Ruthenium Catalysis

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Ruthenium-Catalyzed Coupling of Oxabenzonorbornadienes with Alkynes Bearing a Propargylic Oxygen Atom: Access to Stereodefined Benzonorcaradienes**

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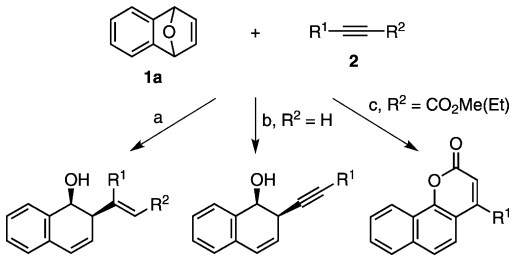
Dedicated to Professor Barry M. Trost on the occasion of his 70th birthday

The transition-metal-catalyzed alkylative ring-opening reaction of bridgehead benzoxabicyclic alkenes is an efficient route to 2-substituted-1,2-dihydronaphthols, which result from the cleavage of one C–O bond.[1] To date, such ring-opening reactions using alkynes have been scarcely investigated. For instance, the nickel-catalyzed couplings of oxabenzonorbornadiene **1a** with alkynes **2** led to various ring-opening adducts according to the substitution patterns of alkynes as well as the nature of catalyst systems (Scheme 1).[2]

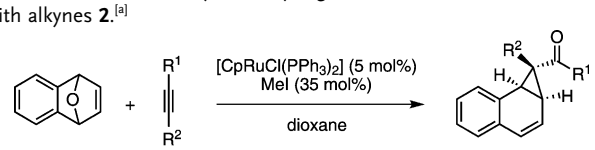
In the course of our investigations on ruthenium-catalyzed cycloadditions,[3] we were interested in the development of catalytic reactions of oxabenzonorbornadienes with alkynes, particularly those reactions in which the alkyne may insert into a C–O bond to form ring-expanded oxabicyclic compounds. Herein, we describe an unprecedented ruthenium-catalyzed reconstitutive coupling[4] of alkynes with oxabenzonorbornadienes; this reaction occurs through the cleavage of two bridgehead C–O bonds, thus giving rise to benzonorcaradienes with remarkable diastereoselectivity.



Scheme 1. Coupling reactions of oxabenzonorbornadiene **1a** with alkynes **2**. a) [Cp_2ZrClH], then [$Ni(PPh_3)_2Cl_2$] cat./Zn, THF, 50 °C; b) [Ni(dppe)Cl_2] cat./$ZnCl_2$/Zn, toluene, 90 °C; c) [Ni(dppe)Br_2] cat./Zn, MeCN, 90 °C. dppe = 1,2-bis(diphenylphosphino)ethane, THF = tetrahydrofuran.

We previously reported the [2+2] cycloaddition of bicyclic alkenes with internal alkynes to give cyclobutenes using a [$CpRuCl(PPh_3)_2$]/MeI catalyst system.[5] Under these reaction conditions,[6] we were pleased to find that an equimolar mixture of oxabenzonorbornadiene **1a** and but-2-yn-1,4-diacetate **2a** in dioxane at 60 °C for 24 hours afforded *exo*-benzonorcaradiene **3a** as a single diastereomer (Table 1, entry 1). The ^{1}H NMR spectrum of **3a** revealed four connected nonaromatic protons: two ethylenic protons in a *cis* relationship ($\delta = 6.66$ ppm (d, $J = 9.6$ Hz) and $\delta = 6.15$ ppm (dd, $J = 9.6, 5.2$ Hz)) and two aliphatic protons ($\delta = 3.37$ ppm (d, $J = 8.7$ Hz) and $\delta = 2.99$ ppm (dd, $J = 8.7, 5.1$ Hz)) attributable to cyclopropanic protons. The presence of a carbonyl group ($\delta = 203.5$ ppm) and cyclopropane carbons with signals at $\delta = 24.1$ (C), 35.7 (CH) and 38.0 ppm (CH) and $J_{C\text{-}H}$ values close to 170 Hz were shown by ^{13}C NMR spectroscopy. The stereochemistry was clearly established by a NOESY experiment and the structure of **3a** was confirmed by single-crystal X-ray analysis.[7] This unusual coupling reaction was examined with various alkynes, and Table 1 summarizes the effect of alkyne substitution on the reaction. Symmetrical alkynes

Table 1: Ruthenium-catalyzed coupling of oxabenzonorbornadiene **1a** with alkynes **2**.[a]



Entry	Alkyne	*T* [°C]	*t* [h]	Adduct	Yield [%][b]
1	**2a** R^1, $R^2 = CH_2OAc$	60	24	**3a**	49
2	**2b** R^1, $R^2 = CH_2OMe$	60	24	**3b**	60
3	**2c** R^1, $R^2 = CH_2OMOM$	60	24	**3c**	63
4	**2d** R^1, $R^2 = CH_2OBn$	60	48	**3d**	60
5	**2e** R^1, $R^2 = CH_2OTBDMS$	60	62	**3e**[c]	30 (77)
6	**2f** R^1, $R^2 = CH_2OCO_2Me$	60	14	**3f**	81
7	**2g** R^1, $R^2 = CH_2OH$	60	24	**3g**	94
8	**2h** R^1 = Me, $R^2 = CH_2OH$	90	2.5	**3h**	30
9	**2i** R^1 = Bu, $R^2 = CH_2OH$	60	48	**3i**[d]	57
10	**2j** R^1 = Bu, $R^2 = CH_2OBn$	60	32	**3j**	46
11	**2k** R^1, R^2 = Et	90	60	**3k**[e]	18

[a] Reaction conditions: **1a**/**2**/$CpRuCl(PPh_3)_2$/MeI (0.5/0.5/0.025/0.175 mmol), dioxane (4 mL). [b] Yields are of the isolated products. Yield in parentheses is based on recovered alkyne. [c] 66% of 1-naphthol was formed. [d] 15% of 1-naphthol was formed. [e] See text. Bn = benzyl, MOM = methoxymethyl, TBDMS = tert-butyldimethylsilyl.

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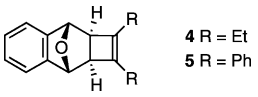
such as but-2-yn-1,4-diol (**2g**) and the corresponding bis(ethers) **2b–e** or mixed bis(carbonate) **2f** were converted into the expected benzonorcaradienes **3**, as single diastereomers in fair to good yields (Table 1, entry 2–7). As much as possible the reactions were carried out at 60 °C to prevent the competitive isomerization of **1a** to 1-naphthol.[8]

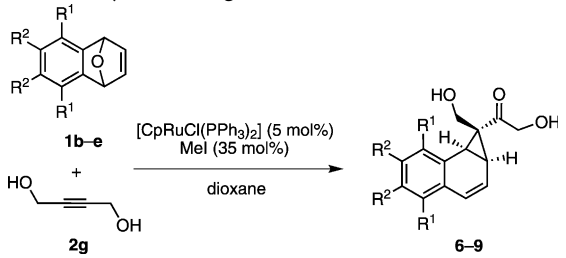
Unsymmetrical alkynes such as propargyl alcohols **2h**, **2i**, or ether **2j** react with excellent regio- and stereoselectivity to provide the desired adducts **3h**, **3i**, and **3j**, respectively (Table 1, entries 8–10).[9] Oxygen atoms at the propargylic position of **2** play a decisive role in influencing the pathway of the reaction; in the presence of an oxygen substituent the pathway leading to benzonorcaradienes **3** is favored. For instance, hex-3-yne (**2k**) led to norcaradiene **3k** in only 18% yield (Table 1, entry 11) along with the [2+2] cycloadduct **4**[10] (21%) and an intractable mixture of by-products, and diphenylethyne (**2l**) afforded exclusively the [2+2] cycloadduct **5**[10] in 98% yield (Scheme 2). Furthermore, an oxygen atom at the homopropargylic position of the alkyne turns out to be detrimental for the reaction. Hence, the coupling reaction with pen-3-yn-1-ol (**2m**; 60 °C, 48 h) gave a complex mixture of products among which 1-naphthol is the main component and the expected benzonorcaradiene is detected in trace amounts.



Scheme 2. Structure of [2+2] cycloadducts **4** and **5**.

The effect of the substitution pattern on the aromatic ring of **1** was then examined (Table 2). The coupling of electron-rich oxabenzonorbornadienes **1b–d** with but-2-yn-1,4-diol (**2g**) afforded the expected adducts **6–8** in excellent yields. The coupling with the electron-poorer bicyclic alkene **1e** was sluggish and required a second addition of catalyst (10 mol% overall) to provide **9** in 57% yield.

Table 2: Ruthenium-catalyzed coupling of oxabenzonorbornadienes **1b–e** with but-2-yn-1,4-diol **2g**.[a]

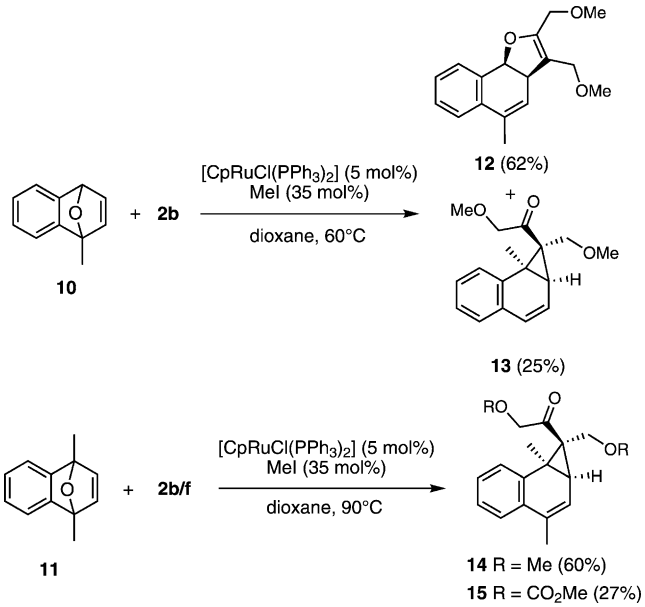


Entry	Alkyne	*T* [°C]	*t* [h]	Adduct	Yield [%][b]
1	**1b** R^1 = H, R^2 = Me	60	24	**6**	90
2	**1c** R^1 = Me, R^2 = H	90	48	**7**	84
3	**1d** R^1 = OMe, R^2 = H	90	24	**8**	87
4[c]	**1e** R^1 = H, R^2 = Br	90	96	**9**	57

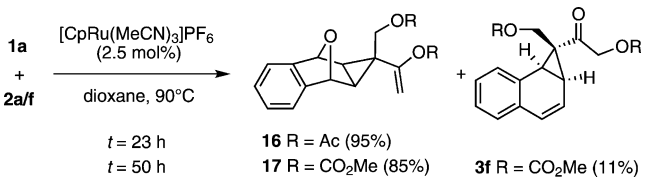
[a] Reactions conditions: **1**/**2g**/$CpRuCl(PPh_3)_2$/MeI (0.5/0.5/0.025/0.175 mmol), dioxane (4 mL). [b] Yields are of the isolated products. [c] New addition of $[CpRuCl(PPh_3)_2]$/MeI (0.025/0.175 mmol) after 72 h.

The reactions of oxabenzonorbornadienes **10** and **11**, with methyl substituents at the bridgehead positions, with alkynes **2b** and **2f** were also examined (Scheme 3). Interestingly, new regio- and stereoselective issues were observed. The reaction of unsymmetrical alkene **10** with bis(ether) **2b** led unexpectedly to the stable dihydronaphthofurane **12**[11,12] (62%) and *endo*-benzonorcaradiene **13** (25%), which features an inverted relative configuration of the quaternary centre α to the carbonyl group compared to that of adducts **3**. With the symmetrically disubstituted alkene **11**, the reactions with alkynes **2b** and **2f** required a higher temperature (90 °C) to form *endo*-benzonorcaradienes[13] **14** (60%) and **15** (27%) respectively. The structure and stereochemistry of **15** was confirmed by single-crystal X-ray analysis.[14]

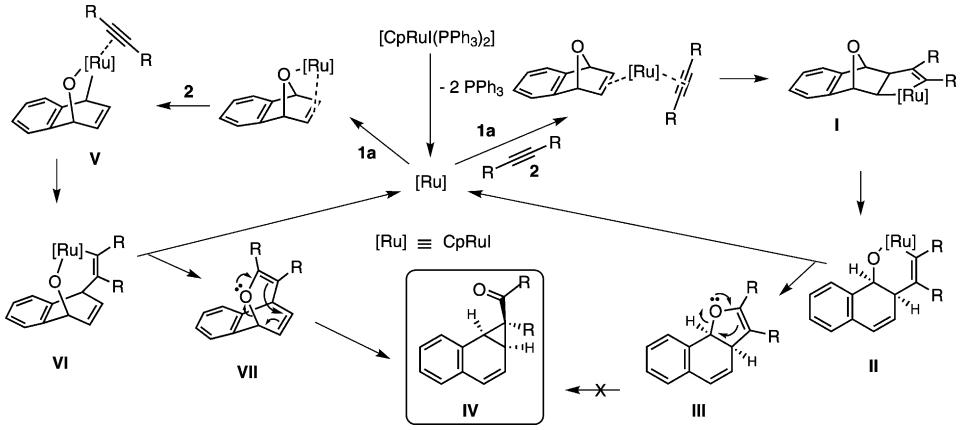
In an ancillary study aimed to discriminate between the neutral and cationic nature of active ruthenium species, the reactions of **1a** with alkynes **2a** and **2f** were conducted in the presence of $[CpRu(MeCN)_3]PF_6$ as the catalyst (Scheme 4). In these reactions, a diastereoselective vinylcyclopropanation[3c] was observed as the high yielding sole or predominant pathway. Single-crystal X-ray analysis of compound **16** confirmed both its tetracyclic structure as well as its stereochemistry.[15] These results suggested that a neutral ruthenium species could be involved in the reconstitutive coupling of oxabenzonorbornadienes with alkynes leading to benzonorcaradienes.



Scheme 3. Coupling reactions of oxabenzonorbornadienes **10** and **11**, with substituents at the bridgehead positions.



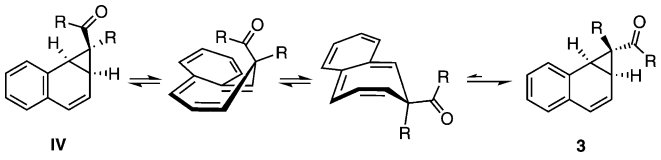
Scheme 4. Outcome of the coupling reaction according to the catalyst.



Scheme 5. Proposed mechanisms for the coupling of oxabicyclic alkenes with alkynes.

The formation of benzonorcaradienes is quite intriguing and involves the cleavage of two carbon–oxygen bonds, the formation of two carbon–carbon bonds, and the transfer of the bridgehead oxygen atom to a carbon atom of the alkyne linkage to form a carbonyl group. On the basis of well-documented ruthenium chemistry,[16] a plausible mechanism is provided in Scheme 5. The catalytic cycle starts with the formation of the coordinatively unsaturated CpRuI and subsequent coordination of **1a** and alkyne **2**. Oxidative cyclometalation generates ruthenacyclopentene **I**, which upon reductive elimination releases a cyclobutene adduct (not shown). Alternatively, β-alkoxy elimination can form ruthenacycle **II**, which undergoes reductive elimination to give dihydronaphthofurane **III**. A possible thermal isomerization of **III** to **IV** could also be envisaged. Control experiments showed that such an event did not occur under our reaction conditions.[17] As an alternative pathway, coordination of **1a** followed by insertion of ruthenium into a bridgehead C–O bond and alkyne coordination generates the oxaruthenacycle **V**.[18] Migratory insertion of the alkyne[19] into the Ru–C bond of **V** delivers a novel ruthenacycle **VI**,[20] which upon reductive elimination releases the cyclic allylvinyl ether **VII**. An alicyclic Claisen rearrangement[21] of **VII** generates norcaradiene **IV**, which features the opposite stereochemistry at the quaternary cyclopropanic carbon atom to **3**. *Endo*-to-*exo* norcaradiene isomerization should occur through norcaradiene-cycloheptatriene equilibrium,[22] thus leading to the thermodynamically more stable *exo*-norcaradiene **3** as depicted in Scheme 6. Interestingly, this equilibrium is not observed in reactions involving the substituted oxabenzonorbornadienes **10** and **11** (Scheme 3).

In summary, we have developed an atom-economical ruthenium-catalyzed coupling of oxabenzonorbornadienes with alkynes bearing oxygen atoms at the propargylic position leading to stereodefined benzonorcaradienes.[23] The diastereoselectivity of the coupling depends on the presence of the substituents at bridgehead positions of oxabenzonorbornadienes. To the best of our knowledge, this unusual coupling reaction, related to the Büchner reaction[24,25] of naphthalene, is unprecedented. Further investigations are underway to elucidate the effect of the substituents at bridgehead positions on the diastereoselectivity of the coupling.



Scheme 6. *Endo*-to-*exo* norcaradiene valence isomerization through norcaradiene–cycloheptatriene equilibrium.

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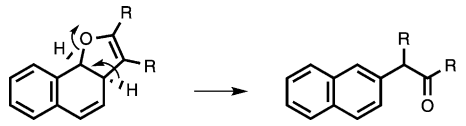
[1] a) M. Lautens, K. Fagnou, S. Hiebert, *Acc. Chem. Res.* **2003**, *36*, 48–58; b) D. K. Rayabarapu, C.-H. Cheng, *Acc. Chem. Res.* **2007**, *40*, 971–983.
[2] a) D. K. Rayabarapu, T. Sambaiah, C.-H. Cheng, *Angew. Chem.* **2001**, *113*, 1326–1328; *Angew. Chem. Int. Ed.* **2001**, *40*, 1286–1288; b) D. K. Rayabarapu, C.-F. Chiou, C.-H. Cheng, *Org. Lett.* **2002**, *4*, 1679–1682; c) M.-S. Wu, D. K. Rayabarapu, C.-H. Cheng, *J. Org. Chem.* **2004**, *69*, 8407–8412; for an overview, see: d) D. K. Rayabarapu, C.-H. Cheng, *Pure Appl. Chem.* **2002**, *74*, 69–75.
[3] a) A. Tenaglia, L. Giordano, *Synlett* **2003**, 2333–2336; b) A. Tenaglia, L. Giordano, *Tetrahedron Lett.* **2004**, *45*, 171–174; c) A. Tenaglia, S. Marc, *J. Org. Chem.* **2006**, *71*, 3569–3575.
[4] For inter- and intramolecular ruthenium-catalyzed couplings of alkynes with alkenes occurring with structural reorganization, see: a) B. M. Trost, G. Dyker, R. J. Kulawiec, *J. Am. Chem. Soc.* **1990**, *112*, 7809–7811; b) N. Chatani, T. Morimoto, T. Muto, S. Murai, *J. Am. Chem. Soc.* **1994**, *116*, 6049–6050; c) H.-C. Shen, S. Pal, J.-J. Lian, R.-S. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 15762–15763; d) R. J. Madhushaw, C.-Y. Lo, C.-W. Hwang, M.-D. Su, H.-C. Shen, S. Pal, I. R. Shaikh, R.-S. Liu, *J. Am. Chem. Soc.* **2004**, *126*, 15560–15565.
[5] The activation of $[CpRuCl(PPh_3)_2]$ with MeI generates $[CpRuI(PPh_3)_2]$ in situ and provides superior results compared to preformed $[CpRuI(PPh_3)_2]$ in terms of chemical yields, see Ref. [3a].
[6] For iodide screening results, see the Supporting Information.
[7] CCDC 817594 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[8] a) M. Ballantine, M. L. Menard, W. Tam, *J. Org. Chem.* **2009**, *74*, 7570–7573; b) K. Villeneuve, W. Tam, *J. Am. Chem. Soc.* **2006**, *128*, 3514–3515.
[9] For a divergent pathway in the coupling of oxabenzonorbornadiene with propargyl alcohols, thus leading to isochromenes, see: a) K. Villeneuve, W. Tam, *Eur. J. Org. Chem.* **2006**, 5449–5453; b) K. Villeneuve, W. Tam, *Organometallics* **2007**, *26*, 6082–6090.

[10] K. C. Chao, D. K. Rayabarapu, C.-C. Wang, C.-H. Cheng, *J. Org. Chem.* **2001**, *66*, 8804 – 8810.

[11] In some of the coupling reactions dihydronaphthofurans were detected as by-products (ca 5–10 %) by ^{1}H NMR spectroscopy of the crude reaction mixtures, but owing to their sensitivity on silica they were transformed to 2-(β-ketoalkyl)naphthalenes during purification by chromatography.



[12] The formation of dihydronaphthofurans through rhodium-catalyzed cross-coupling of oxabenzonorbornadienes with an electron-poor alkyne (DMAD) was recently reported, see: T. Nishimura, T. Kawamoto, K. Sasaki, E. Tsurumaki, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 1492 – 1493.

[13] The propensity of *endo*-benzonorcaradienes bearing an electron-withdrawing group to undergo thermal isomerization to the more stable *exo*-benzonorcaradienes is well established, see for instance: a) W. Adam, M. Ahrweiler, M. Balci, O. Çakmak, C. R. Saha-Möller, *Tetrahedron Lett.* **1995**, *36*, 1429 – 1430; b) M. Kato, K. Takatoku, S. Ito, T. Miwa, *Tetrahedron Lett.* **1979**, *20*, 867 – 870; c) P. Müller, J.-L. Toujas, G. Bernardinelli, *Helv. Chim. Acta* **2000**, *83*, 1525 – 1534. The thermal stability of *endo*-benzonorcaradienes **13** – **15** could be attributed to the presence of a methyl substituent on the cyclopropane.

[14] CCDC 818012 (**15**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] CCDC 820547 (**16**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] a) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067 – 2096; b) B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem.* **2005**, *117*, 6788 – 6825; *Angew. Chem. Int. Ed.* **2005**, *44*, 6630 – 6666; c) C. Bruneau, P. H. Dixneuf in *Topics in Organometallic Chemistry*, *Vol. 11*, Springer, Berlin, **2004**; d) S.-I. Murahashi in *Ruthenium In Organic Synthesis*, Wiley-VCH, Weinheim, **2004**.

[17] See the Supporting Information for details.

[18] For a similar ruthenacycle, which was postulated for the ruthenium-catalyzed isomerization of oxabenzonorbornadienes to 1,2-naphthalene oxides, see Ref. [7b].

[19] The propargylic oxygen atom acting as a temporary ligand may assist the migratory insertion.

[20] The structure of adducts **3h**–**3j** suggest that migratory insertion of unsymmetrical alkynes occurred regioselectively with the oxygen substituent distal to the metal centre.

[21] For the term "alicyclic Claisen rearrangement", see: M. M. Abelman, R. L. Funk, J. D. Munger, Jr., *J. Am. Chem. Soc.* **1982**, *104*, 4030 – 4032, for examples of these rearrangements forming cyclopropyl-substituted carbonyl compounds, see: a) R. L. Funk, J. B. Stallman, J. A. Wos, *J. Am. Chem. Soc.* **1993**, *115*, 8847 – 8848; b) M. F. Mahon, K. Molloy, C. A. Pittol, R. J. Pryce, S. M. Roberts, G. Ryback, V. Sik, J. O. Williams, J. A. Winders, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1255 – 1263; c) R. L. Funk, M. M. Abelman, J. D. Munger, Jr., *Tetrahedron* **1986**, *42*, 2831 – 2846; d) R. L. Funk, J. D. Munger, Jr., *J. Org. Chem.* **1985**, *50*, 707 – 709.

[22] For a review, see: O. A. McNamara, A. R. Maguire, *Tetrahedron* **2011**, *67*, 9 – 40.

[23] For a synthesis of benzonorcaradienes through gold(I)-catalyzed [4+3] annulation of styrenes with 1,3-diynes, see: D. J. Gorin, P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 14480 – 14481.

[24] a) E. Büchner, T. Curtius, *Chem. Ber.* **1885**, *18*, 2371 – 2377; b) R. Huisgen, G. Juppe, *Chem. Ber.* **1961**, *94*, 2332 – 2349.

[25] For recent transition metal variants of the Büchner reaction, see: a) C. A. Merlic, A. L. Zechman, M. M. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 11101 – 11102; b) M. C. Pirrung, H. Liu, A. T., Jr. Morehead, *J. Am. Chem. Soc.* **2002**, *124*, 1014 – 1023; c) B. R. Galan, M. Gembicky, P. M. Dominiak, J. B. Keister, S. T. Diver, *J. Am. Chem. Soc.* **2005**, *127*, 15702 – 15703; d) P. Panne, J. M. Fox, *J. Am. Chem. Soc.* **2007**, *129*, 22 – 23; e) C. P. Park, A. Nagle, C. H. Yoon, C. Chen, K. W. Jung, *J. Org. Chem.* **2009**, *74*, 6231 – 6236.

