)$_2$)	**a**		**8a**	78%
19	**9** (X= CH_2)	**a**		**9a**	33%

[a] Reaction conditions: $Ni(COD)_2$ (5 mol %), DPPB (5 mol %), diyne (1 equiv, 0.1 M), and ketene (1.2 equiv) in toluene at 60 °C for 5 h. [b] Isolated yields. [c] Average of at least two runs. [d] Crude ketene was used.

reaction was observed under the standard reaction conditions (5 mol % catalyst and 0.1 M diyne at 60 °C in toluene). However, a carbocyclic product was generated when the temperature was elevated to 80 °C. Although a relatively low yield (38%) was obtained, excellent enantioselectivity (99%) was observed (eq 3). A higher yield was obtained when the reaction temperature was increased to 100 °C. Gratifyingly, only a slight decrease in enantioselectivity was observed at a higher temperature (100 °C).

In conclusion, we have successfully incorporated ketenes in [2 + 2+2] cycloaddition reactions with diynes. Decarbonylation of the ketene starting materials was not observed. Instead, a variety of 2,4-cyclohexadienones were formed. An enantiopure cyclohexadienone product was obtained when (*R*)-BINAP was used as the ligand. Efforts to develop a general asymmetric catalyst system and understand the mechanistic details of this cycloaddition chemistry are underway.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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(10) When DPPF was employed as the ligand in the cycloaddition of other substrates, such as diynes **5** and **7** with **a**, a complex mixture of products that included diyne dimer, ketene dimer, and cycloadduct was formed, hampering purification. In general, reactions run with DPPB were cleaner. Therefore, our optimized conditions employed DPPB as the ligand of choice.

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(13) When 3-hexyne and phenyl ethyl ketene (**a**) were subjected to the optimized conditions, the cycloaddition product was not obtained. Instead, only ketene dimerization was observed by GC.

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