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Novel cyclization and reductive coupling of bicyclic olefins with alkyl propiolates catalyzed by nickel complexes*

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Abstract: In this article, new metal-mediated cyclization and reductive coupling reactions of bicyclic olefins with alkynes are described. Oxabicyclic alkenes undergo cyclization with alkyl propiolates at 80 °C catalyzed by nickel complexes to give benzocoumarin derivatives in high yields. The reaction of bicyclic alkenes (oxa- and azacyclic alkenes) with alkyl propiolates at room temperature in the presence of the same nickel complex gave 1,2-dihydronapthelene derivatives in good-to-excellent yields. This reductive coupling reaction proceeds under very mild conditions in complete regio- and stereoselective fashion. A mechanism to account for the coumarin formation and the reductive coupling is proposed.

INTRODUCTION

The use of transition-metal complexes as catalysts in the intermolecular carbocyclization of enynes offers a unique means to construct a variety of synthetically important carbocycles and heterocycles with high efficiency not generally accessible by traditional methods [1]. Coumarin and its derivatives occur as structural subunits in numerous natural products that exhibit a wide range of biological activity [2]. Benzo-annulated coumarin derivatives show wide application in organic light-emitting devices and are used as electron-transporting emitters [3]. In addition, coumarin family is an important building block for the synthesis of a variety of fascinating polycyclic unnatural products. In this report, we show that $Ni(dppe)X_2$ in the presence of zinc powder efficiently catalyzes a novel cyclization of oxanorbornenes with propiolates to give benzocoumarins in good yields with complete regioselectivity [4]. To the best of our knowledge, this is the first example for the synthesis of benzocoumarins in a catalytic manner. In addition, we describe the reductive coupling of oxa- and azabicyclic alkenes with propiolates to give reductive ring-opening addition products in good yields with remarkable regio- and stereoselectivity [5]. The reaction is highly atom-economical [6], an important consideration of modern chemistry, and is also a convenient method to synthesize dihydronaphthalenes under mild conditions. The dihydronaphthalene skeleton was found in a wide range of naturally occurring compounds [7]. This report is related to our early results in the nickel-catalyzed cocylodimerization [8] and cocyclotrimerization [9] of olefins and alkynes.

[2+2] COCYCLODIMERIZATION OF BICYCLIC OLEFINS WITH ALKYNES

The reaction of oxa- and azabenzonorbornadienes **1** with internal and terminal alkynes **2** in the presence of $NiCl_2(PPh_3)_2$, PPh_3 and zinc powder in toluene at 90 °C for 24 h gave *exo* cyclobutene derivatives **3** in high yields (Scheme 1). The *exo* stereochemistry of these [2+2] cycloaddition products

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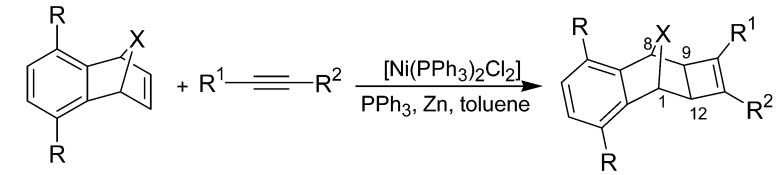


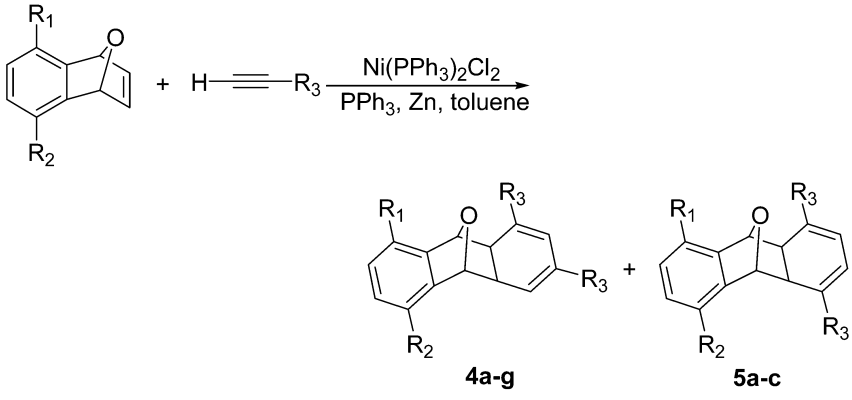
1a X = O, R = H **2** **3**
1b X = O, R = OCH_3
1c X = NCO_2Me, R = H

Scheme 1 Nickel-catalyzed [2+2] cycloaddition of bicyclic alkenes with alkynes.

was established based on the coupling constant of bridgehead protons and ring junction protons. The [2+2] cycloaddition reaction is highly sensitive to reaction conditions and the alkynes used.

[2+2+2] COCYCLOTRIMERIZATION OF BICYCLIC OLEFINS WITH ALKYNES

The reaction of oxabenzonorbornadiene with terminal aliphatic alkyne, such as 1-pentyne (**2a**) in the presence of $NiCl_2(PPh_3)_2$, PPh_3, and zinc powder in toluene at 18 °C for 24 h afforded a pair of two [2+2+2] cocyclotrimerization regio isomers **4a** and **5a** in excellent yield (Scheme 2). Whereas terminal acetylenes having bulkier substituents such as phenylacetylene (**2d**) and 1-ethynyl-1-cyclohexene (**2e**) reacted with oxabenzonorbornadiene regioselectively afforded only **4d** and **4e**, respectively, in high yields. Similarly, other substituted oxabenzonorbornadienes also underwent cocyclotrimerization smoothly with alkynes to afford the desired products.



4a-g **5a-c**

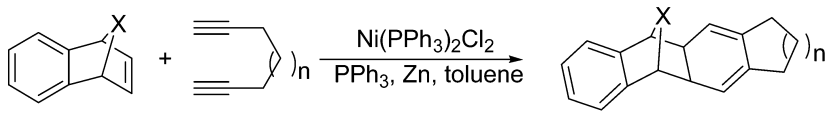
1a $R_1 = R_2 = H$
1d $R_1 = OMe$, $R_2 = H$
1b $R_1 = R_2 = OMe$

2a $R_3 = (CH_2)_2CH_3$
2b $R_3 = (CH_2)_3CH_3$
2c $R_3 = (CH_2)_4CH_3$
2d $R_3 = Ph$
2e R_3 = 

4a, 5a $R_1 = R_2 = H$, $R_3 = (CH_2)_2CH_3$
4b, 5b $R_1 = R_2 = H$, $R_3 = (CH_2)_3CH_3$
4c, 5c $R_1 = R_2 = H$, $R_3 = (CH_2)_4CH_3$
4d $R_1 = R_2 = H$, $R_3 = Ph$
4e $R_1 = R_2 = H$, R_3 = 
4f $R_1 = OCH_3$, $R_2 = H$, $R_3 = Ph$
4f' $R_1 = H$, $R_2 = OCH_3$, $R_3 = Ph$
4g $R_1 = R_2 = OCH_3$, $R_3 = Ph$

Scheme 2 [2+2+2] Cocycotrimerization of oxanorbornadienes with alkynes.

Interestingly, [2+2+2] cocyclotrimerization of diynes with oxanorbornadiene under standard reaction conditions afforded multiple-ring products in good yields (Scheme 3). Thus, 1,6-heptadiyne (**6a**) and 1,7-octadiyne (**6b**) react with **1a** and **1e** to give pentacyclic adducts **7a-d** in 62–75% yields.



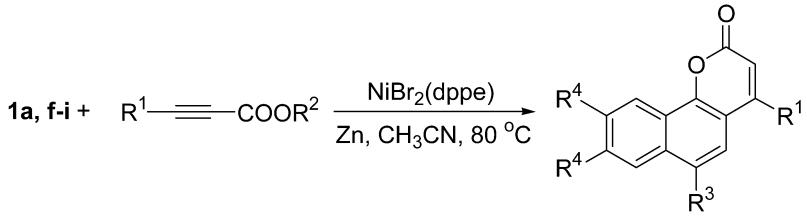
1a X= O **6a** n= 1
1e X= NSO_2Ph-*p*-CH_3 **6b** n= 2

7a. X= O, n= 1 62 %
7b X= O, n= 2 70 %
7c X= NSO_2Ph-*p*-CH_3, n= 1 71 %
7d X= NSO_2Ph-*p*-CH_3, n= 2 75 %

Scheme 3 Nickel-catalyzed [2+2+2] cycloaddition of bicyclic olefins with diynes.

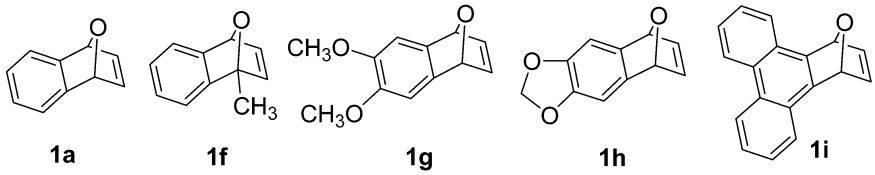
CYCLIZATION OF OXABICYCLIC ALKENES WITH PROPIOLATES CATALYZED BY Ni(dppe)X_2

When 7-oxabenzonorbornadiene (**1a**) was treated with methyl butyn-2-oate (**8a**) in the presence of $NiBr_2$(dppe) [dppe: bis(diphenylphosphino)ethane] and zinc metal powder in acetonitrile at 80 °C, a benzocoumarin product **9a** derived from one molecule of **1a** and **8a** (Scheme 4) was isolated in



8a-h **9a-o**

8a $R^1 = CH_3$, $R^2 = CH_3$
8b R^1 = Ph, $R^2 = CH_2CH_3$
8c R^1 = *n*-Bu, $R^2 = CH_3$
8d $R^1 = (CH_2)_4CH_3$, $R^2 = CH_3$
8e R^1 = TMS, $R^2 = CH_2CH_3$
8f $R^1 = CH_2OCH_3$, $R^2 = CH_3$
8g $R^1 = CH{=}CHCOOCH_3$, $R^2 = CH_3$
8h R^1 = H, $R^2 = CH_3$

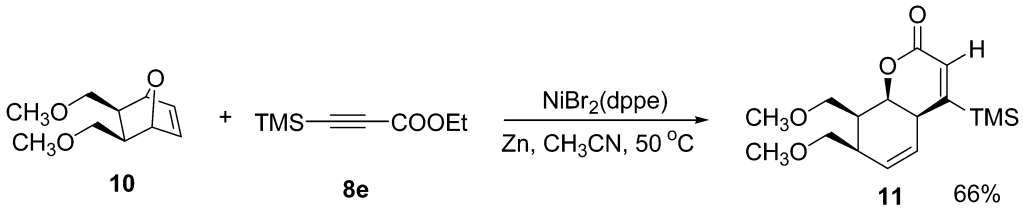


1a **1f** **1g** **1h** **1i**

Scheme 4 Nickel-catalyzed cyclization of 7-oxabenzonorbornadienes with alkyl propiolates.

87% yield. The phosphine ligand employed in the present catalytic reaction is crucial for the success of the reaction. A bidentate phosphine is required for the reaction to proceed, and among several bidentate phosphine ligands employed, dppe gave the best result. The choice of solvent is also vital to the catalytic reaction. The best solvent for the present catalytic reaction is acetonitrile. To test the efficacy of our catalyst system, we performed cyclization reaction of **1a** with a variety of substituted alkyl propiolates **8** ($R^1C{\equiv}CCO_2R^2$). Thus, the reaction of **1a** with **8b–e**, where R^1 = Ph, *n*-Bu, *n*-$CH_3(CH_2)_4$, and $(CH_3)_3Si$, gave the corresponding benzocoumarin derivatives **9b–e** in good yields.

The present cyclization is successfully extended to substituted 7-oxabenzonorbornadienes **1f–i** and **10**. Thus, the reaction of **1f** bearing a methyl group at a bridgehead with alkynes **8a** and **8d** gave regioselectively benzocoumarins **9i** and **9j** in 62 and 71% yields, respectively. Similarly, treatment of substituted 7-oxabenzonorbornadienes **1g** and **1h** with propiolates gave the corresponding benzocoumarins in moderate to good yields and the reaction of **1i** with **8a** afforded **9o** in 73% yield. The cyclization of substituted 7-oxanorbornene **10** with $TMSC{\equiv}CCO_2Et$ in CH_3CN at 50 °C also proceeded smoothly in completely regio- and stereoselective fashion to give tetrahydyocoumarin **11** (Scheme 5).

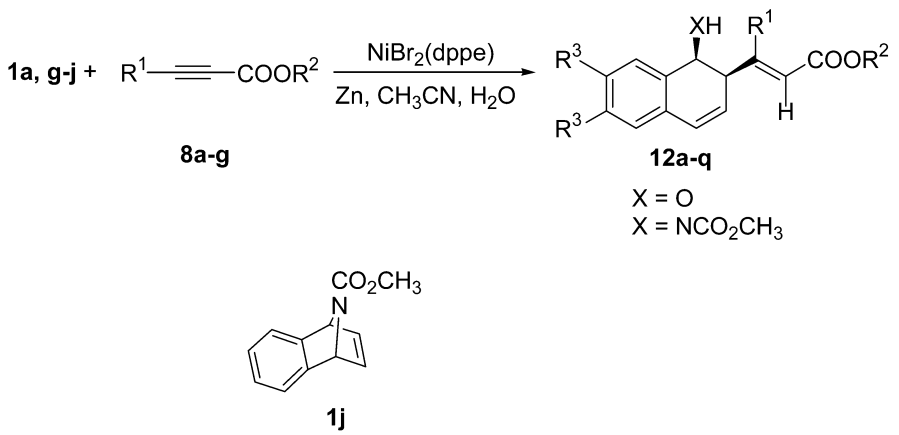


Scheme 5 Cyclization of 7-oxanorbornene **10** with propioate **8e**.

REDUCTIVE COUPLING OF OXABICYCLIC ALKENES WITH PROPIOLATES

The reaction of **1a** with methyl-2-butynoate in the presence of $Ni(dppe)Br_2$ and zinc powder in acetonitrile at room temperature gave 2-alkenyl-1,2-dihydronapthalen-1-ol **12a** in 60% yield. Addition of water (1.5 equiv) greatly increases the yield to 91% (Scheme 6). This new interesting reductive coupling reaction is remarkably regio- and stereoselective.

Under similar reaction conditions, **1a** also undergoes reductive coupling with various propiolates ($R^1C{\equiv}CCO_2R^2$) (Scheme 6) to give the corresponding *cis*-1,2-dihydronapthalene derivatives **12b–g** in

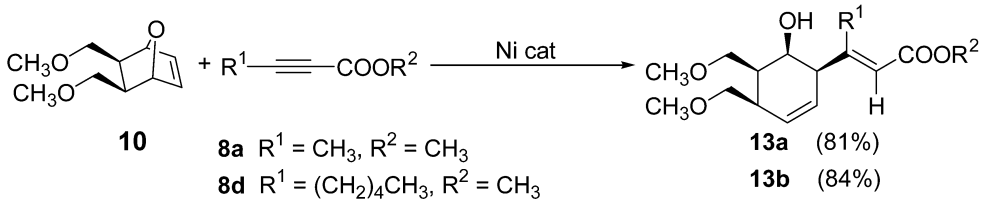


Scheme 6 Reductive coupling of 7-oxa- and azabenzonorbornadienes with alkyl propiolates catalyzed by nickel complexes.

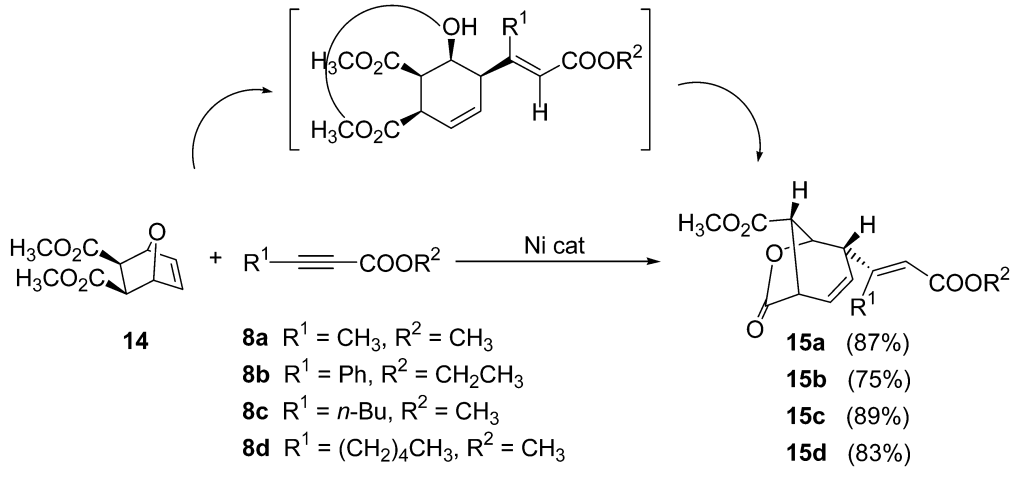
59–93% yields. In the same way, treatment of substituted 7-oxabenzonorbornadienes **1g** and **1h** with different propiolates provides the corresponding reductive coupling products in good to excellent yields. Furthermore, the reductive coupling can also be applied to the reaction of phenanthrene derivative **1i** with **8a** and **8e** affording *cis*-1,2-dihydrotriphenylenes **12m** and **12n** in 81% and 72% yields, respectively.

Similar to 7-oxabenzonorbornadienes, azabenzonorbornadiene **1j** couples with propiolates cleanly in the presence of Ni(dppe)Br_2, Zn, and water to give *cis*-1,2-dihydronapthalene derivatives **12o–q** in fair-to-good yields. In all these reactions, the products show *trans* geometry on the alkenyl groups. The *trans* stereochemistry was established based on the results of NOE experiments and on the coupling constant (J = 16 Hz) of the two olefinic protons of product **12g**.

The present catalytic reaction is successfully extended to substituted 7-oxanorbornenes. The reaction of oxabicyclic alkene **10** with **8a** in acetonitrile proceeded efficiently to give cyclohexene derivative **13a** with all substituents *cis* to each other in 81% yield at room temperature (Scheme 7). Four stereocenters are readily constructed in a single step in this catalytic reaction. Surprisingly, treatment of **14** with propiolate **8a** under similar conditions did not afford the anticipated product, but gave instead a bicyclic γ-lactone **7a** in 87% (Scheme 8). Other substituted propiolates **8b–d** also react with **14** under similar conditions to afford the corresponding bicyclic γ-lactones **15b–d**, respectively, in 75–89% yields.



Scheme 7 Reductive coupling of 7-oxanorbornene **10** with propiolates.

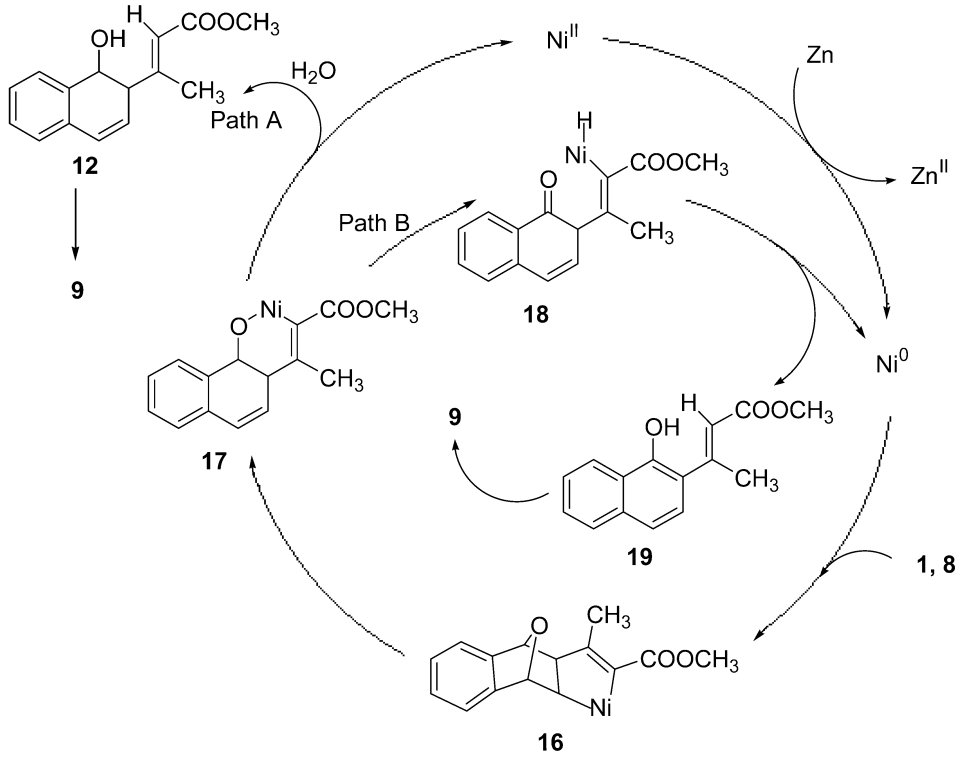


Scheme 8 Cyclization of 7-oxanorbornene **14** with propiolates.

MECHANISM FOR CYCLIZATION AND REDUCTIVE COUPLING

The mechanism for benzocoumarin formation is intriguing in view of the extensive bond formation and breaking processes required. While the detailed pathways is not clear, key steps are proposed as shown

in Scheme 9 on the basis of the preceding results and the established nickel chemistry. The reduction of $NiBr_2$(dppe) by zinc likely initiates the catalytic reaction. Coordination of both **1** and **8** to the Ni(0) followed by cyclometalation forms a nickelacyclopentene [10] intermediate **16**. Subsequent β-oxy elimination to give **17** [11] and protonation affords intermediate **12** and Ni(II) species. The latter is reduced by Zn to regenerate the Ni(0) catalyst, while **12** undergoes *cis-trans* isomerization, dehydrogenation, and lactonization to give the final benzocoumarin product. Compound **12** is the reductive coupling product of **1** and **8**. Another pathway (B) involving β-hydride elimination of **17** to give ketone **18** cannot be ruled out. The intermediate then undergoes reductive elimination and tautomerization to afford napthol **19**. Further E/Z isomerization and subsequent lactonization provides product **9**.



Scheme 9 Plausible catalytic cycle for benzocoumarin formation and reductive coupling reaction.

CONCLUSION

In conclusion, we have demonstrated a novel nickel-catalyzed cyclization and a reductive coupling reaction of bicyclic alkenes **1** with propiolates **8** to give coumarin and 1,2-dihydronapthalene derivatives, respectively, in one pot in high regio- and stereoselectivity. The mechanism is interesting, involving extensive bond formation and breaking for the cyclization reaction. In addition, the reductive coupling reaction proceeds under very mild conditions with high atom economy. Studies on the asymmetric version of this nickel-catalyzed reaction, the scope, and the application in organic synthesis are in progress.

ACKNOWLEDGMENTS

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