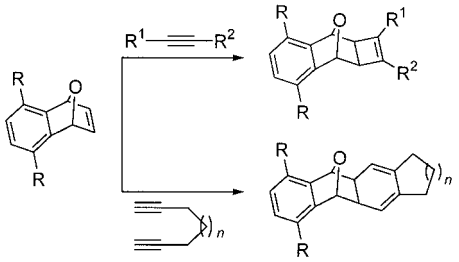
Nickel-Catalyzed Highly Regio- and Stereoselective Cyclization of Oxanorbornenes with Alkyl Propiolates: A Novel Method for the Synthesis of Benzocoumarin Derivatives**

Dinesh K. Rayabarapu, Thota Sambaiah, and Chien-Hong Cheng*

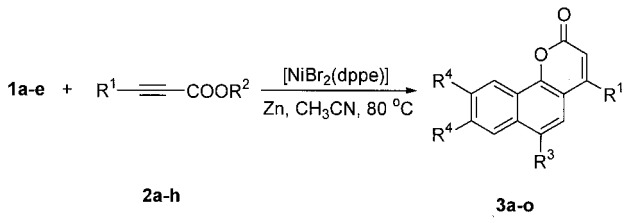
Transition metal catalyzed cyclizations of alkenes and alkynes are powerful methods for the synthesis of various carbocyclic and heterocyclic compounds.[1] Recently, we[2, 3] and others[4, 5] observed that nickel complexes effectively catalyze the cycloaddition of 7-oxa- and 7-azabenzonorbornadienes with alkynes to give [2+2][2] and [2+2+2][3a,b] cycloadducts (Scheme 1). The reactions of alkenes with



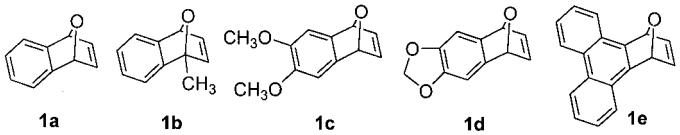
Scheme 1. Ni-catalyzed [2+2] and [2+2+2] cycloaddition of 7-oxabenzonorbornadienes with alkynes.

alkynes depend greatly on the reaction conditions. Here we report a new cyclization of 7-oxabenzonorbornadienes and alkyl propiolates with catalysis by nickel complexes to give benzocoumarin derivatives with remarkably high regio- and stereoselectivity (Scheme 2). The coumarins are an important class of naturally occurring compounds, many of which exhibit useful biological activity.[6] Benzo-annulated coumarin derivatives are also known as electron-transporting emitters.[7] However, the traditional methods for synthesizing benzocoumarin derivatives are limited by poor yields and harsh reaction conditions.[8] The present nickel-catalyzed reaction provides a very convenient method for the one-pot synthesis of benzocoumarins under mild conditions. In addition, the catalytic mechanism for product formation is of interest.

Treatment of 7-oxabenzonorbornadiene (**1a**) with methyl butyn-2-oate (**2a**) in the presence of [$NiBr_2$(dppe)] (dppe = bis(diphenylphosphanyl)ethane) and zinc metal powder in acetonitrile at 80 °C gave the cyclization product **3a** in 87% yield. The structure of **3a** was confirmed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and X-ray structure analysis.[13] To the best of our knowledge, this cyclization is



2a: $R^1 = CH_3$, $R^2 = CH_3$
2b: $R^1 = Ph$, $R^2 = CH_2CH_3$
2c: $R^1 = n$Bu, $R^2 = CH_3$
2d: $R^1 = (CH_2)_4CH_3$, $R^2 = CH_3$
2e: $R^1 = SiMe_3$, $R^2 = CH_2CH_3$
2f: $R^1 = CH_2OCH_3$, $R^2 = CH_3$
2g: $R^1 = CH{=}CHCOOCH_3$, $R^2 = CH_3$
2h: $R^1 = H$, $R^2 = CH_3$



Scheme 2. Cyclization of 7-oxabenzonorbornadienes **1** with alkyl propiolates **2**. Spectroscopic data of the new compounds can be found in the supporting information.

unprecedented. Control experiments showed that in the absence of either [$NiBr_2$(dppe)] or zinc metal, the desired product was not obtained.

The phosphine ligand employed is crucial to the success of the present catalytic reaction. A bidentate phosphine is required for the reaction to proceed. Among several bidentate phosphine ligands examined, dppe gave the best results and afforded **3a** in 95% yield. Other bidentate phosphines such as 1,1′-bis(diphenylphosphanyl)ferrocene (dppf), methylenebis(diphenylphosphane) (dppm), and 1,3-propanediylbis(diphenylphosphane) (dppp) are less effective, giving **3a** in 53, 47, and 26% yield, respectively. Nickel complexes of monodentate phosphines that are efficient catalysts for the [2+2][2] and [2+2+2][3a,b] cycloaddition of **1a** with various alkynes are essentially inactive in the formation of **3a**.

The choice of solvent is also vital to the catalytic reaction. The best solvent is acetonitrile, in which **3a** was obtained in 95% yield. Dimethylformamide is also effective (44% yield). In THF and toluene, only the [2+2+2] cycloadduct was observed,[3] while no cycloaddition product was detected in dichloromethane.

Under similar conditions, **1a** underwent cyclization with a variety of substituted alkyl propiolates **2** to give the corresponding benzocoumarin derivatives. Thus, the reaction of **1a** with **2b**–**e** gave the corresponding benzocoumarin derivatives **3b**–**e** in good yields (see Scheme 2 and Table 1). Alkyne **2f** gave, in addition to **3f** (70%), the naphthalene derivative **4f** (21%; entry 6). The reaction of propiolate **2g** with **1a** did not give any desired cyclization product under standard conditions, but proceeded smoothly in the presence of one equivalent of acetic acid to give **3g**. The α,β-unsaturated carbon–carbon double bond of **2g** is hydrogenated in **3g**. Unsubstituted propiolate **2h** reacts with **1a** to give **4h** in 57% yield instead of the cyclization product. The present Ni

[*] Prof. C.-H. Cheng, D. K. Rayabarapu, Dr. T. Sambaiah
Department of Chemistry
Tsing Hua University
Hsinchu, 300 (Taiwan)
Fax: (+886) 3-5724698
E-mail: chcheng@mx.nthu.edu.tw

[**] We thank the National Science Council (NSC 89-2119-M-007-010) and the Ministry of Eduction (89-FAO4-AA) of the Republic of China for support of this research.

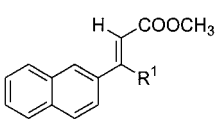
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/01/4007-1286 $ 17.50+.50/0

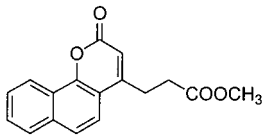
Table 1. Results of nickel-catalyzed cyclization of 7-oxanorbornadienes **1** with propiolates **2**.[a]

Entry	Alkene	Alkyne	Product (yield [%])[b]
1	**1a**	**2a**	**3a** (87)
2	**1a**	**2b**	**3b** (75)
3	**1a**	**2c**	**3c** (89)
4	**1a**	**2d**	**3d** (83)
5	**1a**	**2e**	**3e** (60)[d]
6	**1a**	**2f**	**3f** (70) + **4f** (21)
7[c]	**1a**	**2g**	**3g** (68)
8	**1a**	**2h**	**4h** (57)
9	**1b**	**2a**	**3i** (62)
10	**1b**	**2d**	**3j** (71)[d]
11	**1c**	**2a**	**3k** (80)
12	**1c**	**2c**	**3l** (72)
13	**1d**	**2a**	**3m** (65)[d]
14	**1d**	**2d**	**3n** (56)
15	**1e**	**2a**	**3o** (73)

[a] Unless stated otherwise, all reactions were carried out with [$NiBr_2$(dppe)] (0.05 mmol), Zn (2.75 mmol), **1** (1.0 mmol), **2** (1.2–2.0 mmol), and CH_3CN (3.0 mL) at 80 °C for 12 h under 1 atm N_2. [b] Yield of isolated product. [c] 1.0 mmol of acetic acid was added. [d] Yield determined by ^1H NMR spectroscopy with mesitylene as internal standard.



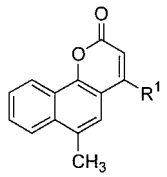
4f $R^1 = CH_2OCH_3$
4h $R^1 = H$



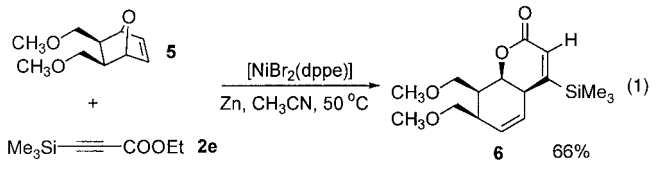
3g

catalyst system is inactive for the cyclization of $EtO_2CC{\equiv}C$-CO_2Et with **1a**. The results of these studies are summarized in Table 1. All benzocoumarin products show a characteristic peak at around $\delta = 6.4$ in the ^1H NMR spectrum for the olefinic α-proton of the lactone ring. The presence of an α,β-unsaturated carbonyl group in these benzocoumarins is evidenced by a signal at $\delta \approx 160$ in the ^{13}C NMR spectrum and a strong absorption at about 1710 cm^{-1} in the IR spectrum. Naphthalene derivatives **4f** and **4h** were also fully characterized by spectroscopic methods. The alkenyl substituents on both products have *trans* stereochemistry according to the results of NOE experiments with **4f** and the coupling constant (16 Hz) of the two olefinic protons of **4h**.

The present cyclization was successfully extended to substituted 7-oxabenzonorbornadienes **1b–e** and **5** [see Eq. (1)] The reaction of **1b**, which bears a methyl group at a bridgehead atom, with alkynes **2a** and **2d** gave regioselectively benzocoumarins **3i** and **3j** in 62 and 71% yield, respectively. Similarly, treatment of substituted 7-oxabenzonorbornadienes **1c** and **1d** with propiolates gave the corresponding benzocoumarins in moderate to good yields (Table 1, entries 11–14), and the reaction of **1e** with **2a** afforded **3o** in 73% yield. The cyclization of substituted 7-oxanorbornene **5** with **2e** in CH_3CN at 50 °C also proceeded smoothly in completely regio- and stereoselective[9] fashion to give tetrahydrocoumarin **6** [Eq. (1)]. This product was fully characterized by

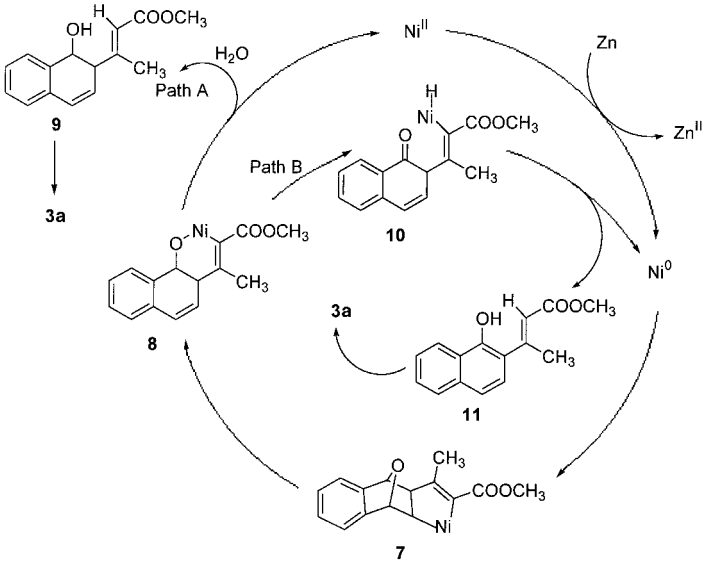


3i $R^1 = CH_3$
3j $R^1 = (CH_2)_4CH_3$



spectroscopic methods. In the ^1H NMR spectrum, the four characteristic methine signals appear at $\delta = 4.82$, 3.21, 2.53, and 2.13. The ^{13}C NMR data, the results of DEPT experiments, and MS data are also consistent with the proposed structure. It is noteworthy that tetrahydrocoumarins are intermediates for the synthesis of natural products.[10]

The mechanism for benzocoumarin formation is intriguing in view of the extensive bond-formation and bond-breaking processes required. While the detailed pathway is not clear, key steps are proposed in Scheme 3 for the synthesis of **3a** on



Scheme 3. A plausible catalytic cycle for benzocoumarin formation.

the basis of the above results and the established nickel chemistry. The reduction of [$NiBr_2$(dppe)] by zinc likely initiates the catalytic reaction. Coordination of both **1a** and **2a** to Ni^0 followed by cyclometalation forms a nickelacyclopentene[11, 12] intermediate **7**. Subsequent β-oxy elimination to form **8** and protonation give the intermediate organic product **9** and an Ni^{II} species (path A). The latter is reduced by Zn to regenerate the Ni^0 catalyst, while **9** undergoes *cis–trans* isomerization, dehydrogenation, and lactonization to give the final benzocoumarin product. Compound **9** may be considered as a reductive coupling product of **1a** and **2a**. Evidence supporting this intermediate comes from the observation of products **4f**, **4h**, and tetrahydrocoumarin **6** [Eq. (1)]. Presumably, **4f** and **4h** are obtained from dehydration of the corresponding reductive coupling products similar in structure to **9**, while **6** results from *cis–trans* isomerization followed by cyclization of the reductive coupling product of **5** and **2e**. Another pathway (B) involving β-hydride elimination of **8** to give ketone **10** cannot be ruled out. The intermediate then undergoes reductive elimination and tau-

  1433-7851/01/4007-1287 $ 17.50+.50/0

tomerization to afford naphthol **11**. Further *E*/*Z* isomerization and subsequent lactonization provide product **3a**.

In conclusion, we have demonstrated a novel nickel-catalyzed cyclization of tricyclic alkenes **1** with propiolates **2** to give benzocoumarins or tetrahydrocoumarins in a one-pot reaction. More detailed studies on the scope, mechanism, and utility of this reaction are in progress.

Experimental Section

General procedure for the cyclization of 7-oxabenzonorbornadienes **1** with alkyl propiolates **2**: Freshly distilled CH_3CN (3.0 mL) and **2** (1.2–2.0 mmol) were added to **1** (1.00 mmol), [$NiBr_2$(dppe)] (0.05 mmol), and zinc powder (0.180 g, 2.75 mmol) under nitrogen. The reaction mixture was heated with stirring at 80 °C for 12 h and then cooled and stirred in air for 15 min. The mixture was filtered through Celite and silica gel and washed with dichloromethane. The filtrate was concentrated, and the residue was purified on a silica gel column with hexane/ethyl acetate as eluent to afford the desired cyclization product **3**.

Received: October 23, 2000 [Z15981]

[1] a) For recent reviews on metal-catalyzed carbocyclizations, see D. B. Grotjahn in *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, L. S. Hegedus), Pergamon, Oxford, **1995**, p. 703, 741; b) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; c) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635; d) H. W. Frühauf, *Chem. Rev.* **1997**, *97*, 523.

[2] D.-J. Huang, D. K. Rayabarapu, L.-P. Li, T. Sambaiah, C.-H. Cheng, *Chem. Eur. J.* **2000**, *6*, 3706.

[3] a) D.-J. Huang, T. Sambaiah, C.-H. Cheng, *New J. Chem.* **1998**, *22*, 1147; b) T. Sambaiah, D.-J. Huang, C.-H. Cheng, *J. Chem. Soc. Perkin. Trans. 1* **2000**, 195; c) T. Sambaiah, L.-P. Li, D.-J. Huang, C.-H. Lin, D. K. Rayabarapu, C.-H. Cheng, *J. Org. Chem.* **1999**, *64*, 36; d) T.-Y. Hsiao, K. C. Santhosh, K.-F. Liou, C.-H. Cheng, *J. Am. Chem. Soc.* **1998**, *120*, 12232.

[4] For recent Ni-catalyed [2+2+2] cycloadditions, see a) S. Ikeda, N. Mori, Y. Sato, *J. Am. Chem. Soc.* **1997**, *119*, 4779; b) N. Mori, S. Ikeda, Y. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 2722.

[5] a) J. Seo, H. M. P. Chui, M. J. Heeg, J. Montgomery, *J. Am. Chem. Soc.* **1999**, *121*, 476; b) T. Tsuda, T. Kiyoi, T. Miyane, T. Saegusa, *J. Am. Chem. Soc.* **1988**, *110*, 8570; c) Y. Sato, T. Nishimata, M. Mori, *J. Org. Chem.* **1994**, *59*, 6133.

[6] a) Antitumor activity: T. Harayama, H. Yasuda, *Heterocycles* **1997**, *46*, 61, and references therein; b) Anticoagulants: R. M. Pauli in *Handbook of Experimental Pharmacology*, *Vol. 124* (Eds.: R. J. Kavlock, G. P. Daston), **1997**, p. 191; c) HIV-1 protease inhibitors: S. Wang, G. W. A. Milne, X. Yan, I. J. Posey, M. C. Nicklaus, L. Graham, W. G. Rice, *J. Med. Chem.* **1996**, *39*, 2047; d) Antimetastatics: E. Gorelik, *Cancer Res.* **1987**, *47*, 809.

[7] a) *Organic Electroluminescent Materials and Devices* (Eds.: S. Miyata, H. S. Nalwa), Gordon and Breach, Amsterdam, **1997**, Chaps. 5, 8, 12, 14; b) T. Shibata (Konishiroku Photo), JP 6122874, **1994**; c) J. Stampfl, S. Tasch, G. Leising, U. Scherf, *Synth. Met.* **1995**, *71*, 2125; d) C. W. Tang, S. A. Van Slyke, C. H. Chen, *J. Appl. Phys.* **1989**, *65*, 3610.

[8] a) J. Somoid, B. Stanovnik, *Tetrahedron* **1998**, *54*, 9799; b) R. Toplak, L. Selic, G. Sorsak, B. Stanovnik, *Heterocycles* **1997**, *45*, 555; c) T.-S. Li, Z.-H. Zhang, F. Yang, C.-G. Fu, *J. Chem. Res. Synop. 1* **1998**, 38; d) V. Singh, J. Singh, K. P. Kaur, G. L. Kad, *J. Chem. Res. Synop. 2* **1997**, 58; e) D. T. Connor, R. J. Sorenson, *J. Heterocycl. Chem.* **1981**, *18*, 587; f) D. N. Nicolaides, S. G. Adampoulos, D. A. Lefkaditis, K. E. Litnas, *J. Chem. Soc. Perkin Trans. 1* **1990**, 2127.

[9] For compounds with similar stereochemistry, see a) M. Lautens, J.-H. Renaud, S. Hiebert, *J. Am. Chem. Soc.* **2000**, 122, 1804, and references therein; b) C.-C. Feng, M. Nandi, T. Sambaiah, C.-H. Cheng, *J. Org. Chem.* **1999**, *64*, 3539.

[10] C. A. Broka, B. Ruhland, *J. Org. Chem.* **1992**, *57*, 4888.

[11] J. Montgomery, *Acc. Chem. Res.* **2000**, 33, 467.

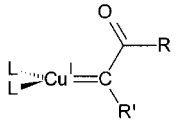
[12] For oxanickelacycles see: a) M. Kimura, S. Matsuo, K. Shibata, Y. Tamaru, *Angew. Chem.* **1999**, *111*, 3586; *Angew. Chem. Int. Ed.* **1999**, *38*, 3386; b) Y. Sato, T. Takanashi, M. Mori, *Organometallics* **1999**, *18*, 4891.

[13] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-151946. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Copper(I) Carbenes: The Synthesis of Active Intermediates in Copper-Catalyzed Cyclopropanation**

Bernd F. Straub and Peter Hofmann*

The cyclopropanation of olefins with α-carbonyldiazoalkanes mediated by homogeneous copper catalysts has been known for more than 30 years, and was the first reported example of enantioselective transition metal catalysis.[1] Despite this long history, copper(I) α-carbonyl carbene complexes of type **1**, which are generally assumed to be the active intermediates, have remained undetected so far.[2] It is crucial to know their structure in solution to understand the enantiomeric and diastereomeric selectivities that can be achieved if chiral spectator ligands are utilized in cyclopropanation catalysis.[3]



1

L = nitrogen or oxygen donor ligand
R = alkyl, aryl, alkoxy, amide
R' = aryl, acyl

Copper carbene complexes in the literature are limited to the linear d^{10}-ML_2 type, with Wanzlick–Arduengo carbene ligands substituted with strong donor groups.[4] These complexes are inactive in cyclopropanation chemistry. Generally, nickel-triad and coinage-metal carbene complexes of the d^{10}-ML_3 type are scarce,[5] probably as a result of the antibonding interaction between the metal d^{10} subshell and the sp^2 lone pair of a singlet carbene fragment.[6]

We have recently introduced an extremely basic, sterically demanding, and highly symmetric iminophosphanamide ligand into organometallic copper chemistry.[7] It stabilizes otherwise elusive or labile copper coordination modes by enhanced metal-to-ligand back donation and by steric shielding of the copper fragment.[7] We used the stable and neutral copper(I) ethylene complex **2**[7a] to isolate the α-carbonyldiazoalkane complex **3**, which is a stabilized model for

[*] Prof. Dr. P. Hofmann, Dr. B. F. Straub
Organisch-Chemisches Institut
der Ruprecht-Karls-Universität Heidelberg
INF 270, 69120 Heidelberg (Germany)
Fax: (+49) 6221-54-4885
E-mail: ph@phindigo.oci.uni-heidelberg.de

[**] B.F.S. thanks the Fonds der Chemischen Industrie for a doctoral fellowship.

  1433-7851/01/4007-1288 $ 17.50+.50/0