ORGANIC LETTERS

2010
Vol. 12, No. 7
1604−1607

Highly Efficient, Facile, Room Temperature Intermolecular [5 + 2] Cycloadditions Catalyzed by Cationic Rhodium(I): One Step to Cycloheptenes and Their Libraries

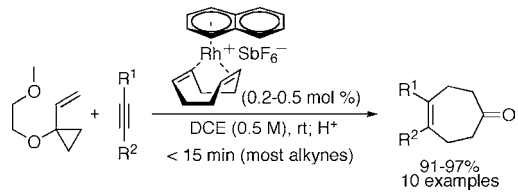
Paul A. Wender,* Lauren E. Sirois, René T. Stemmler, and Travis J. Williams†

Departments of Chemistry and of Chemical and Systems Biology, Stanford University, Stanford, California 94305-5080

wenderp@stanford.edu

Received February 9, 2010

ABSTRACT



A cationic rhodium(I) complex—$[(C_{10}H_8)Rh(cod)]^+$ SbF_6^-—catalyzes the remarkably efficient intermolecular [5 + 2] cycloaddition of vinylcyclopropanes (VCPs) and various alkynes, providing cycloheptene cycloadducts in excellent yields in minutes at room temperature. The efficacy and selectivity of this catalyst are also shown in a novel diversification strategy, affording a cycloadduct library in one step from nine commercially available components.

New reactions play a uniquely important role in the evolution of synthesis as they enable new ways to think about bond construction, often leading to practical, step economical, and green options for high value target preparation.[1] Guided by this view, we reported in 1995 the first examples[3a] of a metal-catalyzed [5 + 2] cycloaddition involving vinylcyclopropanes (VCPs) and π-systems, a formal homologue of the Diels−Alder reaction that provides a facile route to seven-membered rings.[2] While we[3] and others[4] have since reported new catalysts for the intramolecular process and applications in synthesis,[5] the intermolecular [5 + 2] process,[6] which draws benefit from the abundance of alkyne feedstocks and from its convergent nature, has thus far been reported only with $[RhCl(CO)_2]_2$. Other catalysts (vide infra) either do not work or give low yields. This severely limits what can be done in optimizing efficiency and selectivity with problematic substrates. Moreover, the use of $[RhCl(CO)_2]_2$ in [5 + 2] reactions often requires heating, which in turn promotes competing cyclotrimerization of alkyne starting materials, decomposition of the VCP, or formation of undesired secondary isomerization products. Such transition metal-catalyzed intermolecular cycloadditions pose particular chemo- and regioselectivity challenges as well as entropic penalties not encountered in intramolecular processes, as the latter benefit from tether-derived alignment and proximity of reactive functionalities not possible in the former. As evident from the multitude of catalysts reported for the Diels−Alder cycloaddition, for example, the introduction of alternative

† Present address: Loker Hydrocarbon Research Institute, University of Southern California, Los Angeles, CA 90089-1661.

(1) (a) Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25. (b) Wender, P. A.; Gamber, G. G.; Williams, T. J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; WILEY-VCH: Weinheim, Germany, 2005; p 263. (c) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505, and references cited therein. (d) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (e) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197.

10.1021/ol100337m
Published on Web 03/02/2010

or improved catalysts for a given process allows for its broader utilization in synthesis.

Recently, we described a general synthetic method for accessing bicyclo[5.3.0]decanes in which $[RhCl(CO)_2]_2$ (or $[RhCl(cod)]_2$) and $AgSbF_6$ are used to catalyze in one synthetic operation both a [5 + 2] cycloaddition and Nazarov cyclization.[7] While in preliminary earlier work we found that cationic rhodium complexes gave low yields in intermolecular [5 + 2] cycloadditions of VCPs and alkynes, their encouraging performance in these serial reactions involving enynones prompted a more in-depth examination of their utility as catalysts for intermolecular [5 + 2] reactions. We report herein a catalyst (**1**)[8] and optimized conditions for intermolecular [5 + 2] cycloadditions of VCPs with a structurally and electronically diverse set of alkynes that provide cycloadducts in excellent yields (>90%) and often in only minutes at room temperature.

The reaction of VCP **2** and propargyl ether **3b** served as a starting point for screening the activities of a range of neutral and cationic rhodium(I) catalysts, including $[(C_{10}H_8)Rh(cod)]^+ SbF_6^-$ (**1**), $[RhCl(CO)_2]_2$, $[RhCl(cod)]_2$, $RhCl(CO)(PPh_3)_2$, and $RhCl(PPh_3)_3$ (vide infra). Of these, **1** proved to be vastly superior, providing, after brief hydrolytic workup, the cycloheptenone **4b** in 94% isolated yield (Scheme 1). The reaction was complete in less than 15 min at 23 °C and required only 1 equiv of **2** and 1.1 equiv of **3b**. More thorough investigation of reaction conditions established that halogenated solvents (e.g., 1,2-dichloroethane, dichloromethane, or 2,2,2-trifluoroethanol[9]) gave the fastest rates and highest yields, though the cycloaddition is also reasonably efficient at room temperature in nonhalogenated ethereal solvents.[10]

Scheme 1. [5 + 2] Cycloaddition of VCP **2** and Propargyl Ether **3b** at Room Temperature, Using $[(C_{10}H_8)Rh(cod)]^+ SbF_6^-$ (**1**)

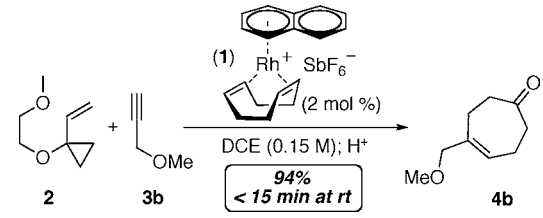
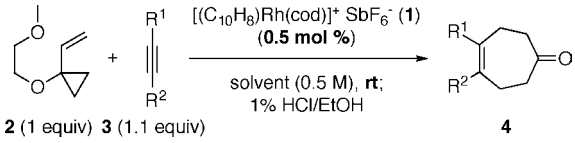


Table 1 summarizes the exceptional efficacy of this catalyst in cycloadditions with a wide range of alkynes. With just 0.5 mol % of **1** at a substrate concentration of 0.5 M, VCP **2**

Table 1. Intermolecular [5 + 2] Cycloadditions Catalyzed by Complex **1**



entry		alkyne	solvent[a]	product	time (min)	yield[b]
1	**3a**	$SiMe_3$	DCE	**4a**	5	96%
2[c]	**3a**	$SiMe_3$	DCE	**4a**	60	93%
3	**3b**	OMe	DCE:TFE	**4b**	5	94%
4	**3c**	NHTs	DCE:TFE	**4c**	150	94%
5	**3d**	O, OMe	DCE:TFE	**4d**	10	97%
6	**3e**	O	DCE:TFE	**4e**	5	97%
7	**3f**		DCE	**4f**	5	92%
8[d]	**3g**	O, NH_2	DCE:TFE[d]	**4g**	24 h	92%
9	**3h**	O, OMe	DCE	**4h**	5	95%
10	**3i**		DCE	**4i**	10	91%
11	**3j**	MeO, OMe	DCE:TFE	**4j**	15	91%

[a] 1,2-Dichloroethane:2,2,2-trifluoroethanol (90:10, v:v). [b] Isolated yield. [c] 0.2 mol % of catalyst **1**. [d] 60 °C, 0.4 M, DCE:TFE (80:20).

(2) For reviews on metal-mediated synthesis of seven-membered and other medium-sized rings, see: (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (b) Wender, P. A.; Croatt, M. P.; Deschamps, N. M. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Oxford, UK, 2007; Vol. 10, p 603. (c) Butenschön, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5287.

(3) (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (b) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164. (c) Wender, P. A.; Williams, T. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4550. (d) Wender, P. A.; Love, J. A.; Williams, T. J. *Synlett* **2003**, 1295. (e) Wender, P. A.; Haustedt, L. O.; Lim, J.; Love, J. A.; Williams, T. J.; Yoon, J.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 6302. (f) Gómez, F. J.; Kamber, N. E.; Deschamps, N. M.; Cole, A. P.; Wender, P. A.; Waymouth, R. M. *Organometallics* **2007**, *26*, 4541.

(4) (a) Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075. (b) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379. (c) Wang, B.; Cao, P.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 8041. (d) Trost, B. M.; Shen, H. C.; Horne, D. B.; Toste, F. D.; Steinmetz, B. G.; Koradin, C. *Chem.—Eur. J.* **2005**, *11*, 2577. (e) Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5798. (f) Lee, S. I.; Park, S. Y.; Park, J. H.; Jung, I. G.; Choi, S. Y.; Chung, Y. K.; Lee, B. Y. *J. Org. Chem.* **2006**, *71*, 91. (g) Saito, A.; Ono, T.; Hanzawa, Y. *J. Org. Chem.* **2006**, *71*, 6437. (h) Fürstner, A.; Majima, K.; Martín, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992. (i) Shintani, R.; Nakatsu, H.; Takatsu, K.; Hayashi, T. *Chem.—Eur. J.* **2009**, *15*, 8692.

(5) (a) Wender, P. A.; Fuji, M.; Husfeld, C. O.; Love, J. A. *Org. Lett.* **1999**, *1*, 137. (b) Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, *2*, 2323. (c) Wender, P. A.; Bi, F. C.; Brodney, M. A.; Gosselin, F. *Org. Lett.* **2001**, *3*, 2105. (d) Ashfeld, B. L.; Martin, S. F. *Tetrahedron* **2006**, *62*, 10497. (e) Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781. (f) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2008**, *130*, 16424.

(6) Reactions with alkynes: (a) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976. (b) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Scanio, M. J. C. *Org. Lett.* **2000**, *2*, 1609. (c) Wender, P. A.; Barzilay, C. M.; Dyckman, A. J. *J. Am. Chem. Soc.* **2001**, *123*, 179. (d) Wender, P. A.; Gamber, G. G.; Scanio, M. J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 3895. Reactions with allenes: (e) Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 6530.

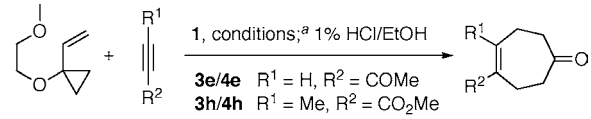
(7) Wender, P. A.; Stemmler, R. T.; Sirois, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 2532.

(8) For the X-ray structure and use of **1** in intramolecular [5 + 2] cycloadditions, see ref 3c. For pioneering cycloaddition work with a related catalyst, see: (a) Paik, S.-J.; Son, S. U.; Chung, Y. K. *Org. Lett.* **1999**, *1*, 2045. For representative other uses of **1**, see: (b) Evans, P. A.; Baum, E. W. *J. Am. Chem. Soc.* **2004**, *126*, 11150. (c) Barluenga, J.; Vicente, R.; López, L. A.; Rubio, E.; Tomás, M.; Álvarez-Rúa, C. *J. Am. Chem. Soc.* **2004**, *126*, 470. (d) Brummond, K. M.; You, L. *Tetrahedron* **2005**, *61*, 6180. (e) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186. (f) Wender, P. A.; Croatt, M. P.; Kühn, B. *Organometallics* **2009**, *28*, 5841.

engages in fast, room temperature [5 + 2] cycloadditions with sterically and electronically diverse internal and terminal alkynes. The majority of these reactions were complete in 15 min or less, with isolated yields of cycloheptenones **4** greater than 90% in all cases. Only 1 equiv of **2** and 1.1 equiv of alkyne were used. The ability to conduct these reactions at room temperature allows one to avoid heating procedures and the loss of starting materials or products to thermal decomposition pathways. In these experiments, neither significant alkyne cyclotrimerization, VCP decomposition, nor cycloadduct isomerizations were observed. Ether, silane, sulfonamide, ester, ketone, and aryl functionalities were all well-tolerated, as was an unfunctionalized internal alkyne (entry 10). Only 2-butynamide (**3g**) required a higher temperature and longer time to reach full conversion but still gave the [5 + 2] product in excellent (92%) isolated yield (entry 8). The slower rate for this reaction is presumably a consequence of lower effective catalyst concentration due to reversible coordination of rhodium to the amide functionality.

Reducing the catalyst loading to 0.2 mol % had no impact on the high isolated yields and led to only moderate increases in reaction time in some cases (Table 1, entry 2; Table 2, entries 3 and 5). Catalyst loadings of 0.1 mol % or less on small laboratory scales resulted in incomplete conversion of starting material; however, at higher concentration and temperature (1.0 M, 60 °C), cycloadduct **4e** could be isolated in 54% yield (TON = 540 at 0.1 mol % catalyst loading, Table 2, entry 4).

Table 2. Temperature, Catalyst Loading, and Concentration Effects on the [5 + 2] Cycloaddition of Vinylcyclopropane **2**



2 (1 equiv) **3** (1.1 equiv) **4**

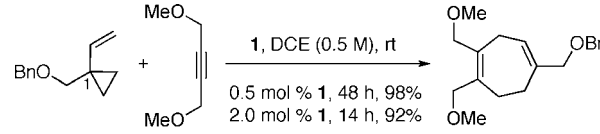
entry	alkyne	cat. loading (mol %)	concn (M)	t (°C)	time	yield[b] (%)	TON[c]
1[d]	**3e**	0.5	0.5	0	60 min	97	194
2[d]	**3e**	0.5	0.5	−23	7 h	96	192
3	**3e**	0.2	0.5	23	15 min	97	485
4[e]	**3e**	0.1	1.0	60	48 h	54	540
5[f]	**3h**	0.2	0.5	23	75 min	97	485
6[f]	**3h**	0.2	1.0	23	75 min	86	430
7[g]	**3h**	0.2	0.5	23	120 min	85	425

[a] Solvent for **3e**: DCE:TFE (90:10); solvent for **3h**: DCE. [b] Isolated yield. [c] Turnover number. [d] Catalyst solution was cooled to the indicated temperature prior to addition of VCP **2** and alkyne **3e**. [e] Unreacted VCP **2** was recovered. [f] 1.0 mmol scale. [g] 10.0 mmol scale (1.42 g of **2**).

While a room temperature process would generally be preferred, lower temperature cycloadditions can also be effected with **1**. For example, the cycloaddition of VCP **2** and 3-butyn-2-one (**3e**) catalyzed by **1** was found to proceed at 0 °C and even at −23 °C to give **4e** in nearly quantitative yields (Table 2, entries 1 and 2). Moreover, in another example of reduced catalyst loading (0.2 mol %), the cycloaddition of **2** with methyl 2-butynoate (**3h**) can be performed at 1.0 M concentration with only a modest decrease in isolated yield (86%, entry 6). A gram-scale [5 + 2] reaction of VCP **2** and **3h** also proceeded smoothly (entry 7).

1-Siloxy- or 1-alkoxy-VCPs (such as commercially available compound **2**)[11] are known to be more reactive than unsubstituted or 1-alkyl-VCPs in rhodium(I)-catalyzed intermolecular [5 + 2] cycloadditions;[12] the latter typically require higher temperature, catalyst loading, or dilution and often provide lower yields. In contrast, with only 0.5 mol % of **1**, 1-alkyl-VCP **5** reacted with 1,4-dimethoxy-2-butyne (**3j**) at room temperature to provide cycloadduct **6** in nearly quantitative yield (Scheme 2). Full conversion of starting materials could be achieved in 14 h by increasing the catalyst loading to 2 mol %, providing an excellent (92%) isolated yield of cycloheptadiene **6**.

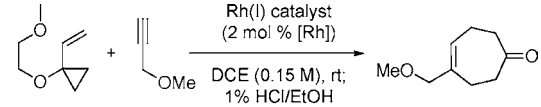
Scheme 2. Room Temperature Cycloadditions of VCP **5**



5 (1 equiv) **3j** (1.1 equiv) **6**

Complex **1** is easily prepared from $[RhCl(cod)]_2$ by treatment with silver salt, filtration, and subsequent introduction of the naphthalene ligand.[3c] Complex **1** is also air- and moisture-stable and retains its significant activity even after long-term storage (>6 months), adding to its attractiveness as a robust precatalyst for intermolecular [5 + 2] cycloadditions. Importantly, however, an active catalytic species can also be formed in situ by treatment of $[RhCl(cod)]_2$ with $AgSbF_6$ prior to addition of VCP and alkyne, thereby providing an equally efficient and operationally convenient [5 + 2] reaction procedure. Reaction of **2** with **3b** using this alternative protocol afforded a 93% isolated yield of **4b** in less than 15 min at room temperature (2 mol % of [Rh], Table 3, entry 2). The active catalyst formed from either

Table 3. Comparison of Rhodium(I) Catalysts for the Intermolecular [5 + 2] Cycloaddition of VCPs and Alkynes



2 (1 equiv) **3b** (1.1 equiv) **4b**

entry	Rh(I) catalyst	additive[a]	time	yield[b] (%)
1	$[RhCl(cod)]_2$	none	24 h[c]	29
2	$[RhCl(cod)]_2$	$AgSbF_6$	<15 min	93
3	$[RhCl(cod)]_2$	$AgBF_4$	<15 min	85
4	$[RhCl(cod)]_2$	AgOTf	<15 min	79
5	$[RhCl(CO)_2]_2$	none	24 h[c]	45
6	$[RhCl(CO)_2]_2$	$AgSbF_6$	24 h[c]	61
7	$RhCl(CO)(PPh_3)_2$	$AgSbF_6$	24 h[c]	39
8	$RhCl(PPh_3)_3$	$AgSbF_6$	24 h[c]	5

[a] 1:1 ratio of Ag^+ to Cl^-. [b] Isolated yield. [c] VCP **2** was recovered.

protocol significantly outperformed at room temperature all other common neutral or cationic rhodium(I) catalysts investigated (Table 3). When forming the active catalyst by using silver salts with somewhat more coordinating counterions, no difference in reaction rates and only subtle differences in product yields were observed (Table 3, entries 3 and 4).[13]

The remarkable activity and mode selectivity of $[(C_{10}H_8)Rh(cod)]^+$ SbF_6^- (**1**) can also be harnessed for the rapid generation of [5 + 2] cycloadduct libraries.[14] In an initial demonstration of this diversification concept, VCP **2** was treated with a mixture of eight commercially available alkynes at room temperature in the presence of 1 mol % of **1** (Figure 1). Within 15 min, all VCP **2** had been consumed. GC analysis of the unpurified reaction mixture after brief hydrolytic workup confirmed the corresponding eight cycloheptenones to be the overwhelmingly major products formed in ca. 70% to >95% yield each (Figure 1, see the SI for details).

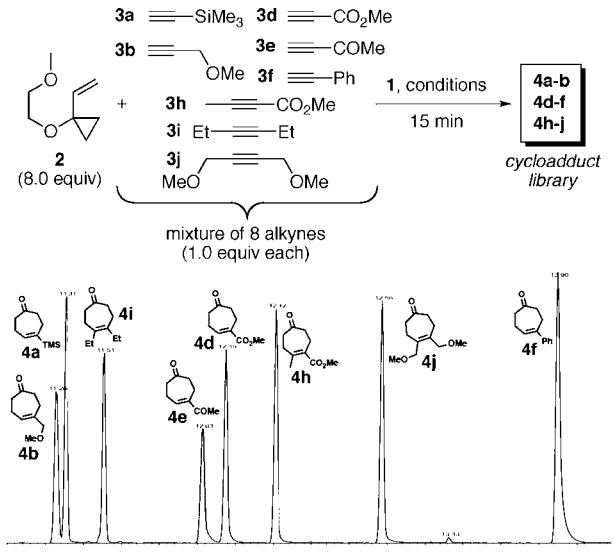


Figure 1. Synthesis and GC analysis of a cycloheptenone library generated with catalyst **1** (portion of chromatogram of unpurified cycloadducts). Conditions: $[(C_{10}H_8)Rh(cod)]^+$ SbF_6^- (1 mol % with respect to VCP **2**), DCE:TFE (90:10, 0.2 M), rt, then 1% HCl/EtOH.

In summary, the cationic rhodium(I) complex $[(C_{10}H_8)Rh(cod)]^+$ SbF_6^- (**1**) is a convenient and highly effective catalyst for the intermolecular [5 + 2] cycloaddition of 1-alkoxy- or 1-alkyl-VCPs and a wide range of terminal and internal alkynes, many of which are commercially available feedstocks. At low catalyst loadings (0.2−0.5 mol % of [Rh]) and practical reaction concentrations (0.5−1.0 M), highly efficient (>90% isolated yields) [5 + 2] reactions were achieved, in most cases within minutes at room temperature. Successful application of **1** to low-temperature and gram-scale cycloadditions and to small molecule library generation was also demonstrated. If desired, the active catalyst for these transformations can be generated in situ from a commercially available rhodium(I) precatalyst. Investigations of the remarkable reactivity of complex **1** in [5 + 2] and related cycloadditions are ongoing.

Acknowledgment. This work was funded by the National Science Foundation (CHE-0450638), the NSF Graduate Research Fellowship (L.E.S.), and the German Academic Exchange Service (DAAD, R.T.S.). We thank Sigma-Aldrich for a generous gift of 1-(2-methoxyethoxy)-1-vinylcyclopropane (**2**).

Supporting Information Available: Complete experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100337M

(9) For a review on the beneficial effects of fluorinated alcohols as solvents or co-solvents in metal-catalyzed reactions, see: Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, 2925.

(10) These include dioxane, tetrahydrofuran, and 2-methyltetrahydrofuran. For a more comprehensive solvent screen, see the SI.

(11) Available from Sigma-Aldrich (product no. 666246).

(12) Liu, P.; Cheong, P. H.-Y.; Yu, Z.-X.; Wender, P. A.; Houk, K. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3939, and references cited therein.

(13) The effects of different counterions on reaction rate or product yield for complexes similar to **1** were also found to be minimal in the case of intramolecular [5 + 2] reactions, though complex stabilities differ. See ref 3c.

(14) For library synthesis using an intramolecular [5 + 2] cyclization, see: Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3635.