Angewandte Chemie

DOI: 10.1002/ange.200704452

Synthetic Methods

Nickel-Catalyzed Reductive Cyclization of Unactivated 1,6-Enynes in the Presence of Organozinc Reagents[**]

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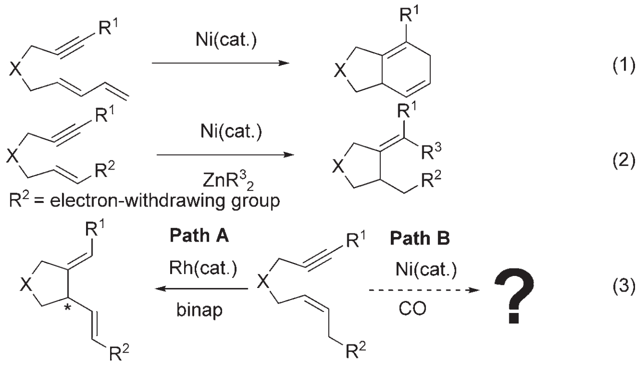
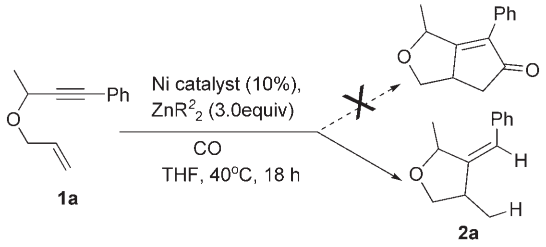
The transition-metal-catalyzed cyclization of 1,6-enynes is one of the most convenient and efficient methods for the synthesis of a variety of carbocyclic and heterocyclic compounds.[1–4] By this approach, enynes can be transformed into cyclic skeletons in a one-pot fashion with impressive regio- and stereoselectivity.[3,5,6] The readily available and inexpensive metal nickel stands out for its remarkable power in catalyzing cycloisomerization and cycloaddition reactions of enynes.[7–9] Important examples include a Ni-catalyzed [4+2] cycloaddition developed by Wender and co-workers[10,11] and a series of cyclization reactions of activated 1,6-enynes described by Montgomery and co-workers [Scheme 1, Eq. (1,2)].[7,12–15] These strategies have established new approaches for the highly stereoselective formation of ring systems decorated with exocyclic trisubstituted or tetrasubstituted C=C bonds. Viable substrates for these processes, however, usually bear electron-withdrawing substituents. To our knowledge, very few studies have been described to date in which the potential of Ni catalysis in direct cyclizations of electronically unactivated enynes has been explored [Scheme 1, Eq. (3)]. Such unactivated enynes have historically been used in combination with catalytic systems based on Pd,[16–19] Au,[20] Ru,[21] and Rh.[19,22–24] We and others have described highly enantioselective Rh-mediated cycloisomerization reactions of 1,6-enynes [Scheme 1, Eq. (3), path A].[25–29] To further explore this cyclization chemistry, we have now investigated a Ni-based system with the aim of uncovering new reactivity and selectivity in a Ni-mediated Pauson–Khand-type cyclization under a reductive atmosphere, such as CO gas.[30–34]



Scheme 1. Ni-mediated cyclization of enynes. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

Unlike Ni^{II} species, most Ni^0 complexes are extremely air-sensitive and are thus rather difficult to manipulate.[35] Consequently, many known processes have resorted to the generation of these compounds in situ from air-stable Ni^{II} precursors in the presence of an appropriate reducing reagent, such as diisobutylaluminum hydride or a dialkyl zinc reagent.[7,36] We initially set out to probe the feasibility of the Pauson–Khand reaction (PKR) of enyne **1a** in the presence of $[Ni(PPh_3)_2Cl_2]$ (5 mol%) and iPr_2Zn (30 mol%) under a CO atmosphere (balloon pressure).[36,37] Despite extensive experimentation, this system failed to deliver any of the desired PKR product. However, a new compound was detected by serendipity when 3.0 equivalents of iPr_2Zn were used. The compound was isolated and identified as **2a**, that is, a compound into which a molecule of dihydrogen has formally been incorporated following cyclization, rather than a molecule of CO as intended (Scheme 2).



Scheme 2. Ni-catalyzed cyclization of the 1,6-enyne **1a**.

Compound **3a** was established to be a superior substrate to **1a** upon subsequent optimization of the reaction and was therefore chosen as the substrate for the further screening of catalyst systems. The reactions were carried out at 40 °C for 18 h at a concentration of 0.1 M in THF. It was found that a combination of $[Ni(acac)_2]$ (10 mol%) and iPr_2Zn (3.0 equiv) furnished the product of reductive cyclization **4a** in 95% yield with exclusive formation of the *Z* alkene (Table 1, entry 3). A decrease in the temperature, the catalyst loading, or the

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[**] This research was supported by the National Natural Science Foundation of China (20502020) and a startup fund from Wuhan University.

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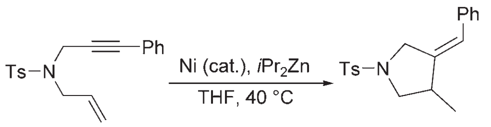
Table 1: Ni-catalyzed reductive cyclization of **3a** under different conditions.[a]



3a **4a**, $Z/E > 99:1$

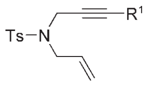
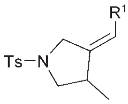
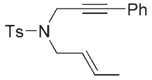
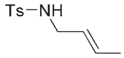
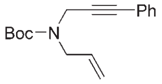
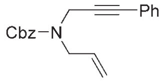
Entry	Catalyst (mol %)	Ligand (mol %)	iPr$_2$Zn [equiv]	Yield [%]
1[b]	[Ni(acac)$_2$] (10)	–	3.0	64
2	[Ni(acac)$_2$] (5)	–	3.0	69[c]
3	[Ni(acac)$_2$] (10)	–	3.0	95[c]
4	[Ni(acac)$_2$] (10)	–	2.0	64
5	[Ni(acac)$_2$] (10)	–	1.0	40
6	[Ni(PPh$_3$)$_2$Cl$_2$] (10)	–	3.0	94[c]
7	[Ni(PPh$_3$)$_4$] (10)	–	3.0	45
8	[Ni(acac)$_2$] (10)	PPh$_3$ (10)	3.0	94
9	[Ni(acac)$_2$] (10)	PPh$_3$ (20)	3.0	90
10	[Ni(acac)$_2$] (10)	PPh$_3$ (40)	3.0	85

[a] All reactions were carried out at a substrate concentration of 0.1 M for 18 h. The yields and the selectivities were determined by GC. [b] The reaction was carried out at 28 °C. [c] Yield of the isolated product. acac = acetylacetonate, Ts = *p*-toluenesulfonyl.

amount of iPr$_2$Zn used resulted in a lower yield of **4a** (Table 1, entries 1, 2, 4, and 5). When [Ni(PPh$_3$)$_4$] was used as the catalyst, the product was formed in 45 % yield. However, an almost identical result was observed with [Ni(PPh$_3$)$_2$Cl$_2$] (Table 1, entry 6) to that with [Ni(acac)$_2$]. Further experiments revealed that the presence of PPh$_3$ as a ligand in a 1:1 ratio with [Ni(acac)$_2$] did not effect the outcome of the reaction; at higher ratios of 2:1 or 4:1, PPh$_3$ inhibited the reaction to a certain extent (Table 1, entries 8–10).[12,13,38]

A variety of N-tethered enynes were tested as substrates under the optimized reaction conditions (Table 2). In most cases, the desired cyclized product was generated with exceedingly high selectivity for the *Z*-configured alkene,[39] as confirmed unambiguously by an NOE experiment. The steric and electronic properties of the substituent on the aryl group attached to the alkyne affected the reaction. Compound **3b** with a *p*-MeO group was transformed into the desired product in 89 % yield with high selectivity for the *Z* alkene, whereas lower yields were observed for the reactions of **3c** and **3d**; the position of the methoxy substituent did not have an influence on the stereoselectivity (Table 2, entries 2–4). When an electron-withdrawing ester substituent was present, the product was obtained in 65 % yield, and the selectivity dropped to Z/E 74:24 (Table 2, entry 5).[40] When the aromatic substituent on the alkyne was exchanged for an alkyl group, the product was furnished in moderate yield but with a selectivity of greater than 99:1 (Table 2, entry 6). A substrate with an internal alkene in the side chain was transformed into **4g** in 66 % yield. Compound **4j** was also obtained in 24 % yield, and no cyclic product with an isomerized alkene side chain was detected (Table 2, entry 7). When the protecting group on the N tether was changed from a tosyl group to Boc (**3h**) or Cbz (**3i**), the catalyst system still afforded the cyclized products in satisfactory yields with high selectivity.

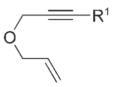
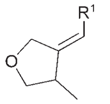
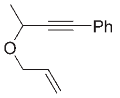
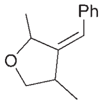
Table 2: Ni-catalyzed reductive cyclization reactions of compounds **3** to give pyrrolidine derivatives.[a]

Entry	3		4	Yield [%][b]	Z/E[c]
					
1	**3a**	R^1 = Ph	**4a**	95	> 99:1
2	**3b**	R^1 = Ph-4-OMe	**4b**	89	> 99:1
3	**3c**	R^1 = Ph-3-OMe	**4c**	56	> 99:1
4	**3d**	R^1 = Ph-2-OMe	**4d**	36	> 99:1
5	**3e**	R^1 = Ph-4-COOEt	**4e**	65	74:26
6	**3f**	R^1 = C$_5$H$_{11}$	**4f**	62	> 99:1
7	**3g**		**4g**	66	> 99:1
				24	
8	**3h**		**4h**	72	> 99:1
9	**3i**		**4i**	66	> 99:1

[a] All reactions were carried out with [Ni(acac)$_2$] (10 mol %) and iPr$_2$Zn (3.0 equiv) in THF at 40 °C for 18 h. [b] Yield of the isolated product. [c] The Z/E ratio was determined by GC. Boc = *tert*-butoxycarbonyl, Cbz = carbobenzyloxy.

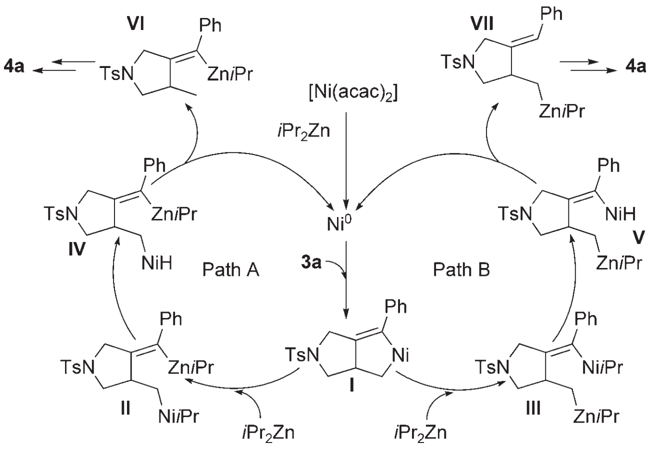
To further explore the scope of application of this method, we tested the use of O-tethered enynes as substrates (Table 3). Good selectivity for the *Z* isomer and moderate yields were observed when substrates with an aryl or an alkyl group attached to the alkyne were used. Again, only when a *p*-COOEt group was present on the aromatic ring did the yield and selectivity drop (to 39 % and 75:25; Table 3, entry 3). This result is similar to that observed with **3e**. Poor diastereoselectivity was observed for the reaction of **1a**, with a methyl substituent at the 5-position, but the Z/E ratio of the product was still greater than 99:1 (Table 3, entry 5).

Table 3: Ni-catalyzed reductive cyclization reactions of compounds **1** to give tetrahydrofuran derivatives **2**.[a]

Entry	1		2	Yield [%][b]	Z/E[c]
					
1	**1b**	R^1 = Ph	**2b**	66 (84)	> 99:1
2	**1c**	R^1 = Ph-4-OMe	**2b**	65 (77)	> 99:1
3[d]	**1d**	R^1 = Ph-4-COOEt	**2b**	39	75:25
4	**1e**	R^1 = C$_5$H$_{11}$	**2b**	65	> 99:1
5	**1a**			72	> 99:1

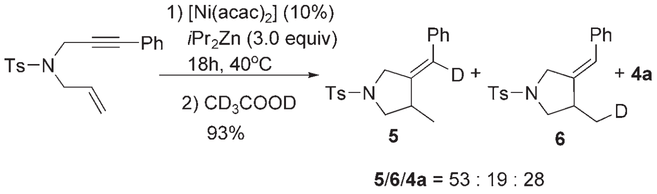
[a] Reactions were carried out in the presence of iPr$_2$Zn (3.0 equiv) and [Ni(acac)$_2$] (10 mol %) at 40 °C for 12 h. [b] Yield of the isolated product. Yields determined by GC are reported in parentheses. [c] The Z/E ratio was determined by GC. [d] Reaction time: 18 h.

A speculative catalytic cycle is shown in Scheme 3. Oxidative cyclization of the enyne to Ni^0, derived from $[Ni(acac)_2]$ through reduction by iPr_2Zn,[41] would afford a nickel metallocyclopentene intermediate **I**,[42–44] which could undergo transmetalation with iPr_2Zn through two possible pathways to form intermediate **II** or **III**. Subsequent β-H elimination and reductive elimination would generate **VI** and **VII**, respectively, both of which would be converted into the product of reductive cyclization upon hydrolysis. Montgomery et al. suggested the formation of five- or seven-membered nickel metallacycle intermediates through the oxidative cyclization of an alkynal or an alkynone to a Ni^0 species and subsequent generation of ring-opened intermediates by transmetallation between the nickel metallacycle and an organozinc reagent, in direct analogy to the formation of **II** and **III** in Scheme 3.[7] Furthermore, Knochel and co-workers have demonstrated such an exchange between organonickel intermediates and Et_2Zn.[45–49] The palladium-catalyzed reductive cyclization of carbon-tethered 1,6-enynes in the presence of a silicon hydride and HOAc provided similar products, but the mechanism was different from our hypothesis.[50]



Scheme 3. Proposed mechanism for the reductive cyclization promoted by $[Ni(acac)_2]$.

To gain more information about the reaction mechanism, we quenched the reaction of **3a** with CD_3COOD.[12] Compound **5**, with the deuterium label on the C=C bond, and compound **6**, with a deuterium-labeled methyl group, were obtained as 53 and 19 % of the product mixture, respectively (Scheme 4), a result that indicates the existence of both **VI** and **VII** as intermediates. Moreover, the high selectivity for the formation of products with the *Z* configuration is also consistent with the formation of a Ni metallacycle. It is still unclear why we have never observed alkylated cyclization products. Such products were reported to be dominant when electron-deficient enynes were used as substrates.



Scheme 4. Confirmation of the proposed mechanism by a quenching experiment with CD_3COOD.

In conclusion, we have developed an inexpensive $[Ni(acac)_2]$-catalyzed reductive cyclization of unactivated 1,6-enynes in the presence of iPr_2Zn under mild conditions. Through a simple procedure, functionalized pyrrolidine and tetrahydrofuran derivatives were produced in a generally highly stereoselective manner in moderate to high yields. Our proposed mechanism was confirmed through a quenching experiment with CD_3COOD. Studies into the scope of the reaction and mechanistic studies are under way.

Experimental Section

Typical procedure: iPr_2Zn (6 mL, 0.5 M in THF) was added to a solution of **3b** (355 mg, 1.0 mmol) and $[Ni(acac)_2]$ (25.6 mg, 0.1 mmol) in anhydrous THF (4 mL) at −78 °C. The reaction mixture was stirred at 40 °C for 18 h under N_2, and then 2 M HCl (25 mL) was added to quench the reaction. The mixture was extracted with dichloromethane, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and then concentrated in vacuo. The residue was purified by column chromatography over silica gel (ethyl acetate/petroleum 1:20, v/v) to give **4b** (318 mg, 89 %) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.63$ (d, $J = 8.1$ Hz, 2 H), 7.20 (d, $J = 7.8$ Hz, 2 H), 6.98 (d, $J = 8.4$ Hz, 2 H), 6.78 (d, $J = 8.7$ Hz, 2 H), 6.06 (s, 1 H), 4.12 (d, $J = 14.7$ Hz, 1 H), 3.93 (d, $J = 14.4$ Hz, 1 H), 3.70 (s, 3 H), 3.44 (t, $J = 7.8$ Hz, 1 H), 2.76 (m, 1 H), 2.62 (t, $J = 8.4$ Hz, 1 H), 2.30 (s, 3 H), 1.05 ppm (d, $J = 6.6$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.7$, 143.8, 139.6, 133.0, 129.9, 129.7, 129.5, 127.9, 121.6, 114.1, 55.4, 54.1, 51.0, 39.1, 21.7, 17.1 ppm; HRMS (APCI): calcd for $C_{20}H_{23}NO_3S$: 357.1399 $[M]^+$; found: 357.1404.

Received: September 27, 2007
Revised: December 21, 2007
Published online: February 8, 2008

Keywords: cyclization · enynes · nickel · organozinc reagents · synthetic methods

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[39] When the reactions were monitored by TLC, we observed only the spot of the desired product and a spot at the baseline, which we suspect to be an oligomeric product. Oligomerization may be the reason behind the isolation of the desired product in low yields in entries 3 and 4 of Table 2.

[40] We do not have enough data as yet to explain the difference between the selectivity of the reaction of **3e** and that of the reactions of substrates **3a**–**3d** and **3f**–**3h**.

[41] When $[Ni(cod)_2]$ (10 mol%) was employed as the catalyst precursor (cod = 1,5-cyclooctadiene), the reductive cyclization of **3a** was equally efficient. The desired product was isolated in 85% yield.

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