

Copper-Catalyzed Oxidative Alkynylation of Diaryl Imines with Terminal Alkynes: A Facile Synthesis of Ynimines

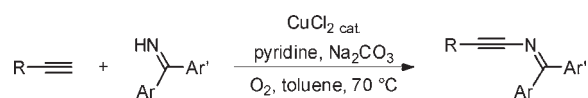
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ABSTRACT



An efficient copper-mediated method for the oxidative alkynylation of diaryl imines with terminal alkynes is reported. This reaction provides the first catalytic and general synthesis of ynimines and allows for an easy preparation of these useful building blocks. An improved copper-catalyzed oxidative dimerization of imines to azines and the synthesis of dienes and azadienes from ynimines are also described.

Nitrogen-substituted alkynes, ynamines **1**, probably represent the most versatile class of acetylenic compounds. The electron-donating ability of the nitrogen strongly polarizes the triple bond, which allows for an exceptionally high level of reactivity together with a strong differentiation of the two *sp* carbon atoms.¹ Despite their enormous potential, their synthetic use remains rather limited, which is most certainly due to their difficult preparation, handling, and their high sensitivity. A solution to this problem was found in the use of ynamides **2**, in which one of the alkyl groups on the nitrogen atom is replaced by an electron-withdrawing group (Figure 1). They display an exceptionally fine balance of stability and reactivity, offer

unique and multiple opportunities for the insertion of nitrogen-based functionalities into organic molecules, and are emerging as especially useful and versatile building blocks.^{2–4}

Another option to increase the stability of ynamines would rely on the use of ynimines **3**. While these building blocks clearly hold great potential and would benefit from the use of an easily removable protecting group, they have been only scarcely studied and their use in organic synthesis is still rather limited,⁵ which is in sharp contrast with ynamides.

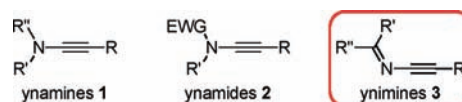


Figure 1. Ynamines, ynamides, and ynimines.

The development of the chemistry of ynimines **3** has been in fact hampered by the lack of general and practical methods for their preparation. There is indeed to date a

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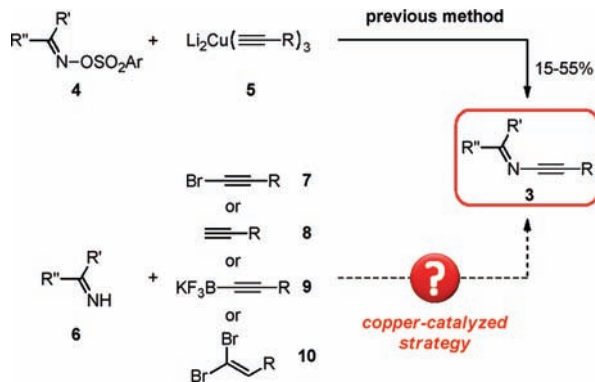
[‡] Université de Monastir.

(1) For reviews on the chemistry of ynamines, see: (a) Ficini, J. *Tetrahedron* **1976**, *32*, 1449. (b) Himbert, G. In *Methoden Der Organischen Chemie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1993; p 3267.

(2) For reviews, see: (a) Zifcsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (c) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455. (d) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (e) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.

single procedure available for their synthesis based on the reaction between oxime tosylates **4** with higher-order alkynylcuprates **5** which produces the corresponding ynamines **3** in low to moderate yields (typically 15%–55%).^{5,6}

Scheme 1. Synthesis of Ynamines: Previous Method and Strategy

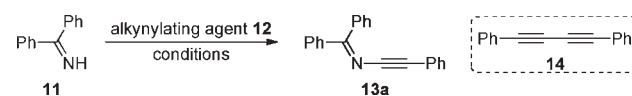


Based on our recent interest in the chemistry of ynamides^{3e,g,7} and copper catalysis,^{8,9} we decided to investigate whether ynamines could be obtained through a copper-mediated alkylation of imines with alkynylating agents such as bromoalkynes **7**,^{3a–c} terminal alkynes **8**,^{3d} potassium alkynyltrifluoroborates **9**,^{3g} or vinyl dibromides **10**,^{3e} which might provide a straightforward entry to these useful and underdeveloped building blocks (Scheme 1).

(3) For selected methods for the synthesis of ynamides, see: (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (b) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011. (c) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151. (d) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (e) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381. (f) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000. (g) Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272. (h) Jouvin, K.; Heimbürger, J.; Evano, G. *Chem. Sci.* DOI: 10.1039/c2sc00842d.

(4) For the use of ynamides in synthetic organic chemistry in 2011 alone, see: (a) Barbazanges, M.; Meyer, C.; Cossy, J.; Turner, P. *Chem.—Eur. J.* **2011**, *17*, 4480. (b) Davies, P. W.; Cremonesi, A.; Martin, N. *Chem. Commun.* **2011**, *47*, 379. (c) DeKorver, K. A.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H. F.; Deng, J.; Lohse, A. G.; Zhang, Y. S. *J. Org. Chem.* **2011**, *76*, 5092. (d) Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Org. Lett.* **2011**, *13*, 2030. (e) Garcia, P.; Harrak, Y.; Diab, L.; Cordier, P.; Ollivier, C.; Gandon, V.; Malacria, M.; Fensterbank, L.; Aubert, C. *Org. Lett.* **2011**, *13*, 2952. (f) Hashmi, A. S. K.; Schuster, A. M.; Zimmer, M.; Rominger, F. *Chem.—Eur. J.* **2011**, *17*, 5511. (g) Kramer, S.; Friis, S. D.; Xin, Z.; Odabachian, Y.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 1750. (h) Kramer, S.; Odabachian, Y.; Overgaard, J.; Rottlander, M.; Gagosz, F.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 5090. (i) Li, C. Q.; Zhang, L. M. *Org. Lett.* **2011**, *13*, 1738. (j) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852. (k) Nissen, F.; Detert, H. *Eur. J. Org. Chem.* **2011**, 2845. (l) Nissen, F.; Richard, V.; Alayrac, C.; Witulski, B. *Chem. Commun.* **2011**, *47*, 6656. (m) Pizzetti, M.; Russo, A.; Petricci, E. *Chem.—Eur. J.* **2011**, *17*, 4523. (n) Saito, N.; Saito, K.; Shiro, M.; Sato, Y. *Org. Lett.* **2011**, *13*, 2718. (o) Schotes, C. S. C.; Mezzetti, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3072. (p) Shindoh, N.; Kitaura, K.; Takemoto, Y.; Takasu, K. *J. Am. Chem. Soc.* **2011**, *133*, 8470. (q) Wang, Y. P.; Danheiser, R. L. *Tetrahedron Lett.* **2011**, *52*, 2111–2114. (r) Xu, C. F.; Xu, M.; Jia, Y. X.; Li, C. Y. *Org. Lett.* **2011**, *13*, 1556.

Table 1. Screening Results for the Copper-Mediated Alkylation of Benzophenone Imine



| entry | alkynylating agent | conditions ^a | yield ^b |
|-------|-------------------------------------|---|--------------------|
| 1 | Br—C≡C—Ph 12a | CuSO ₄ (10%) 1,10-phenanthroline (20%) K ₃ PO ₄ (2 equiv) toluene, 65 °C | - |
| 2 | Br—C≡C—Ph 12a | CuI (1 equiv) KHMDS (1 equiv) pyridine, rt | - |
| 3 | KF ₃ B—C≡C—Ph 12b | CuCl ₂ ·2H ₂ O (15%) 1,2-dimethylimidazole (40%) MS 4 Å, O ₂ (1 atm) CH ₂ Cl ₂ , rt | - |
| 4 | Br—C≡C—Ph 12c | CuI (10%) <i>N,N'</i> -dimethylethylenediamine (20%) Cs ₂ CO ₃ , dioxane, 60 °C | - |
| 5 | C≡C—Ph 12d | CuCl ₂ (20%) pyridine (2 equiv) Na ₂ CO ₃ (2 equiv) O ₂ (1 atm) toluene, 70 °C | 72% |

^a All reactions were run using 3 equiv of imine **11**. ^b Yield of pure, isolated product.

To evaluate the feasibility of such cross-coupling reactions, we initiated our studies by examining the reaction of commercially available benzophenone imine **11** with representative reagents and conditions typically used for the synthesis of ynamides (Table 1). While the use of bromoalkyne **12a**,^{3b,c} potassium alkynyl trifluoroborate **12b**,^{3g} or vinyl dibromide **12c**^{3c} only led to the formation of 1,4-diphenylbuta-1,3-diyne **14** without a trace of the desired ynamine, the use of Stahl's copper-catalyzed oxidative conditions^{3d} turned out to be a lot more efficient. Indeed, the combination of copper(II) chloride, pyridine, and sodium carbonate in toluene at 70 °C significantly reduced the formation of Glaiser–Hay dimer **14** and gave ynamine **13** in a synthetically useful yield (72%, Table 1, entry 5). While we were pleased to note that this compound

(5) For reactions involving ynamines, see: (a) David, W. M.; Kerwin, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 1464. (b) Hoffner, J.; Schottelius, M. J.; Feichtinger, D.; Chen, P. *J. Am. Chem. Soc.* **1998**, *120*, 376. (c) Feng, L.; Kumar, D.; Kerwin, S. M. *J. Org. Chem.* **2003**, *68*, 2234. (d) Feng, L.; Kerwin, S. M. *Tetrahedron Lett.* **2003**, *44*, 3463. (e) Feng, L.; Zhang, A.; Kerwin, S. M. *Org. Lett.* **2006**, *8*, 1983.

(6) Würthwein, E.-U.; Weigmann, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 923. For an isolated example involving reaction of an imine with perchlorobut-1-en-3-yne, see: Humbert, G.; Faul, D. *Tetrahedron Lett.* **1988**, *29*, 5355. For an isolated report involving preparation from *N,N*-bis(trimethylsilyl)ynamines, see: Weigmann, R. H.; Würthwein, E.-U. *Tetrahedron Lett.* **1989**, *30*, 6147.

was perfectly stable and could be stored for months without noticeable degradation, it however turned out to be more sensitive than regular ynamides to acidic conditions, mostly giving benzophenone and traces of phenylacetamide as byproducts, and its purification on silica gel required prior deactivation with triethylamine.

With optimized conditions in hand for the copper-mediated synthesis of ynamines, we next turned our attention to the scope of this reaction. The coupling of benzophenone imine **11** with various terminal alkynes **8** was therefore investigated: results from these studies are shown in Figure 2. Thus, a representative set of ynamines **13** was prepared in moderate-to-good yields, and the reaction was found to be compatible with a variety of aromatic and alkyl-substituted alkynes. Terminal enynes were also found to be excellent substrates, yielding to the corresponding ennymines **13j** and **13k** in good yields. However, the presence of a chelating group such as a benzoate (**13l**) was found to have a detrimental effect on the oxidative cross-coupling since all starting materials were completely recovered at the end of the reaction.

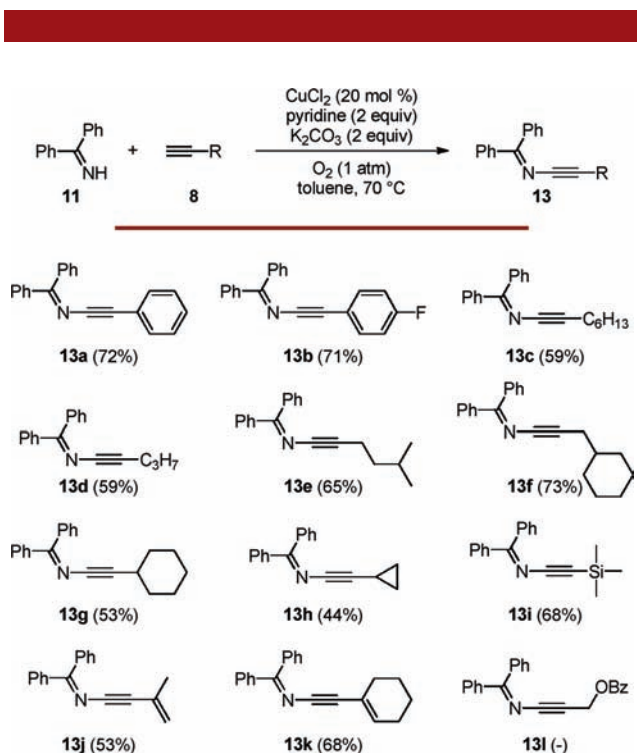


Figure 2. Copper-catalyzed alkylation of benzophenone imine with terminal alkynes.

The reaction scope was also investigated in respect to the imine cross-coupling partner using two representative terminal alkynes: pentyne **15a** and octyne **15b** (Figure 3). The use of the later typically gave higher yields of the

corresponding ynamines **16–20**, which was attributed to the lower volatility of octyne compared to pentyne.

Attempts at lowering the reaction temperature did not however significantly improve the yields since most reactions did not go to completion at 40 °C. The substitution pattern of the starting imine was found to have a strong impact on the outcome of the reaction: while *ortho*-substituted diaryl imines yielded to the formation of a single stereoisomer of ynamines **16–19**,¹⁰ the use of a remote *meta*-substituent gave rise to equimolar amounts of *E*- and *Z*-isomers of the corresponding ynamine **20**. The reaction was however found to be rather general and allowed for the synthesis of a wide range of ynamines possessing representative substitution patterns. Only (2-bromophenyl)(phenyl) methanimine (**19**) and 2,2,4,4-tetramethylpentan-3-imine (**21**) led to notably inferior results, which could be attributed to the presence of the *ortho*-activated aromatic bromide and steric hindrance, respectively.

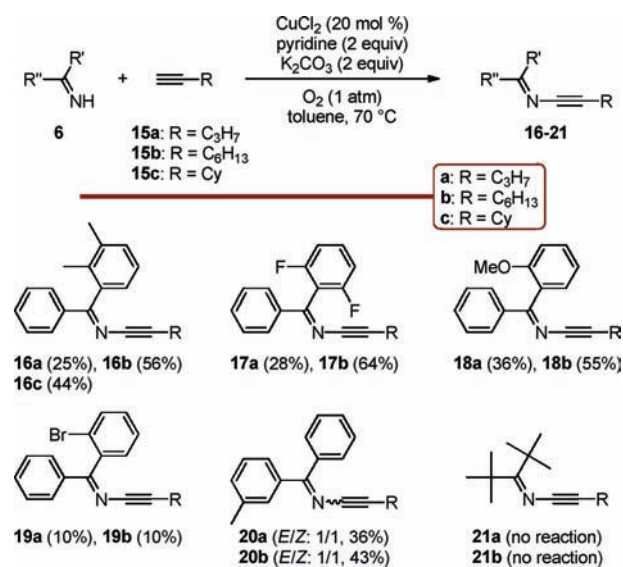


Figure 3. Copper-catalyzed alkylation of representative imines with pent-1-yne and oct-1-yne.

In all these oxidative cross-coupling reactions, we noticed the formation of azine byproducts **22** (Figure 4) resulting from a copper-catalyzed dimerization of the starting imines, a reaction that is usually performed starting from 25 to 50% weight solutions of ketimines and copper(I) chloride.¹¹ Because the scope of this reaction yielding to valuable azine building blocks has not been extensively studied and is still mostly restricted to the dimerization of benzophenone imine, we therefore initiated a brief study of this oxidative dimerization. We found that the reaction was best conducted in 1,4-dioxane

(7) (a) Coste, A.; Couty, F.; Evano, G. *Org. Lett.* **2009**, *11*, 4454. (b) Fadel, A.; Legrand, F.; Evano, G.; Rabasso, N. *Adv. Synth. Catal.* **2011**, *353*, 263.

(8) Evano, G.; Toumi, M.; Coste, A. *Chem. Commun.* **2009**, 4166.

(9) (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954.

(10) The *Z*-stereochemistry of compound **16c** was demonstrated by X-ray analyses. See Supporting Information for details.

(11) (a) Meyer, R.; Pillon, D. U.S. Patent 2,870,206, Jan 20, 1959. (b) Nawata, T.; Sakaguchi, S.; Kohzaki, T.; Aoki, O.; Takeda, N.; Shimpo, M. U.S. Patent 4,751,326, Jun 14, 1988. (c) Jautelat, M.; Leidinger, W. U.S. Patent US2002/0013495, Jan 31, 2002.

at 80 °C for 12–14 h and that the use of both pyridine and sodium carbonate was crucial. Using these conditions, aromatic ketimines **6** are readily dimerized into the corresponding azines **22** in good to excellent yields. *Ortho*-substituted arylketimines typically yielded the corresponding dimers as single isomers while the use of a *para*-substituent, such as in the case of **22d**, yielded a 1/1/1 mixture of (*E,E*), (*E,Z*), and (*Z,Z*) isomers. Noteworthy, the chloro-substituent was perfectly compatible with the copper catalyst and no competitive amination or reduction could be observed.

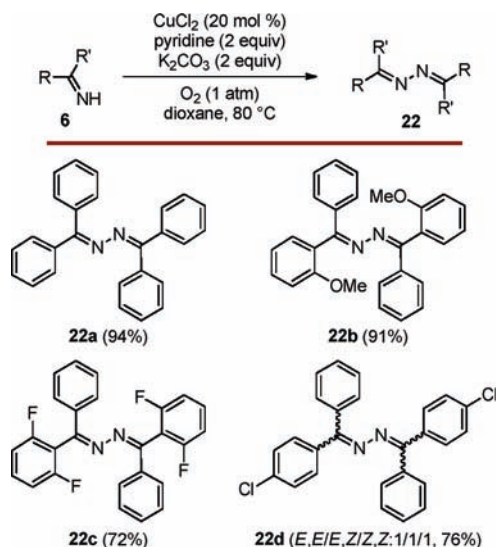


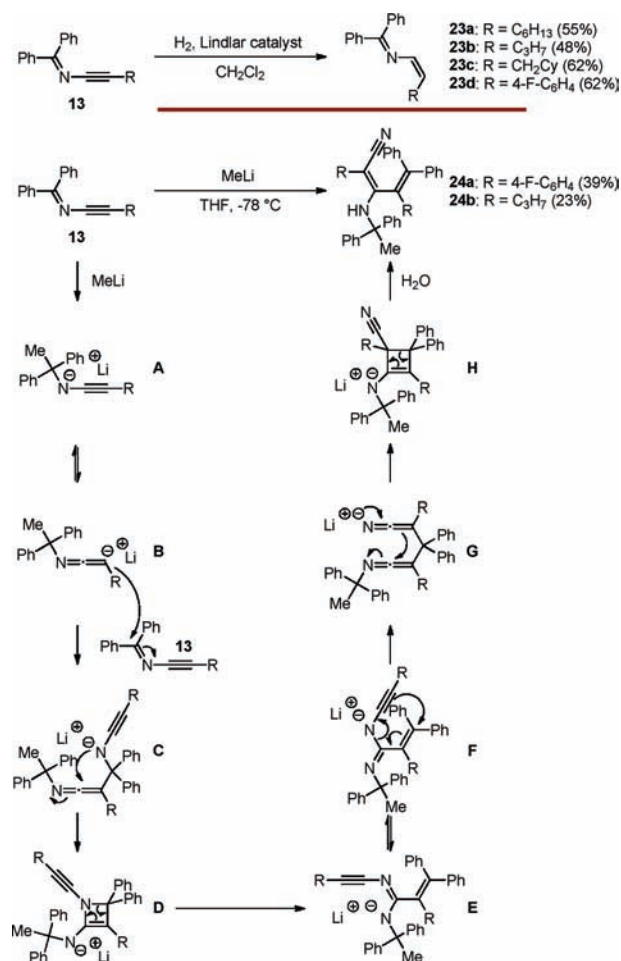
Figure 4. Copper-catalyzed dimerization of imines to azines.

We finally briefly assessed the synthetic utility of our ynimines. With this goal in mind, a series of *Z*-azadienes **23** was first prepared by partial hydrogenation of the corresponding ynimines **13** with a Lindlar catalyst (Scheme 2). This method represents an interesting entry to the *Z*-enamines, compounds for which there is no general synthesis to date.

An especially intriguing reaction was observed upon treatment of ynimines **13** with 1 equiv of methyllithium in THF at -78 °C. This reaction resulted in the unexpected formation of polysubstituted dienes **24** with moderate yield, compounds whose structure could be secured by X-ray analysis performed on **24a**.¹² A possible mechanism that would account for the formation of these highly substituted dienes is shown in Scheme 2. Addition of methyllithium onto the starting ynimine **13** would generate a metalated secondary ynamine **A** which would be in equilibrium with the lithiated ketenimine **B**. Addition of a second equivalent of **13** would yield the formation of lithiated ketenimino-ynamine **C** whose cyclization would afford a dihydroazete **D**. Electrocyclic ring opening of this strained intermediate¹³

would then generate a metalated *N*-alkynyl-enamidine **E**, a compound that would be in equilibrium with **F**. Finally, a [3,3] sigmatropic rearrangement followed by intramolecular nucleophilic attack from **G** and a second electrocyclic ring opening from cyclobutene **H** would account for the formation of highly strained dienes **24** after hydrolysis.

Scheme 2. Azadienes and Dienes from Ynimines



In conclusion, we have developed an efficient synthesis of ynimines by copper-mediated oxidative cross-coupling of imines with terminal alkynes. The building blocks were shown to be especially suitable precursors for the synthesis of azadienes and dienes, and further studies on the use of ynimines will be reported in due time.

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Supporting Information Available. Experimental procedures, characterization, copies of ^1H and ^{13}C NMR spectra for all new compounds. Crystal data for ynimine **16c** and diene **24a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(12) See Supporting Information for details.

(13) (a) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Org. Lett.* **2006**, *8*, 231. (b) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem.—Eur. J.* **2009**, *15*, 7026.