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Cycloadditions of Nonstabilized 2-Azaallyllithiums with Cycloheptatriene

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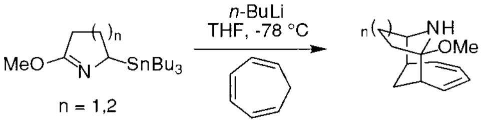
ABSTRACT



Transmetalation of tin-bearing cyclic imidates gave 2-azaallyllithiums that underwent $[\pi 6s + \pi 4s]$ cycloadditions with cycloheptatriene to produce tricyclic adducts, which may be useful as analogs of cocaine. The peri- and stereoselectivity of this process are discussed.

Higher-order cycloadditions, particularly $[\pi 6s + \pi 4s]$ cycloadditions between trienes and dienes, are useful for the generation of complex carbocyclic frameworks from relatively simple starting materials.[1,2] The use of 1,3-dipoles as 4π addends in $[\pi 6s + \pi 4s]$ cycloadditions with trienes is more rare.[1a,b] Dipoles such as nitrile imines,[3] nitrile oxides,[4,5] and mesoionics[6] undergo cycloadditions with tropones and their derivatives, generally with poor periselectivity, producing mainly (or exclusively) $[\pi 4s + \pi 2s]$ cycloadducts. Fulvenes have also been used as triene partners in cycloadditions with 1,3-dipoles, generally leading to $[\pi 4s + \pi 2s]$ products, although $[\pi 6s + \pi 4s]$ cycloadducts have occasionally been observed.[1a,b,7−11] For example, Padwa and Nobs found that a nitrile ylide reacted with a fulvene to give both $[\pi 6s + \pi 4s]$ and $[\pi 4s + \pi 2s]$ products, with the former predominating.[12] Allylic anions should also participate in $[\pi 6s + \pi 4s]$ cycloadditions with trienes.[13] We have been exploring the $[\pi 4s + \pi 2s]$ cycloaddition chemistry of 2-azaallyllithiums (2-azaallyl anions) with alkenes[14] and now wish to examine higher-order reactions of these species. The only report of such a $[\pi 6s + \pi 4s]$ cycloaddition is the reaction of the semistabilized Kauffmann-type[15] 2-azaallyllithiums **2a** and **2b**, derived from the imines **1a** and **1b** with cycloheptatriene to produce the $[\pi 6s + \pi 4s]$ cycloadducts **3** and **4** in 47 and 1.4% yields, respectively (Scheme 1).[16] The latter cycloaddition gave a mixture of diastereomers **4a** and

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[†] To whom correspondence regarding the X-ray crystallographic determinations should be addressed.

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(4) DeMicheli, C.; Gandolfi, R.; Gruenanger, P. *Tetrahedron* **1974**, *30*, 3765.

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(8) Kato, H.; Kobayashi, T.; Ciobanu, M.; Iga, H.; Akutsu, A.; Kakehi, A. *Chem. Commun.* **1996**, 1011−1012.

(9) Kato, H.; Kobayashi, T.; Ciobanu, M. *Tetrahedron* **1997**, *53*, 9921−9934.

(10) Muthusamy, S.; Babu, S. A.; Gunanathan, C.; Suresh, E.; Datidar, P. *Synlett* **2001**, 1407−1410.

(11) Oxidopyridiniums have also been observed to participate in $[\pi 6s + \pi 4s]$ cycloadditions of a different sort, where the mesoionic acts as a 6π addend in reactions with dienes. See ref 7 above and: Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett.* **1999**, *1*, 2017−2019.

(12) Padwa, A.; Nobs, F. *Tetrahedron Lett.* **1978**, 93.

(13) A recent report of the reaction of $CH_2{=}C[PPh_3(+)]CH(-)COR$, which has an allylic anion set of orbitals, with tropone revealed a minor amount of the $[\pi 6s + \pi 4s]$ cycloadduct in addition to the major product, the $[\pi 4s + \pi 2s]$ cycloadduct. See: Kumar, K.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 787−789.

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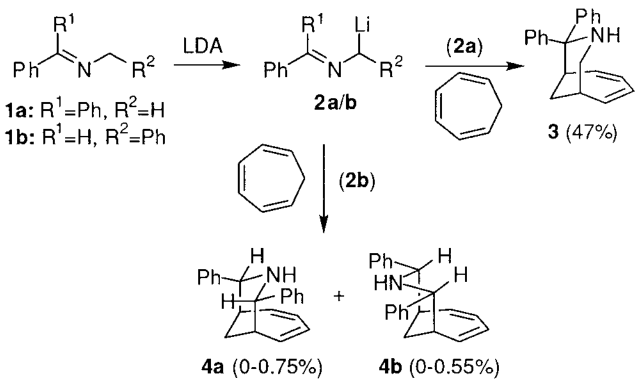
10.1021/ol026423i CCC: $22.00

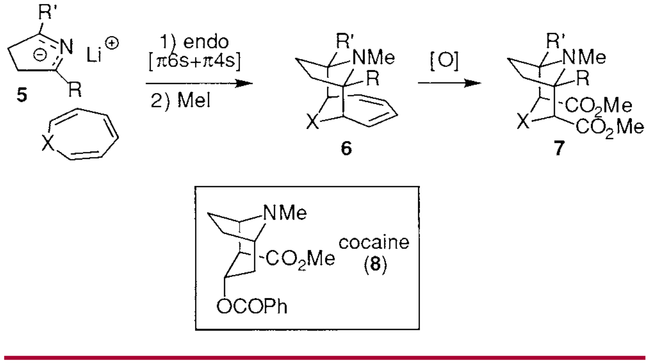
Scheme 1. Bower and Howden's Cycloadditions of Semistabilized 2-Azaallyllithiums with Cycloheptatriene



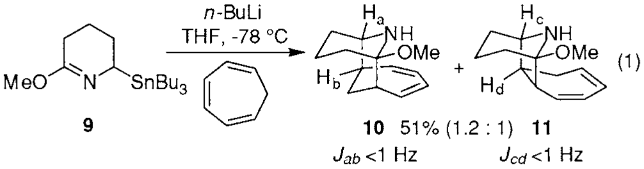
4b. Adduct **4a** presumably results from either an endo or exo cycloaddition of the sickle form of the anion with the triene, whereas **4b** is proposed to arise from an exo cycloaddition involving the W-form of the anion, although the configuration of this compound is uncertain. Surprisingly, no $[\pi4s + \pi2s]$ cycloadducts were reported in either cycloaddition, even though cycloheptatriene is known to react with 4π addends with modest periselectivity and low chemical yield.[1a] Upon repeating Bower and Howden's work in our laboratories to obtain authentic samples, we were not able to isolate any **4**, while comparable yields of **3** were obtained.

Herein we report the reactions of less-stabilized 2-azaallyllithiums with cycloheptatriene. In particular, we wished to study the reactions of *cyclic* 2-azaallyllithiums (e.g., **5**, Scheme 2) with trienes, hopefully affording the tricycles **6**, which might be oxidatively cleaved to the bicycles **7**, analogs of cocaine **8**.[17]

Scheme 2. Proposed Route to Analogues (**7**) of Cocaine (**8**)



Upon addition of a mixture of the imidate **9**[18] and cycloheptatriene to *n*-butyllithium, the $[\pi6s + \pi4s]$ and $[\pi4s + \pi2s]$ adducts **10** and **11**, respectively, were formed in moderate yield (eq 1). The low periselectivity is consistent with the literature of higher-order cycloadditions[2c] and contrasts with the high periselectivity observed by Bower and Howden in Scheme 1. Both **10** and **11** were obtained as single diastereomers, each a result of endo cycloaddition (vide infra). While NOE experiments were inconclusive, the ^{1}H NMR coupling constants J_{ab} and J_{cd} (both <1 Hz) were consistent with predicted values of 2.8 and 2.4 Hz for **10** and **11**, respectively, vs 11 and 7.5 Hz for the corresponding exo isomers.



Reaction of the 2-azaallyllithium derived from the five-membered ring imidate **12** with cycloheptatriene gave the $[\pi6s + \pi4s]$ cycloadduct **13** and the imidate **15** in 63% combined yield after aqueous workup (Scheme 3).[19] Quenching the reaction mixture with iodomethane gave a 93% yield of a mixture of **14** and **16**. The higher-order cycloadducts **13** and **14** were formed as single diastereomers, consistent with the results in eq 1 above. The adducts **15** and **16**, however, were formed as inseparable mixtures of diastereomers.

The cycloadduct **13** was assigned as the endo diastereomer on the basis of its ^{1}H NMR spectrum, where the coupling constant J_{ab} was found to be <1 Hz, consistent with the predicted value of 3.8 Hz. A value of 10.5 Hz is predicted for the exo isomer. This assignment was confirmed by

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(17) For leading references on cocaine analogs and the rationale for making them, see: (a) Kozikowski, A. P.; Saiah, M. K. E.; Johnson, K. M.; Bergmann, J. S. *J. Med. Chem.* **1995**, *38*, 3086−3093. (b) Kozikowski, A. P.; Araldi, G. L.; Ball, R. G. *J. Org. Chem.* **1997**, *62*, 503−509. (c) Lounasmaa, M.; Tamminen, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1993; Vol. 44, pp 1−114. (d) Singh, S. *Chem. Rev.* **2000**, *100*, 925−1024.

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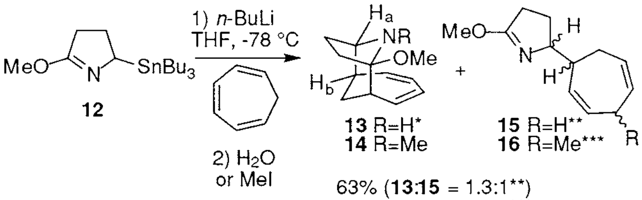
(19) **Preparation of 12 and 14.** *n*-Butyllithium (0.55 mL of a 2.38 M solution in hexanes, 1.3 mmol) was added in a dropwise fashion to a solution of the stannane **11** (0.391 g, 1.00 mmol) and cycloheptatriene (0.52 mL, 0.462 g, 5.0 mmol) in THF (4 mL) at −78 °C. After 30 min, saturated aqueous ammonium chloride was added and the mixture was diluted with ether. The organic layer was washed with water (three times) and brine, dried (Na_2SO_4), and concentrated. Chromatography (0−25% ethyl acetate/hexanes gradient) gave 66.9 mg (35%) of **12** and 53.1 mg (28%) of **14** as clear colorless oils. Data for **12**: R_f 0.06 (25% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 6.19 (dd, 1 H, $J = 11.5, 7.5$ Hz), 5.93 (ddt, 1 H, $J = 11.5, 7.5, 1$ Hz), 5.85 (ddt, 1 H, $J = 11.5, 7.3, 1$ Hz), 5.61 (dd, 1 H, $J = 11.5, 7.0$ Hz), 3.30 (s, 3 H), 3.25 (d, 1 H, $J = 6.5$ Hz), 2.66 (t, 1 H, $J = 6.3$ Hz), 2.04−1.85 (m, 5 H), 1.48 (app d, 1 H, $J = 13.5$ Hz), 1.40 (ddd, 1 H, $J = 12.5, 10.5, 4.8$ Hz), 1.23 (ddd, 1 H, $J = 12, 10, 4$ Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 136.0, 135.9, 127.1, 126.6, 99.9, 61.4, 47.9, 46.7, 42.2, 28.6, 27.3, 24.0; IR (neat) 3309 (m), 1652 (w), 1594 (w) cm^{-1}; MS (EI, 70 eV) *m*/*z* (rel int) 191.1 (59, M^+), 99.1 (64), 84 (100); HRMS (EI, 70 eV) calcd for $C_{12}H_{17}NO$ (M^+) 191.1310, found 191.1309. Data for **14**: R_f 0.37 (30% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 6.01 (dm, 1 H, $J = 11.5$ Hz), 5.79−5.70 (m, 2 H), 5.65−5.60 (m, 1 H), 3.77 (q, 1 H, $J = 7$ Hz), 3.68 (s, 3 H), 2.86 (dm, 1 H, $J = 20$ Hz), 2.77−2.70 (m, 1 H), 2.63 (dt, 1 H, $J = 20, 5.8$ Hz), 2.33 (tm, 1 H, $J = 5.8$ Hz), 2.20−2.10 (m, 3 H), 1.73−1.64 (m, 1 H), 1.46−1.36 (m, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 172.4, 134.5, 130.0, 128.2, 127.9, 71.2, 55.1, 43.7, 31.3, 29.9, 28.8, 27.7; IR (neat) 1650 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (rel int) 191.3 (10), 176.3 (16), 98.2 (100), 84.1 (17), 70.1 (9); HRMS (EI, 70 eV) calcd for $C_{12}H_{17}NO$ (M^+) 191.1310, found 191.1312.

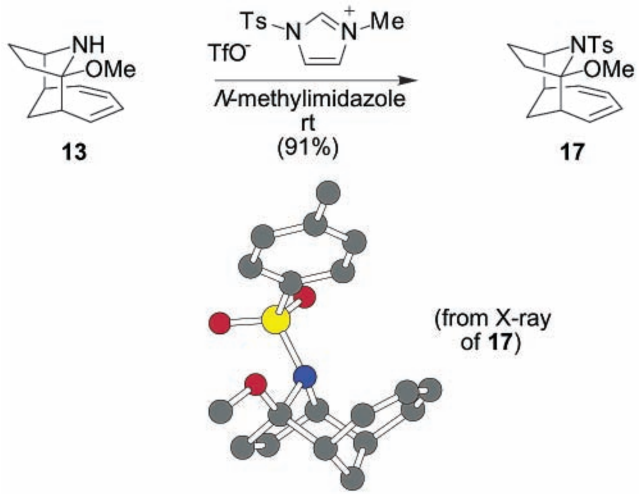
Scheme 3. Reaction of a Five-Membered Ring 2-Azaallyllithium with Cycloheptatriene



*J_{ab} = <1 Hz
**15 is an 8:1 mixture of diastereomers
***16 is a 13.5:5.4:1.2:1 mixture of diastereomers

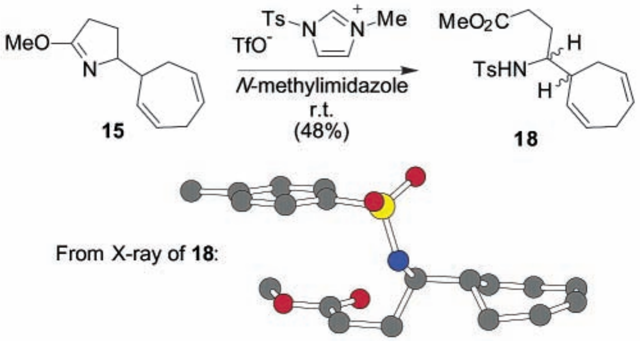
converting **13** to the crystalline *N*-*p*-toluenesulfonamide **17** using Rapoport's method[20,21] and a subsequent X-ray crystallographic determination (Scheme 4). The assignment of the configuration of **10** (eq 1) was strengthened by comparison to **13**.

Scheme 4. Transformation of **13** into **17** and Its X-ray Crystal Structure



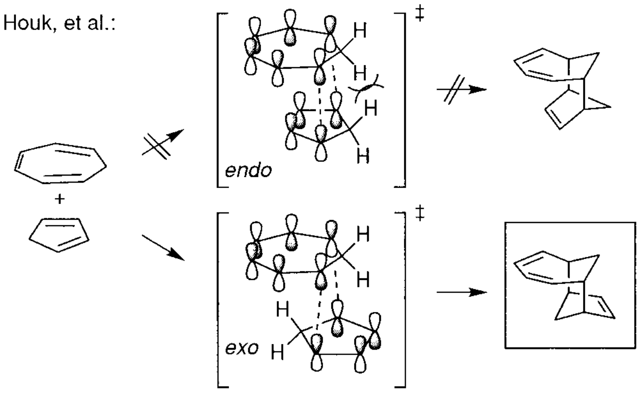
Further evidence for the structure of the minor adduct **15** was gathered upon sulfonylation (Scheme 5). Ring opening of the imidate occurred, producing the crystalline sulfonamide-ester **18**, which was also subjected to X-ray analysis.

Scheme 5. Transformation of **15** into **18** and Its X-ray Crystal Structure



The endo selectivity observed in the formation of **10**, **13**, and **14** is unusual.[22] Hoffmann and Woodward predicted that thermal [π6 + π4] cycloadditions between trienes and dienes would be all-suprafacial and would proceed with exo selectivity, in contrast to endo-selective [π4s + π2s] cycloadditions.[23] Experimental results, e.g., using cycloheptatriene or tropone with cyclopentadiene or cyclopentadienones, verified this prediction.[1a] Rigby has shown that metal-promoted [π6s + π4s] cycloadditions (e.g., chromium complexes of tropones or cycloheptatrienes) may afford good endo selectivity.[2c] The reaction of cycloheptatriene and cyclopentadiene has been studied theoretically by Houk and co-workers and is illustrative of the exo selectivity in thermal [π6s + π4s] cycloadditions.[24] In addition to a small repulsive secondary orbital interaction in the endo transition state, the endo pathway is disfavored by steric interactions between the methylene groups on both partners (Scheme 6). Interestingly, there is a paucity of information on the endo/exo selectivity of the [π6 + π4] cycloadditions of dipoles with trienes.[25]

Scheme 6



To rationalize the stereoselectivity observed in the current work, several factors must be considered (compare **19** to **20**

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(20) O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1992**, *57*, 4775−4777.

(21) For the sulfonylation of nortropanes, see: Kozikowski, A. P.; Saiah, M. K. E.; Bergmann, J. S.; Johnson, K. M. *J. Med. Chem.* **1994**, *37*, 3440−3442.

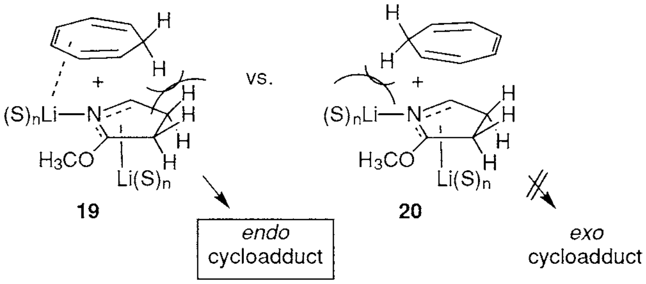
(22) Bower and Howden's work (Scheme 1) is relevant but inconclusive. The formation of **4a** from the sickle form of the anion does not provide information on the endo/exo selectivity issue. The formation of **4b** would seem to indicate that the W-form of the anion reacted with cycloheptatriene via an exo pathway, but the configuration of this cycloadduct is not conclusively assigned. Unfortunately, attempts to prepare a sample of **4b** in our laboratories have failed.

(23) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4388.

(24) Goldstein, E.; Beno, B. R.; Houk, K. N. *Theor. Chem. Acc.* **1999**, *103*, 81−84.

(25) Katritzky (ref 7 above) reports that a 6-arylfulvene reacts with an *N*-aryl-3-oxidopyridinium to produce a mixture of endo and exo isomers of the [π6s + π4s] adducts, but the relevance of this work to the current work is masked by the possibility that these adducts are simply the result of a regioselectivity issue.

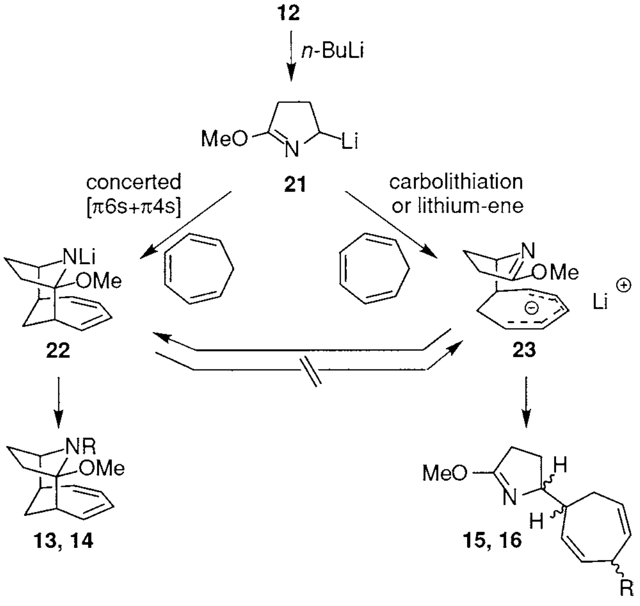
Scheme 7



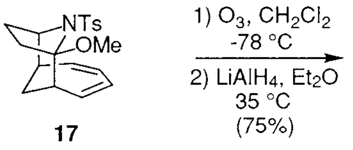
in Scheme 7). First, secondary orbital interactions are likely to be unimportant, since the p-orbital on the nitrogen atom in the HOMO of the 2-azaallyl anion has a very small coefficient. At first glance, one might predict the exo pathway to be preferred for steric reasons, since the methylene group of cycloheptatriene may encounter the ethano portion of the anion, as shown in **19**. However, the presence of the lithium atom (or atoms) and the associated solvent will likely be a dominant influence. It is reasonable to expect that these anions are aggregated species and that, locally, lithium is associated with a π-face of the anion as well as the nitrogen lone pair, as shown.[26] In **19**, a π-complex of lithium ion with the cycloheptatriene may be operational. Further, a steric repulsion between the methylene group of cycloheptatriene and a solvated lithium ion may be influential. Of course, these factors are based on the assumption that such cycloadditions are concerted, which may not be the case.[15,18,26a,b,27,28]

Mechanistically, it is reasonable that the $[\pi 6s + \pi 4s]$ cycloadducts **10**, **13**, and **14** as well as the $[\pi 4s + \pi 2s]$ cycloadduct **11** result from a concerted cycloaddition (e.g., Scheme 8). The adducts **15** and **16** must arise from a stepwise pathway involving an initial carbolithiation[29] or lithium-ene reaction[30] to give the pentadienyllithium **23**. It is possible that **10**, **13**, and **14** arise from the stepwise pathway, i.e., that **23** (or the six-membered ring imidate version) is formed and then undergoes a 9-endo-trig cyclization. It is not likely that **15** and **16** arise from a concerted cycloaddition to **22** followed by ring opening to **23**, since an authentic sample of **22**, prepared from **10**, was found to be kinetically stable. The absence of a $[\pi 4s + \pi 2s]$ cycloadduct in the reaction of **12** with cycloheptatriene is curious, as is the absence of adducts analogous to **15** in the reaction of **9**. Further studies are planned to elucidate the mechanistic details of these processes.

Scheme 8



Finally, we have shown that **17** is a starting point for the further elaboration of our cycloadducts into cocaine-like compounds (eq 2). Ozonolysis of **17** followed by reduction afforded the diol **24**.



(2)

Acknowledgment. Financial support for this research was provided by the National Institutes of Health (GM-52491).

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(27) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329−1345.

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(30) For lithium-ene reactions of allylic organolithiums with alkenes, see the following references and the earlier work cited therein: (a) Dieters, A.; Hoppe, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 546−548. (b) Cheng, D.; Zhu, S.; Liu, X.; Norton, S. H.; Cohen, T. *J. Am. Chem. Soc.* **1999**, *121*, 10241−10242. (c) Cheng, D.; Knox, K. R.; Cohen, T. *J. Am. Chem. Soc.* **2000**, *122*, 412−413.