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Highly Stereoselective Ring-Opening Addition of Terminal Acetylenes to Bicyclic Olefins Catalyzed by Nickel Complexes

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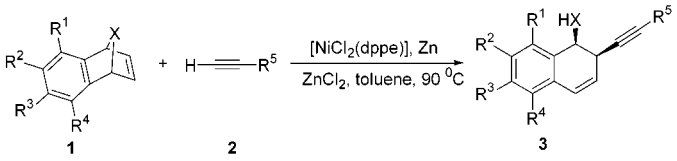
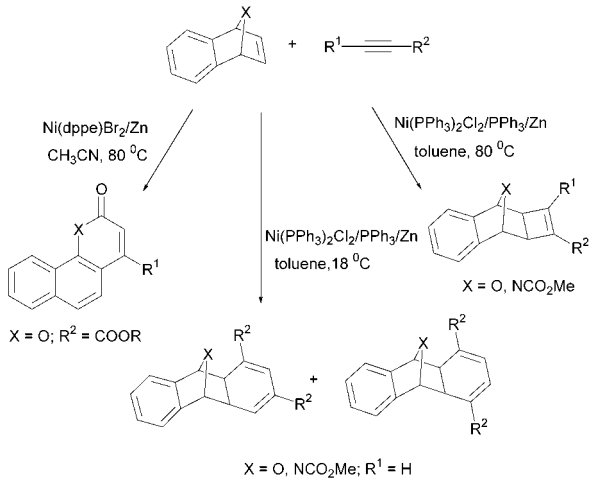
ABSTRACT



Treatment of 7-oxa- and 7-azabenzonorbornadienes with terminal acetylenes in the presence of Ni(dppe)Cl_2, $ZnCl_2$, and Zn powder in toluene at 90 °C afforded the corresponding *cis*-2-alkynyl-1,2-dihydronaphthalene derivatives in moderate to excellent yields with remarkably high stereoselectivity.

Recently, we observed different nickel-catalyzed cycloadditions of oxa- and azabenzonorbornadienes with alkynes. These reactions are highly sensitive to the reaction conditions and substrates employed. By using $NiCl_2(PPh_3)_2/PPh_3/Zn$ as the catalyst, 7-oxa- and 7-azabenzonorbornadienes undergo $[2 + 2 + 2]$[1,2] cycloaddition in toluene with terminal alkynes to give cyclohexadiene derivatives and $[2 + 2]$[3] cycloaddition with internal alkynes to afford *exo*-cyclobutene derivatives (Scheme 1). On the other hand, the reaction of 3-substituted propiolates with 7-oxabenzonorbornadienes gave benzocoumarins[4] in the presence of Ni(dppe)Br_2 and Zn powder in acetonitrile. In this paper, we wish to report a new nickel-catalyzed highly stereoselective ring-opening addition of terminal acetylenes to bicyclic olefins to afford *cis*-2-alkynyl-1,2-dihydronaphthalene derivatives in good to excellent yields (Scheme 2).

Scheme 1



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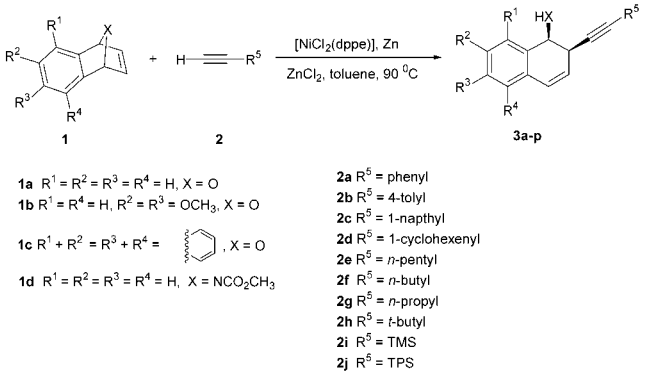
Scheme 2



Metal-catalyzed coupling of terminal acetylenes with alkynes[5] and alkenes[6] has attracted considerable attention recently as a result of the facts that these reactions are totally atom economical and the products may be used as versatile building blocks for organic synthesis,[7] but there is still no example of ring-opening[8−11] addition of acetylenes to bicyclic alkenes reported. Moreover, the dihydronaphthalene skeleton of the products in Scheme 2 is found in a wide range of naturally occurring molecules.[12] This nickel-catalyzed reaction offers a convenient method for the construction of the dihydronaphthalene framework in one pot from easily accessible starting materials.

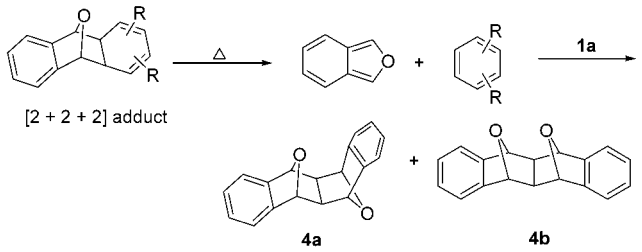
Treatment of 7-oxabenzonorbornadiene (**1a**) (1.0 mmol) with phenylacetylene (2.0 mmol) in the presence of $NiCl_2$-(dppe), (dppe = 1,2-bisdiphenylphosphinoethane) and zinc powder in toluene at 90 °C for 16 h gave the corresponding *cis*-2-alkynyl-1,2-dihydronaphthalen-1-ol **3a** in 54% yield along with substantial amount of products **4a** and **4b** in 20% and 4% yields, respectively (Schemes 2 and 3; Table 1, entry 2). Addition of a catalytic amount of $ZnCl_2$ (0.20 mL of 0.10 M solution) greatly increased the yield of product **3a** to 94% with concomitant decrease of product **4a** and **4b** to less than 2% yield (entry 5). Control experiments indicate that no reaction occurs at all in the absence of nickel catalyst (Table 1, entry 1). The reaction rate is very slow without Zn powder (entries 3 and 4). However, only a small amount of Zn (20 mol % relative to **1a**) is required for the reaction to proceed (entry 6). The stereochemistry of **3a** is established on the basis of the coupling constant in the ^{1}H NMR spectrum of the two methine protons near to the hydroxyl and the alkynyl groups on the ring.[13,14] As shown in Scheme 3, products **4a**

Table 1. Effect of Nickel Complex, Solvent, and Lewis Acid on the Coupling of 7-Oxabenzonorbornadiene (**1a**) with Phenylacetylene (**2a**)[a,b]

entry	catalyst	solvent	lewis acid	**3a**	**4a**	**4b**
1	Zn	toluene	$ZnCl_2$			
2[c]	Ni(dppe)Cl_2/Zn	toluene		54	20	4
3[d]	Ni(dppe)Cl_2	toluene	$ZnCl_2$	5		
4[e]	Ni(dppe)Cl_2	toluene	$ZnCl_2$	18		
5	**Ni(dppe)Cl_2/Zn**	**toluene**	**$ZnCl_2$**	**94**	**2**	
6[f]	Ni(dppe)Cl_2/Zn	toluene	$ZnCl_2$	80		
7	Ni(PPh_3)$_2Br_2$/Zn	toluene	$ZnCl_2$	8	39	10
8[g]	Ni(PPh_3)$_2Br_2$/Zn/PPh_3	toluene	$ZnCl_2$		64	16
9	Ni(dppe)Cl_2/Zn	THF	$ZnCl_2$	28	39	17
10	Ni(dppe)Cl_2/Zn	CH_3CN	$ZnCl_2$	23	12	3
11	Ni(dppe)Cl_2/Zn	DMF	$ZnCl_2$	24	13	5
12	Ni(bipy)Cl_2/Zn	toluene	$ZnCl_2$			
13	Ni(dppm)Br_2/Zn	toluene	$ZnCl_2$	16	11	5
14	Ni(dppe)Br_2/Zn	toluene	$ZnCl_2$	90		
15	Ni(dppp)Br_2/Zn	toluene	$ZnCl_2$	52		
16	Ni(dppb)Br_2/Zn	toluene	$ZnCl_2$	25	14	4
17	Ni(dppe)Cl_2/Zn	toluene	ZnI_2	74		

[a] Unless stated otherwise, all reactions were carried out using a Ni complex (0.0500 mmol), Zn (2.75 mmol), $ZnCl_2$ (0.20 mL of 0.100 M THF solution), 7-oxa- or 7-azanorbornadienes (**1**) (1.00 mmol), phenyl acetylene (**2**) (2.00 mmol), and solvent (5.0 mL) at 90 °C under N_2 for 16 h. [b] Yields were determined by ^{1}H NMR using mesitylene as an internal standard.[c] No $ZnCl_2$ was used. [d] 5.0 mol % Ni catalyst was used in the reaction. [e] 20 mol % Ni catalyst was used. [f] Zinc metal used is 0.200 mmol. [g] Extra PPh_3 (0.80 mmol) was added.

Scheme 3



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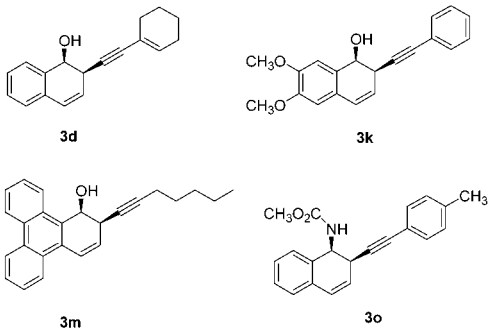
and **4b** are the results of [2 + 2 + 2] cocycloaddition of 7-oxabenzonorbornadiene with phenylacetylene followed by a retro Diels−Alder and Diels−Alder addition reactions.[1]

The present catalytic reaction is greatly influenced by the ligand and solvent used. Table 1 summarizes the effect of reaction conditions on the reaction of **1a** with **2a**. Both Ni(dppe)Cl_2 and Ni(dppe)Br_2 in the presence of Zn and $ZnCl_2$ (entries 5 and 14) give high yields of product **3a**. Ni(dppp)Br_2 affords high selectivity but lower yield of product **3a** (entry 15). Other nickel complexes Ni(bipy)Cl_2, Ni(dppm)Br_2, Ni(dppb)Br_2, and Ni(PPh_3)Br_2 either fail to give the desired product or result in low selectivity of **3a** (entries 7, 8, 12−14, and 16). The solvent used is critical for the present catalytic reaction. Toluene appears to be the best for this catalytic ring-opening addition, giving **3a** in 94% yield (entry 5). The use of THF, CH_3CN, or DMF as solvent led to low selectivity of **3a** and the formation of substantial amount of [2 + 2 + 2] cocycloaddition products (entries 9−11). While the exact reason for the observed ligand and solvent dependence of the present reaction is not entirely clear, it is noteworthy that Ni(dppe)Cl_2 is not readily reduced by zinc in toluene but is reduced to Ni(0) rapidly in coordinating solvent such as acetonitrile and DMF, as indicated by the rate of color change to green of the solution as it is heated at 90 °C. Compared to Ni(dppe)Cl_2, Ni(PPh_3)$_2Br_2$ is reduced much faster to Ni(0) in toluene. These observations provide the base for the mechanism proposed of the present ring-opening addition reaction (vide infra).

Under similar reaction conditions, the ring-opening addition reaction can be extended to various aliphatic and aromatic terminal acetylenes; the results are summarized in Table 2. Thus, **1a** reacts smoothly with **2b**−**i** ($R^5C{\equiv}CH$),



where R^5 = 4-tolyl, 1-naphthyl, cyclohexenyl, *n*-pentyl, *n*-butyl, *n*-propyl, *tert*-butyl, trimethylsilyl, and triphenylsilyl (Scheme 2, Table 2, entries 2−10), to give the corresponding *cis*-2-alkynyl-1,2-dihydronaphthalene derivatives **3b**−**j** in 44−94% yields. In the same way, substituted 7-oxabenzonorbornadienes **1b** reacts with phenylacetylene **2a** and 1-heptyne **2e** to afford the corresponding ring-opening addition products **3k** and **3l** in 74% and 63% yields, respectively (entries 11 and 12). The ring-opening addition can be further applied to the reaction of **1c** with terminal acetylene **2e** affording *cis*-2-alkynyl-1,2-dihydrotriphenylene **3m** in 81% yield. Similar to 7-oxabenzonorbornadienes, 7-azabenzonorbornadiene **1e** undergoes addition reaction with terminal acetylenes **2a,b** and **2e** cleanly in the presence of Ni(dppe)Cl_2, Zn powder and $ZnCl_2$ in toluene at 90 °C to give *cis*-2-alkynyl-1,2-dihydronaphthalenyl carbamate derivatives **3n**−**p** in 92%, 85%, and 69% yields, respectively (entries 14−16).

The mechanism for this unprecedented enyne coupling is appealing in view of the requirement of phosphine, solvent, zinc metal, and zinc halide for the catalytic reaction. While the detailed pathways are not clear, on the basis of the results in Table 1 and the stereochemistry of the products, the key pathways are proposed as shown in Scheme 4. The catalysis is likely initiated by the formation of zinc acetylide,[15] which undergoes transmetalation with nickel(II) species to give intermediate **5**. Coordination of 7-oxabenzonorbornadiene via the exo face of the carbon−carbon double bond to the Ni center and insertion of the double bond to the Ni-alkynyl bond results in the formation of intermediate **6**. Subsequent β-heteroatom elimination leads to intermediate **7**, which then undergoes transmetalation with $ZnCl_2$ to give the nickel(II) catalyst and zinc alkoxide **8**. The latter is converted to the final desired alkynyl product **3** by protonation.

There are several important features of the proposed mechanism.[16] First, the proposed exo coordination of 7-oxabenzonorbornadiene to the nickel center and the insertion of the carbon−carbon double bond to the nickel-alkynyl bond can accurately account for the cis stereochemistry of the hydroxy and alkynyl groups. Second, the active nickel

Table 2. Results of Nickel-Catalyzed Coupling of Bicyclic Olefins (**1**) with Terminal Acetylenes (**2**)[a]

entry	alkene (**1**)	alkyne (**2**)	time (h)	**3** yield[b]
1	**1a**	**2a**	16	**3a** 86 (94)
2	**1a**	**2b**	16	**3b** 80 (89)
3	**1a**	**2c**	16	**3c** 55 (60)
4	**1a**	**2d**	24	**3d** 63 (75)
5	**1a**	**2e**	30	**3e** 61 (68)
6	**1a**	**2f**	30	**3f** 59 (65)
7	**1a**	**2g**	30	**3g** 50 (60)
8	**1a**	**2h**	28	**3h** 64 (69)
9	**1a**	**2i**	24	**3i** 41 (46)
10	**1a**	**2j**	24	**3j** (44)
11	**1b**	**2a**	16	**3k** 62 (74)
12	**1b**	**2e**	28	**3l** 59 (63)
13	**1c**	**2e**	28	**3m** 70 (81)
14	**1d**	**2a**	16	**3n** 81 (92)
15	**1d**	**2b**	16	**3o** 80 (85)
16	**1d**	**2e**	24	**3p** 53 (69)

[a] Unless stated otherwise, all reactions were carried out using Ni(dppe)Cl_2 (0.0500 mmol), Zn (2.75 mmol), $ZnCl_2$ (0.200 mL of 0.100 M THF solution), 7-oxa- and 7-azanorbornadienes (**1**) (1.00 mmol), terminal acetylenes (**2**) (2.00 mmol), and toluene (5.0 mL) at 90 °C under N_2 for an appropriate time mentioned in the table. [b] Isolated yields; yields in the parenthesis were determined by ^1H NMR using mesitylene as an internal standard.

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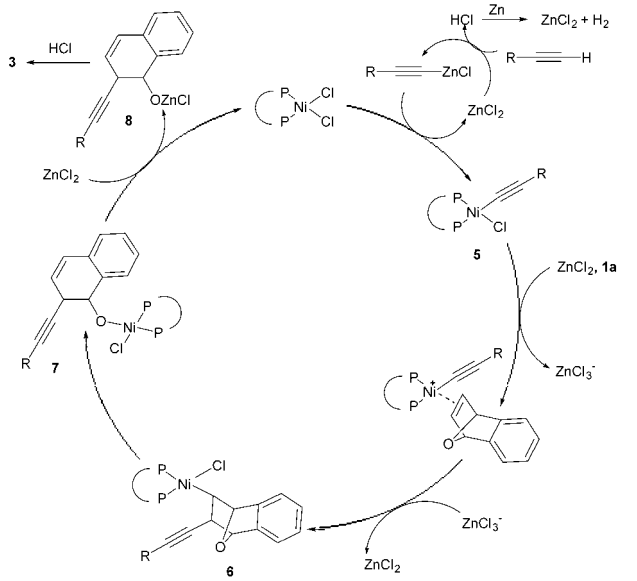
Scheme 4



species remain as Ni(II) during the reaction in contrast to the [2 + 2][3] and [2 + 2 + 2][1,2] cycloadditions of 7-oxa- and azabenzonorbornadienes with alkynes catalyzed by nickel complexes and zinc metal powder. In these cycloaddition reactions, Ni(II) species should be reduced to Ni(0) by zinc metal[17] to initiate the reaction. Finally, only the Ni(II) phosphine complexes that are hard to be reduced by zinc are good catalysts for the present ring-opening addition.

The requirement of zinc powder in the present catalytic reaction appears inconsistent with the proposed mechanism that only Ni(II) species are involved in the catalytic reaction. It should be noted that in many nickel complex and zinc-catalyzed reactions, zinc metal was known to reduce Ni(II) to Ni(0).[1−4,14] However, under the present catalytic conditions, Ni(dppe)X_2 is very difficult to be reduced in toluene by zinc, and even if it is reduced to Ni(0), the HCl produced during the formation of zinc acetylide will react with the Ni(0) species to give back Ni(II). We believe that, for the present reaction, a small amount of zinc metal is necessary particularly at the beginning of the catalytic reaction in order to produce a large enough concentration of zinc acetylide and thus Ni(II) acetylide. Zinc metal serves as an acid scavenger in this case. As the catalytic reaction proceeds, zinc alkoxide **8** is formed; this species competes with zinc metal for the HCl produced. Thus, zinc metal becomes less critical at the later stage of the reaction, and only a small amount of zinc metal is required for the present catalytic reaction. Further evidence supporting the proposed mechanism that only Ni(II) species are involved is the observation that **1a** reacts with zinc phenylacetylide generated in situ from PhCCLi and $ZnCl_2$ in the presence of Ni(dppe)Cl_2 in THF for 1 h at 60 °C to give **3a** in 40% yield.

An alternative pathway involving a key Ni-(π-allyl) intermediate from oxidative addition of **1a** to Ni(0),[16] followed by a nucleophilic addition of zinc acetylide to the π-allyl species, is less probable in view of the observed regiochemistry of the products and the observation that Ni(COD)$_2$/dppe (1:1) does not catalyze the present catalytic reaction.

In conclusion, we have developed a novel nickel-catalyzed ring-opening addition of terminal alkynes to bicyclic alkenes to afford products with extremely high stereoselectivity in fair to excellent yields. This addition reaction, which is highly atom economical, offers a convenient method for the synthesis of functionalized 1,2-dihydronaphthalene derivatives. Studies on the asymmetric version of this nickel-catalyzed reaction and the application in organic synthesis are in progress.

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Supporting Information Available: Experimental procedure, spectral data, and ^{1}H NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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