ORGANIC LETTERS

2010
Vol. 12, No. 7
1396−1399

Highly Diastereoselective Synthesis of Substituted Pyrrolidines Using a Sequence of Azomethine Ylide Cycloaddition and Nucleophilic Cyclization

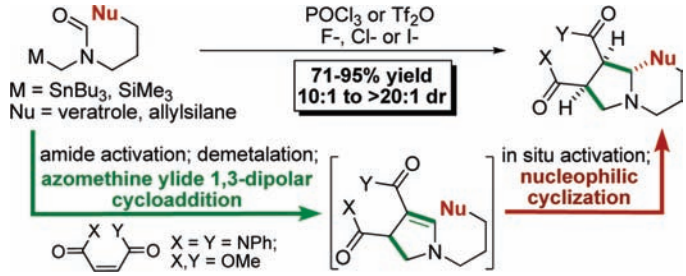
Guillaume Bélanger,* Véronique Darsigny, Michaël Doré, and François Lévesque

Département de Chimie, Université de Sherbrooke, 2500 Boulevard Université, Sherbrooke, Québec J1K 2R1, Canada

guillaume.belanger@usherbrooke.ca

Received December 3, 2009

ABSTRACT



Although cycloadditions of azomethine ylides usually give mixtures of *endo*/*exo* adducts, we successfully tuned the mechanistic path of a new reaction cascade to afford substituted pyrrolidines in high yields and diastereomeric purity. This was achieved by forcing the demetalation of tin- or silicon-substituted iminium ions, followed by azomethine ylide cycloaddition and nucleophilic cyclization. Structural complexity is thus built rapidly in a fully controlled one-pot reaction cascade.

1,3-Dipolar cycloaddition of azomethine ylides is recognized as one of the best ways to prepare pyrrolidines.[1,2] The reaction has been extensively used for their generation, and its exploitation has been documented in very nice and efficient syntheses of alkaloids.[3] Unfortunately, for substituted pyrrolidines, this method usually gives mixtures of *endo* and *exo* cycloadducts, especially in intermolecular cycloadditions.[4] To get around this serious limitation, many reported cases fell back to the use of functional groups or conformational restriction to advantageously bias the diastereoselectivity of the cycloaddition; these biased systems often restrain applications to precise substitution patterns in the resulting pyrrolidines.

(1) For a selection of reviews on the methods for the preparation of azomethine ylides and their 1,3-dipolar cycloadditions, see: (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1.3-Dipolar Cyaloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2003; pp 169−252. (c) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941.

(2) For the gerenation of unstabilized azomethine ylides from demetalation of (trimethylsilyl)methyl- or (tributylstannyl)methyliminium ions, see ref 1 and: (a) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452. (b) Achiwa, K.; Sekiya, M. *Chem. Lett.* **1981**, 1213. (c) Achiwa, K.; Motoyama, T.; Sekiya, M. *Chem. Pharm. Bull.* **1983**, *31*, 3939. (d) Padwa, A.; Chen, Y. *Tetrahedron Lett.* **1983**, *24*, 3447. (e) Padwa, A.; Chen, Y.; Dent, W.; Nimmesgern, H. *J. Org. Chem.* **1985**, *50*, 4006. (f) Pearson, W. H.; Mi, Y. *Tetrahedron Lett.* **1997**, *38*, 5441. (g) Pearson, W. H.; Stoy, P.; Mi, Y. *J. Org. Chem.* **2004**, *69*, 1919.

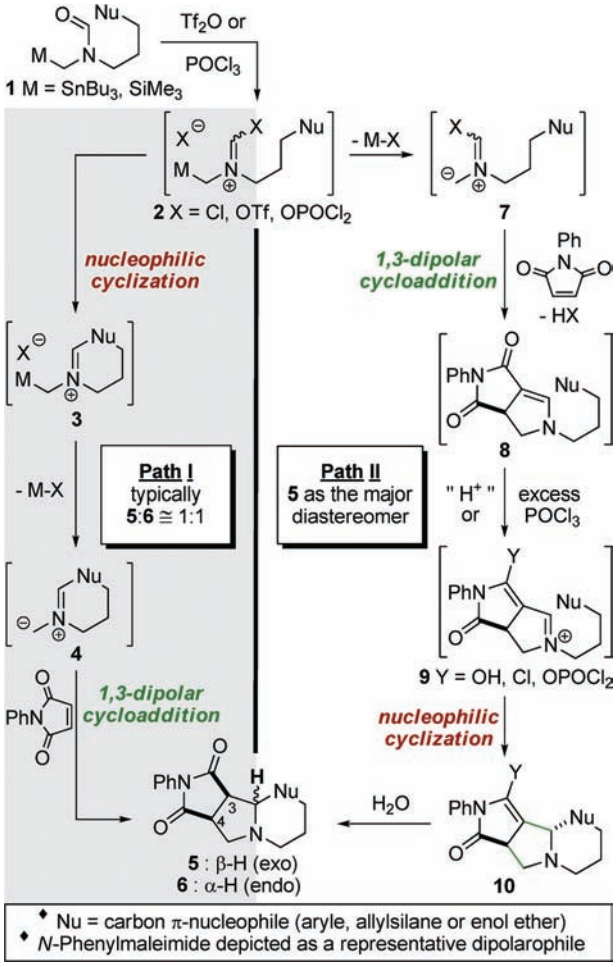
(3) For a selection of recent examples, see: (a) Pandey, G.; Gupta, N. R.; Pimpalpalle, T. M. *Org. Lett.* **2009**, *11*, 2547. (b) Burrell, A. J. M.; Coldham, I.; Oram, N. *Org. Lett.* **2009**, *11*, 1515. (c) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290. (d) Carra, R. J.; Epperson, M. T.; Gin, D. Y. *Tetrahedron* **2008**, *64*, 3629. (e) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6159. (f) Pearson, W. H.; Kropf, J. E.; Choy, A. L.; Lee, Y.; Kampf, J. W. *J. Org. Chem.* **2007**, *72*, 4135. (g) Epperson, M. T.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1778.

(4) For example, see ref 2f,g and: (a) Coldham, I.; Jana, S.; Watson, L.; Pilgram, C. D. *Tetrahedron Lett.* **2008**, *49*, 5408. (b) Alker, D.; Harwood, L. M.; Williams, C. E. *Tetrahedron* **1997**, *53*, 12671. (c) Roussi, G.; Zhang, J. *Tetrahedron* **1991**, *47*, 5161. (d) Grigg, R.; Heaney, F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 198. (e) Grigg, R.; Surendrakumar, S.; Thianpatanagul, S.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 47.

10.1021/ol902767b
Published on Web 03/01/2010

Herein, we describe how we successfully brought a solution to the poor *endo*/*exo* selectivity associated with the unbiased cycloadditions of azomethine ylides, even for the challenging *inter*molecular version. This work is derived from our previously developed reaction cascade that follows path I of Scheme 1.[5] Upon demetalation of silicon- or tin-

Scheme 1. Tunable Reaction Paths for the Diastereoselective Formation of Pyrrolidines and Indolizidines (**5**) from **1**



substituted iminium ions,[2] ylides such as **4** typically lead to an almost equimolar mixture of cycloadducts **5** and **6**, as supported by many examples from the literature.[4] Therefore, we predicted that forcing a reversal of the 1,3-dipolar cycloaddition and the nucleophilic cyclization steps in the reaction cascade would be the key to diastereocontrol in the pyrrolidine formation (path II).[6]

To do so, we planned to induce the demetalation of **2** subsequent to the activation of amide **1**,[7] leading to an ylide **7** bearing a carbon of a higher oxidation state than those normally seen with standard azomethine ylides.[1c,8] After a 1,3-dipolar cycloaddition followed by an elimination, the resulting vinylogous urea **8** would then become activated in situ. The ensuing nucleophilic cyclization should occur predominantly onto the convex face of bicyclic compound **9**, and upon quenching of **10**, the thermodynamically preferred *cis* ring junction (C3−C4) would furnish **5** as the major diastereomer. Hence, by choosing the right metal and demetalation conditions for azomethine ylide preparation, the reaction path could potentially be controlled, along with the relative stereochemistry in the resulting pyrrolidine ring, as the following results will show. Such pyrrolidines (and indolizidines) are ubiquitous moieties found in numerous natural products like in the two important families of alkaloids depicted in Figure 1.

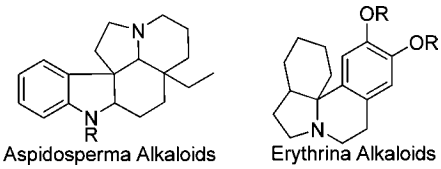


Figure 1. Examples of alkaloid families containing substituted pyrrolidines.

The planned reaction cascade was initially tested with two model compounds, **11a** and **11b**,[9] bearing a 3,4-dimethoxybenzene as the tethered nucleophile, and either a tributylstannyl or trimethylsilyl as the metal fragment for ylide preparation, respectively. When compound **11a** was treated with $POCl_3$[10] in acetonitrile[11] at room temperature to activate the amide, in the presence of *N*,*N*-diisopropyl-*N*-ethylamine[12] and *N*-phenylmaleimide[13] as the dipolarophile, only *exo*-indolizidine **12** was obtained in 79% yield (Table 1, entry 1). The stereochemistry of the latter was unequivocally established by X-ray crystallographic analysis.[14] When dimethyl maleate was used instead of *N*-phenylmaleimide, we were able to intercept pyrroline intermediate **14** bearing an uncyclized aromatic ring in high

(5) Lévesque, F.; Bélanger, G. *Org. Lett.* **2008**, *10*, 4939.

(6) Gin et al. recently reported a somewhat related method, although their system does not allow for an additional nucleophilic cyclization. See ref 3d,g.

(7) Pearson ***et al.*** already proposed a fast destannylation of *N*-(tributylstannyl)methyliminium ions. See ref 2g.

(8) For the preparation of azomethine ylides bearing a carbon of a higher oxidation state, see also: (a) Ohno, M.; Komatsu, M.; Miyata, H.; Ohshiro, Y. *Tetrahedron Lett.* **1991**, *32*, 5813. (b) Washizuka, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, *55*, 12969. (c) Padwa, A.; Haffmanns, G.; Tomas, M. *Tetrahedron Lett.* **1983**, *24*, 4303. (d) Fishwick, C. W. G.; Foster, R. J.; Carr, R. E. *Tetrahedron Lett.* **1996**, *37*, 3915. (e) Tsuge, O.; Hatta, T.; Kakura, Y.; Tashiro, H.; Maeda, H.; Kakehi, A. *Chem. Lett.* **1997**, 945.

(9) Synthesis described in the Supporting Information.

(10) Activation with triflic anhydride was problematic due to competitive irreversible activation of *N*-phenylmaleimide.

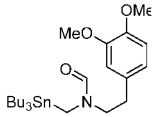
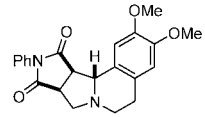
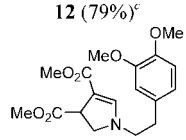
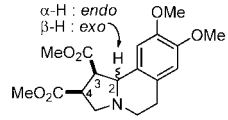
(11) Less polar solvent, such as toluene, caused the precipitation of polar intermediate(s), and the yield was dramatically affected.

(12) 2,6-Di-*tert*-butyl-4-methylpyridine could be employed as well, resulting in similar yields. The use of other bases, or no base at all, resulted in a significant decrease in the overall yield.

(13) Azomethine ylide intermediates should be trapped as soon as they are formed in the reaction medium. The use of 3 equiv of dipolarophile was optimal; below this level, extensive decomposition and low yields were obtained.

(14) See the Supporting Information.

Table 1. Reaction Cascade with the Stannylated Formamido-3,4-Dimethoxybenzene Derivative **11a**

	substrate	conditions[a]	dipolarophile	product (yield)
1	 **11a**	**A**	*N*-Phenylmaleimide	 **12** (79%)[c]
2	**11a**	**A**	Dimethyl maleate	 **14** (80%)
3	**11a**	**B**, Bu_4NI	Dimethyl maleate	**14** (76%)
4	**11a**	**B**, Bu_4NI	Dimethyl fumarate	**14** (91%)
5	**14**	**A**[b]	none	 **15** (*exo*):**16** (*endo*) = 6:1 (71%)[d]
6	**11a**	**A**[b]	Dimethyl fumarate	**15**:**16** = 14:1 (72%)[d]

[a] Conditions A: substrate, dipolarophile (3 equiv), $POCl_3$ (8 equiv), *i*-Pr_2NEt (1.1 equiv), MeCN, 25 °C. Conditions B: substrate, dipolarophile (3 equiv), Tf_2O (1.1 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.1 equiv), *n*-Bu_4NI (1.1 equiv), 1,2-dichloroethane, 25 °C. [b] Reaction run at 80 °C. [c] Only one diastereomer detected by ^1H NMR. [d] Ratio determined by GCMS analysis.

yield (entry 2).[15] Isolation of a pyrroline intermediate (cf. **8**) provided evidence for a path II mechanism.

Pyrroline **14** could also be obtained using milder conditions we developed for the activation of amide substrates in the presence of tethered nucleophiles.[16] The use of only an equimolar amount of triflic anhydride as the activating agent (instead of an excess of $POCl_3$), in the presence of an external source of halogen (*n*-Bu_4NI) to promote desilylation,[17] furnished pyrroline **14** in about the same yield (entry 3). As anticipated from path II, the use of dimethyl fumarate as the dipolarophile led to the same pyrroline **14**, in 91% yield (entry 4).

According to the proposed path II mechanism, pyrroline intermediate **14** needs to be activated in the reaction mixture to form indolizidine **15**/**16**. Hence, upon treatment of **14** with an excess of $POCl_3$ in refluxing acetonitrile (entry 5), adduct **15** was obtained as the major diastereomer in 71% yield. In the same conditions, amide **11a** afforded adduct **15** directly with no isolation of intermediate **14** (entry 6), and the observed yield and diastereomeric ratio were better than those obtained for the two-step sequence (entries 4 and 5 combined).

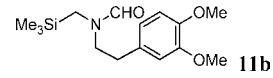
(15) Pyrroline **14** was isolated because of the lower nucleophilicity of the vinylogous carbamate moiety of **14** (compared to a vinylogous urea moiety when *N*-phenylmaleimide is used) that hampered its in situ activation.

(16) (a) Bélanger, G.; Larouche-Gauthier, R.; Ménard, F.; Nantel, M.; Barabé, F. *Org. Lett.* **2005**, *7*, 4431. (b) Bélanger, G.; Larouche-Gauthier, R.; Ménard, F.; Nantel, M.; Barabé, F. *J. Org. Chem.* **2006**, *71*, 704.

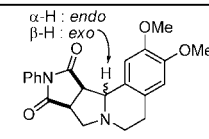
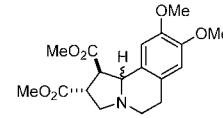
(17) Chloride anion (*n*-Bu_4NCl) promoted the destannylation as well, albeit in lower yield.

The results in Table 1 are all consistent with a path II mechanism when stannylated substrate **11a** was employed. Interestingly, switching to silylated substrate **11b** gave completely different results, now consistent with a path I mechanism. For example, when substrate **11b** was activated with an excess of $POCl_3$ and treated with *N*-phenylmaleimide, diastereomers **12** and **13** were obtained in an equimolar amount (Table 2, entry 1), clearly contrasting with the enhanced diastereocontrol observed when stannylated substrate **11a** was used under the same reaction conditions (Table 1, entry 1).

Table 2. Reaction Cascade with the Silylated Formamido-3,4-dimethoxybenzene Derivative **11b**



11b

	conditions[a]	dipolarophile (# equiv)	product (yield)
1	**A**, *i*-Pr_2NEt (1.1 equiv)[b]	*N*-Phenylmaleimide (5)	 (57%) **12** (*exo*):**13** (*endo*) = 1:1[c]
2	**B**	Dimethyl fumarate (3)	 (42%) **17**, 3.5:1[c]
3	**A**, *i*-Pr_2Net (1.1 equiv)	Dimethyl fumarate (10)	**17**, 6.5:1 (63%)[c]
4	**A**, *i*-Pr_2Net (1.1 equiv)	Dimethyl maleate (10)	**15**:**16** = 1:1.2 (28%)[c]
5	**A**, Bu_4NCl (3.0 equiv)	*N*-Phenylmaleimide (10)	**12** (*exo*):**13** (*endo*) = 10:1 (95%)[d]

[a] Conditions A: **10b**, dipolarophile, $POCl_3$ (1.5 equiv), MeCN, 80 °C. Conditions **B**: (ii) **10b**, Tf_2O (1.1 equiv), *i*-Pr_2NEt (1.1 equiv), 1,2-dichloroethane; (ii) *n*-Bu_4NI (1.0 equiv), dipolarophile, 80 °C. [b] 8 equiv of $POCl_3$ were used at 25 °C. [c] Ratio determined by GCMS analysis. [d] Ratio determined by ^1H NMR analysis.

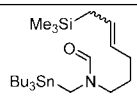
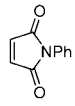
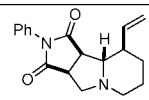
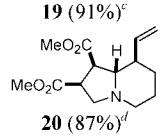
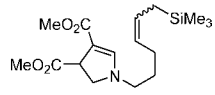
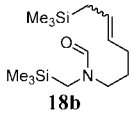
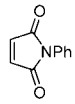
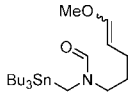
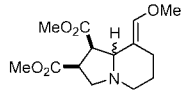
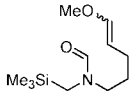
Another remarkable difference arose from the use of dimethyl fumarate as the dipolarophile. With stannylated substrate **11a**, we isolated pyrroline intermediate **14** (Table 1, entry 4), whereas with silylated substrate **11b**, we generated the fully cyclized indolizidine **17** (Table 2, entry 2). It should also be noted that, using either triflic anhydride and *n*-Bu_4NI (entry 2) or $POCl_3$ (entries 3 and 4), the relative stereochemistry of the esters in the dipolarophiles is transposed to the cycloadducts, which could only be explained by the path I mechanism.

From all the results of the key reaction cascade detailed above, we demonstrated that we could tune the reaction path by selecting the right metal: stannylated derivative **11a** followed path II, whereas silylated derivative **11b** followed path I. Most importantly, to avoid the use of organotin due to its toxicity,[18] we successfully forced the desired reaction (path II) even with

silylated substrate **11b** by adding *n*-Bu_4NCl to rapidly cleave the C−Si bond as soon as the formamide was activated (entry 5). Adduct **12** was obtained as the major diastereomer in an excellent yield. Hence, higher yields and diastereoselectivities were obtained when path II was operating.

To further expand the scope of this reaction cascade, we also tested other tethered nucleophiles.[19] When stannylated allylsilane substrate **18a**[9] was activated in the presence of *N*-phenylmaleimide, only cycloadduct **19** was formed (Table 3, entry 1).[20] Confirmation of the reaction path II arose, as

Table 3. Reaction Cascade with a Methyl Enol Ether or an Allylsilane as the Internal Nucleophile

	substrate	conditions[a]	dipolarophile	product (yield)
1	 **18a**	**A**		 **19** (91%)[c]
2	**18a**	**A**		 **20** (87%)[d]
3	**18a**	**B**, Bu_4NI (1.05 equiv)		 **21** (69%)
4	**21**	**C**	none	**20** (91%)[d]
5	**18a**	**B**, Bu_4NI (1.05 equiv); then **C**		**20** (84%)[d]
6	 **18b**	**A**, Bu_4NCl (1.2 equiv)[b]		**19** (80%)[c]
7	 **22a**	**B**, Bu_4N^+ $Ph_2SiF_3^-$ (1.0 equiv)		 **23**, 8:1 (41%)[e]
8	 **22b**	**B**, Bu_4N^+ $Ph_2SiF_3^-$ (1.0 equiv)		**23** (47%)

[a] Conditions A: substrate, dipolarophile (10 equiv), $POCl_3$ (1.5 equiv), MeCN, 25 °C. Conditions B: (i) substrate, Tf_2O (1.1 equiv), *i*-Pr_2NEt (1.1−1.2 equiv), 1,2-dichloroethane; (ii) *n*-Bu_4NI or *n*-$Bu_4NPh_2SiF_3$, dipolarophile (10 equiv), 25 °C. Conditions C: substrate, TFA (1.5 equiv), MeCN, 25 °C. [b] Reaction run at 80 °C. [c] Only one diastereomer detected by ^1H NMR. [d] Only one diastereomer detected by GCMS. [e] Ratio determined by GCMS analysis.

in the 3,4-dimethoxybenzene series, from the treatment of **18a** with dimethyl fumarate leading to adduct **20** bearing a *cis* diester (entry 2).

It should be noted that only 1.5 equiv of $POCl_3$ (with no base) was necessary to effect amide activation, demetalation, and activation of pyrroline intermediate, presumably because of traces of acid present in $POCl_3$, that promoted the latter step. Consequently, when we activated substrate **18a** with triflic anhydride, it was possible to isolate pyrroline **21** (entry 3), and the latter was successfully converted to the desired adduct **20** in acidic conditions (entry 4). Both steps could even be performed in one pot (entry 5).

In the case of silylated substrate **18b**,[9] addition of *n*-Bu_4NCl was needed in order to accelerate the demetalation (entry 6). Path I was thus entirely suppressed, leading to **19** as a single diastereomer. Again, tin could be avoided and path II could be selected at will.

When the allylsilane was traded for an enol ether, the reaction path could no longer be selected. Indeed, treatment of stannylated or silylated substrates **22a**,**b**[9] with triflic anhydride[21] in the presence of dimethyl maleate and a source of fluoride (*n*-$Bu_4NPh_2SiF_3$) afforded cycloadduct **23** in moderate yields and diastereoselectivity (entries 7 and 8). The nucleophilic cyclization in **22a**,**b** presumably occurred prior to demetalation due to the higher nucleophilicity of the enol ethers compared to the 3,4-dimethoxybenzene or the allylsilane, and only path I operates.[22]

In conclusion, we have successfully developed a new synthetic strategy that combines 1,3-dipolar cycloadditions of azomethine ylides and cyclizations of various nucleophiles onto iminium ions. The distinctive advantage and novelty of this approach resides in the method we devised for the preparation of the azomethine ylide, leading to an ylide bearing a carbon of high oxidation state that allowed for an additional carbon−carbon bond formation and a greater increase in structural complexity from a single transformation. We also showed that indolizidine adducts could be obtained in high yields and diastereomeric purity by forcing the desired reaction path II. Synthetic applications of this new reaction cascade will be published in due course.

Acknowledgment. This research was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canadian Fund for Innovation. A Université de Sherbrooke M.Sc. scholarship to M.D. and a Ph.D. scholarship to F.L. as well as a NSERC PGS-M scholarship to V.D. are also gratefully acknowledged.

Supporting Information Available: Experimental details and spectra for all new compounds and X-ray diffractions structures (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL902767B

(18) Thomas, L. D.; Shah, E.; Bankhurst, A. D.; Whalen, M. M. *Arch. Toxicol.* **2005**, *79*, 711.

(19) Formation of 5-membered rings by via Vilsmeier−Haack cyclizations gives poor yields, as previously demonstrated (see ref 16).

(20) Relative stereochemistry on **19** was proven by comparison with the X-ray diffraction stucture of the analogous *p*-bromo-substituted phenyl derivative (see the Supporting Information).

(21) The enol ether was not compatible with $POCl_3$ activation, resulting in partial hydrolysis.

(22) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.