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A Nickel(0)-Catalyzed Process for the Transformation of Enynes to Bicyclic Cyclopentenones

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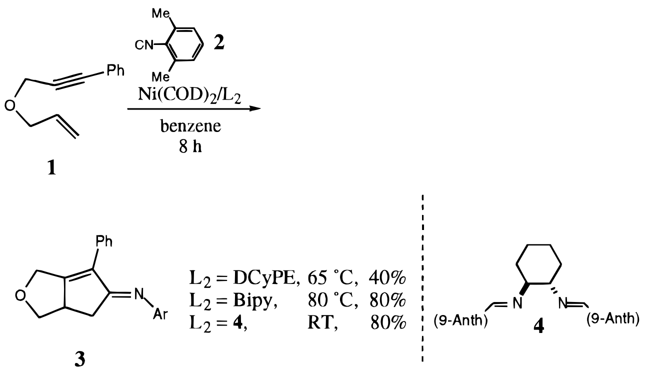
The coupling of an alkyne, an alkene, and carbon monoxide mediated by transition metal complexes to yield a cyclopentenone[1] has attracted a great deal of interest in the past few years. In particular, the conversion of an enyne to a bicyclic enone[2] has been accomplished using a number of metal carbonyl complexes, including $Co_2(CO)_8$ (the Pauson−Khand reaction),[3] $Fe(CO)_4$(acetone) under CO pressure,[4] $W(CO)_6$(THF),[5] and $Cp_2Mo_2(CO)_4$.[6] Metallocene equivalents generated from Cp_2ZrCl_2[7] and Cp_2TiCl_2[8] in combination with CO can also be utilized to effect the transformation. In the latter procedures, the initially formed metallacycles are converted to enone products by carbonylation. In general, these reactions require stoichiometric amounts of transition metal complexes. When an isocyanide is used in lieu of CO, the reaction yields an iminocyclopentene. This process has been accomplished using metallocene reagents,[8] as well as $Ni(COD)_2/Bu_3P$.[9] Our recent success using a titanocene catalyst for this transformation[10] and recent reports of catalytic Pauson−Khand reactions[11] prompted us to search for a catalytic variant of the Ni-mediated process. Here we wish to describe a method for the conversion of an enyne and a trialkylsilyl isocyanide to an iminocyclopentene catalyzed by a Ni(0) complex generated *in situ* from $Ni(COD)_2$ and a bulky bisketimine ligand.

While the stoichiometric $Ni(COD)_2$-mediated reaction of an enyne and an isocyanide to produce an iminocyclopentene required 2 equiv of Bu_3P, the use of a bidentate phosphine ligand such as $Ph_2P(CH_2)_3PPh_2$ (DPPP) was reported to completely inhibit the cyclization.[9] However, we found that the reaction of an equimolar mixture of $Ni(COD)_2$, enyne **1**, 2,6-dimethylphenyl isocyanide, **2**, and chelating ligand $Cy_2P(CH_2)_2PCy_2$ (DCyPE) at 65 °C for 8 h formed the corresponding iminocyclopentene **3** in 40% yield (Scheme 1). As our ultimate goal is to develop an asymmetric catalyst for this process, the successful employment of a bidentate ligand is significant. The increased efficiency of the reaction with the more electron-rich ligand DCyPE relative to DPPP prompted us to investigate the use of highly electron-donating bidentate nitrogen ligands.[12] For example, the reaction of an equimolar mixture of **1**, **2**, $Ni(COD)_2$, and 2,2′-bipyridine (Bipy) at 80 °C for 8 h gave **3** in 80% yield, and the analogous reaction of **1**, **2**, $Ni(COD)_2$, and *rac*-diimine **4** at room temperature for 8 h gave **3** in 80% yield (Scheme 1).

Scheme 1



Attempts to convert **1** to iminocyclopentenes such as **3** with a variety of isocyanides in the presence of as much as 25 mol % of $Ni(COD)_2$/**4** were unsuccessful. However, we observed that after an initial stoichiometric reaction involving **1**, **2**, and $Ni(COD)_2$/**4** addition of a second equivalent of **1** and **2** to the same reaction vessel followed by heating to 65 °C led to the consumption of the substrates with concomitant production of iminocyclopentene **3**. After five such cycles, **3** was obtained in 70% yield [350% based on $Ni(COD)_2$]. These results suggested that the failure of the catalytic coupling of **1** with **2** to form **3** was due to the formation of nickel−isocyanide complexes, which prevent the coordination, and hence, cyclization, of the enyne.[8,10]

We have previously shown that trialkylsilyl cyanides serve as an effective isocyanide source for the titanocene-catalyzed conversion of enynes to iminocyclopentenes.[10] Trialkylsilyl cyanides generate a sufficient yet relatively low equilibrium concentration of the trialkylsilyl isocyanide isomer ($K \approx 0.01$)[13] to effect the desired coupling reaction while avoiding the formation of inactive Ti−isocyanide complexes.[10] Similarly, trialkylsilyl cyanides were also coupled with **1** employing a catalytic amount of $Ni(COD)_2$/**4**. For example, reaction of **1** with *tert*-butyldimethylsilyl cyanide (TBDMSCN) in the presence of 5 mol % of $Ni(COD)_2$/**4** at 130 °C for 36 h followed by acidic hydrolysis of the initially formed intermediate gave cyclopentenone **5** in 60% yield. The reaction proceeded at lower temperature (120 °C) and approximately the same rate using the bulkier bis-ketimine ligand, *N,N′*-bis(diphenylmethylene)ethylenediamine (BDPEDA, **6**). In addition, when the larger (triisopropyl)silyl cyanide (TIPSCN) was used, cyclization occurred at 110 °C (Scheme 2). In all cases, moderately high dilution ($[Ni] \approx 10^{-3}$ M) was required to suppress the formation of nickel−isocyanide complexes. Of interest is that the amounts

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[1] For leading references, see: Trost, B. M. *Science (Washington, D.C.)* **1991**, *254*, 1471.

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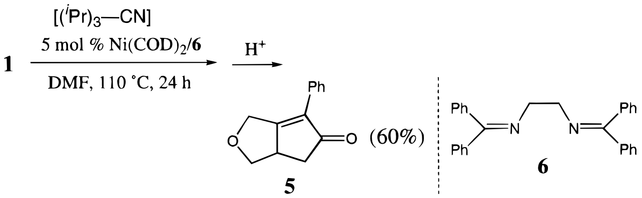
Scheme 2



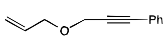
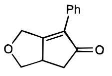
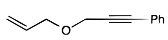
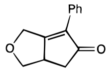
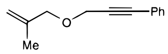
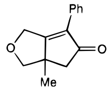
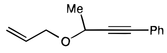
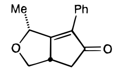
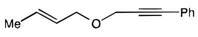
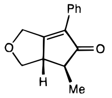
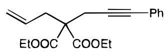
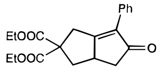
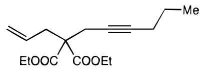
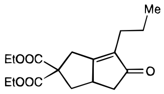
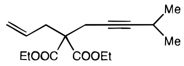
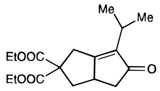
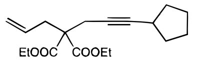
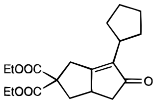
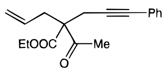
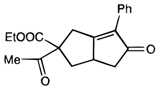
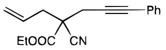
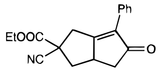
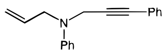
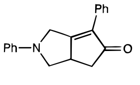
of Ni(COD)$_2$/**6** complex may be reduced to 2 mol % when the reaction was carried out at higher temperature (135 °C).

Some of our results are summarized in Table 1.[14] The nickel-catalyzed conversion of enynes and TIPSCN to cyclopentenones is more tolerant of polar functional groups than the titanocene version;[15] a variety of functional groups including ethers (Table 1, entries 1−5), esters (entries 6−10), ketones (entry 10), nitriles (entry 11), and anilines (entry 12) are compatible with this protocol. In addition, internal alkenes are suitable substrates. For example, the reaction of 3-(2-butenoxy)-1-phenyl-1-propyne (3:1 trans:cis) and TIPSCN with 10 mol % Ni(COD)$_2$/**6** gives a 58% isolated yield of the corresponding cyclopentenone, produced as exclusively the *cis* isomer (entry 5, Table 1).

^{1}H NMR analysis of the crude reaction mixture indicates that the yield of iminocyclopentenes in general is considerably higher than the isolated yield of the corresponding cyclopentenone derivatives. This is indicative of an inefficient hydrolysis and workup protocol. Similar difficulties were encountered in the isolation of cyclopentenone derivatives from the corresponding titanocene-catalyzed procedure.[8,10]

In summary, we have developed a nickel(0)-catalyzed process for the transformation of enynes to bicyclic cyclopentenones. This method is tolerant of a variety of functional groups including esters, ketones, nitriles, ethers, and amines and is effective with more highly substituted olefins than the titanium procedure. Our future efforts will be directed toward improving the efficiency of this and related catalyst systems. In addition, the development of an asymmetric variant is under active study.

Table 1. Ni(0)-Catalyzed Conversion of Enynes to Bicyclic Cyclopentenones

entry	enyne	Ni% (mol), Temp.	product	isolated yield(%) (diastereomer ratio)
1		5%, 110		60
2		2%, 135		60
3		10%, 110		41
4		10%, 110		38 (2:1)
5		10%, 110		58 (> 98:2)
6		10%, 120		85
7		20%, 120		62
8		20%, 120		64
9		20%, 120		70
10		10%, 110		64 (1:1)
11		10%, 120		64 (1:1)
12		5%, 110		40

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Supporting Information Available: Complete experimental procedures as well as analytical and spectroscopic data for all new compounds (6 pages).

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(14) Typical procedure: In an argon-filled glovebox, Ni(COD)$_2$ (14 mg, 0.05 mmol), BDPEDA (24 mg, 0.06 mmol), enyne (1.0 mmol), and (iPr)$_3$SiCN (201 mg, 1.1 mmol) were dissolved in 46 mL of DMF in a 100-mL sealable Schlenk flask. The Schlenk flask was sealed, removed from the glovebox, and heated under argon at 110−135 °C until the enyne was consumed (as determined by GC, 8−36 h). The reaction mixture was cooled to 0 °C, treated with saturated aqueous oxalic acid solution (10 mL), and stirred at room temperature for 12−24 h. Et$_2$O (80 mL) and saturated aqueous NaHCO$_3$ (40 mL) were added to the solution, and layers were separated. The aqueous layer was extracted with Et$_2$O (3 × 50 mL), and the combined ethereal extracts were washed with H$_2$O (3 × 40 mL) and brine (40 mL). The ethereal solution was dried over MgSO$_4$ and concentrated *in vacuo* to give an oily residue that was further purified by flash chromatography (silica gel, Et$_2$O:hexane = 1:1−2) and that yielded the desired cyclopentenone typically as a colorless to pale yellow oil.

(15) Attempts to employ ketone- or nitrile-containing substrates in the Cp$_2$Ti(PMe$_3$)$_2$-catalyzed procedures have been unsuccessful.