Available online at www.sciencedirect.com
ScienceDirect

Tetrahedron Letters 48 (2007) 2477–2480

Tetrahedron Letters

Generation and reaction of heteroaromatic zirconocene: synthetic application to polycyclic heterocycles

Yutaka Ikeuchi,[a] Toshiaki Saitoh,[b] Takeo Taguchi[c] and Yuji Hanzawa[b,*]

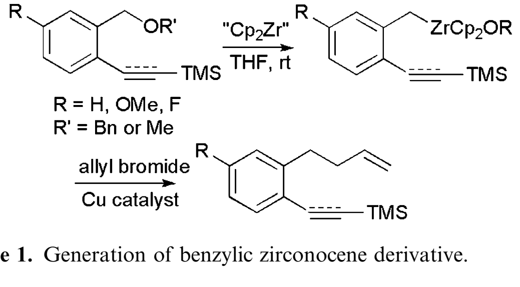
[a] *Sankyo Co., Ltd, Hiratsuka, Kanagawa 254-8560, Japan*
[b] *Showa Pharmaceutical University, 3-3165 Machida, Tokyo 194-8543, Japan*
[c] *Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

Received 23 January 2007; revised 3 February 2007; accepted 8 February 2007
Available online 13 February 2007

Abstract—Heteroaromatic zirconocene intermediates were generated by the reaction of ‘Cp_2Zr’ with alkoxymethyl-(TMS-ethynyl)-indole, -benzofuran or -benzothiophene derivatives under mild conditions in moderate to good yields. Copper-catalyzed C–C bond formation of the zirconocene intermediate with allylic halides gave allylation products, which were transformed into heterocyclic dienes through enyne metathesis. Preliminary Diels–Alder reaction of the dienes with DMAD showed notable site selectivity.

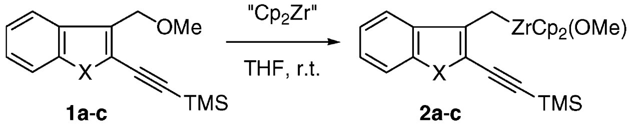
Indole, benzofuran and benzothiophene are important structural motifs that are found in many biologically active molecules. Particularly, indole nucleus is found embedded in natural compounds and/or pharmaceuticals exhibiting a wide range of biological importance.[1] Therefore, the synthesis and/or functionalization of indole molecules received much attention until today.[2]

Recently, we reported that benzylzirconocene intermediates generated from *o*-(alkoxymethyl)styrene or *o*-(alkoxymethyl)phenyl-acetylene derivatives with zirconocene–butene complex (Negishi reagent, ‘Cp_2Zr’)[3] react with allylic halides to give allylation products in good yields (Scheme 1).[4] In this report, we disclose the application of the procedure to alkynyl-indole, -benzofuran or -benzothiophene derivatives and subsequent reactions for the preparation of polycyclic heterocycles.



Scheme 1. Generation of benzylic zirconocene derivative.

The reaction of indole derivative **1a** with 1.2 equiv of ‘Cp_2Zr’ in THF at ambient temperature gave zirconocene intermediate **2a** in a moderate yield (Scheme 2). The yield was not improved either by increasing a quantity of ‘Cp_2Zr’ or by raising the reaction temperature. Similar results were observed by the reaction of benzofuran **1b** or benzothiophene derivatives **1c** with ‘Cp_2Zr’. The formation of intermediates **2a**–**c** was analogously considered as we reported[4] (Scheme 3); (i) the ligand exchange of ‘Cp_2Zr’ with the triple bond of **1a**–**c** giving



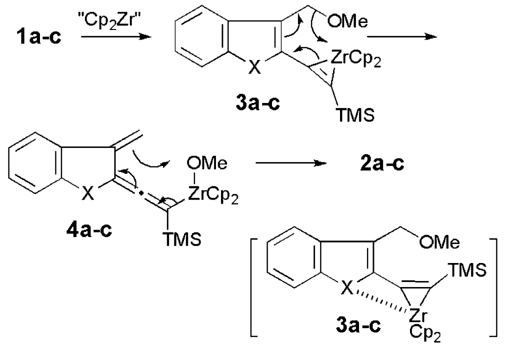
X	Yield%[a]
NMe, **1a**	54 **2a**
O, **1b**	49 **2b**
S, **1c**	42 **2c**

Scheme 2. Reaction of **1** and ‘Cp_2Zr’. All reactions were carried out using ‘CpZr’ (1.2 equiv) in THF at room temperature for 10 h. [a] Isolated yields of 3-methyl derivatives after hydrolytic work-up.

Keywords: Alkynyl indole; Zirconocene–butene complex; Allylation; Enyne metathesis; Diels–Alder reaction.

[*] Corresponding author. Tel./fax: +81 42 721 1569; e-mail: hanzaway@ac.shoyaku.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.02.038



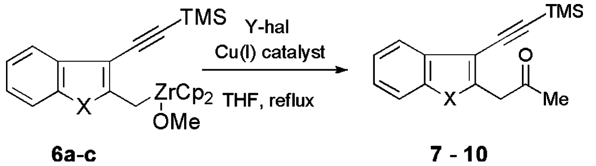
Scheme 3. Generation of **2**.

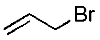
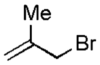
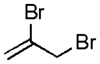
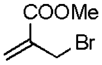
zirconacyclopropene intermediates **3a–c**, (ii) the formation of intermediates **4a–c** by the elimination of the alkoxy group, and (iii) the transfer of Cp_2Zr moiety to afford zirconocene intermediates **2a–c**.

While the generation of **2** from **1** was insufficient, the reaction of regio-isomers **5a–c** with 'Cp_2Zr' gave zirconocene intermediates **6a–c** in good yields (Scheme 4). The poorer reactivities of **1a–c** than that of **5** might be the result of the intervention of the extra coordination of ring heteroatom X to the zirconium atom in the initial intermediate **3** as shown in Scheme 3.

Carbon–carbon bond forming reaction of **6** turns out to be efficient under copper-catalyzed conditions, and thus the acylation and allylation (Table 1)[4b–d] of **6a–c** are carried out. Although the acylation of **6** was sluggish and the reaction mixture was contaminated by prolonged reaction time,[5] ketone derivatives **7a–c** were obtained in moderate yields (entries 1, 6 and 8).[6] Allylic halides react with **6a–c** to give allylation products **8–10** as well. Although indole derivative **6a** gave allylation products **8a–d** in good yields (entries 2–5), the reaction of **6b** or **6c** with allyl bromide under identical conditions turned out to give corresponding allylation products **9**, **10** in lower yields (entries 7 and 9).

Table 1. Allylation of **6**[a]



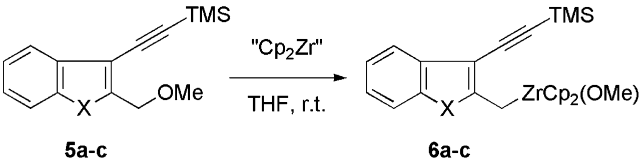
Entry	6	Y-hal	Cu[a]	7–10	Yield[b] (%)
1	**6a**	CH_3COCl	$CuBr/SMe_2$	**7a**	54
2			CuCl	**8a**	83
3				**8b**	72
4				**8c**	73
5				**8d**	85
6	**6b**	CH_3COCl	$CuBr/SMe_2$	**7b**	49
7			CuCl	**9**	37
8	**6c**	CH_3COCl	$CuBr/SMe_2$	**7c**	42
9			CuCl	**10**	60

[a] All reactions were carried out using Y-hal (3.0 equiv), Cu catalyst (0.3 equiv) in THF at reflux temperature for 10–12 h.

[b] Isolated yields.

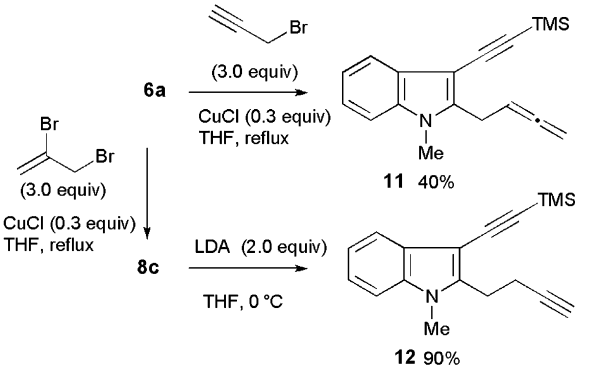
The reaction of **6a** with propargyl bromide gave an allene derivative **11** as sole product. Diyne compound **12**, which is expected to be a useful compound for the construction of polycyclic indole derivatives, was obtained by the treatment of vinyl bromide **8c** with 2 equiv of LDA in a good yield (Scheme 5).

Thus, as an overall process, it is possible for us to substitute the C-2 alkoxy function of **5a** with allyl, propargyl or allenyl unit through the present 'Cp_2Zr' chemistry. In order to examine the utility of the present 'Cp_2Zr'-mediated reaction and the subsequent Cu(I)-catalyzed carbon–carbon bond formation for the construction of biologically attractive molecules, we examined preliminary reactions of **8a**, **9**, **10** to obtain polycyclic heterocyclic compounds.[7] Thus, the reaction[8]

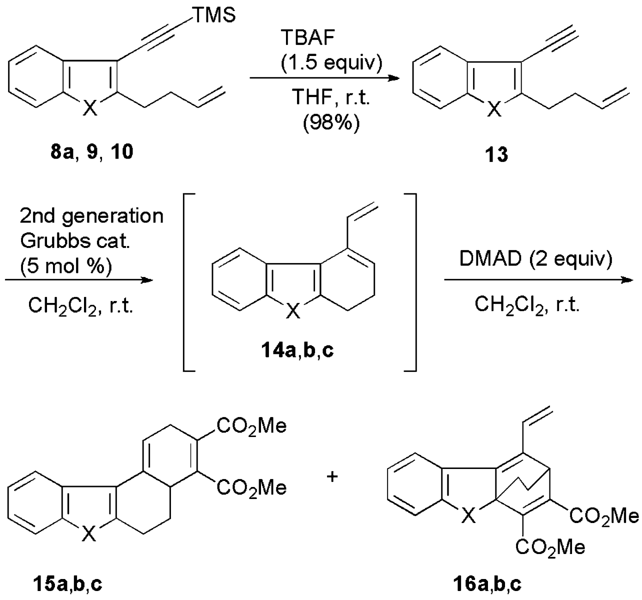


X	Yield%[a]
NMe, **5a**	92 **6a**
O, **5b**	80 **6b**
S, **5c**	75 **6c**

Scheme 4. Reaction of **5** and 'Cp_2Zr': All reactions were carried out using 'CpZr' (1.2 equiv) in THF at room temperature for 10 h. [a] Isolated yields of 3-methyl derivatives after hydrolytic work-up.



Scheme 5. Formation of allenyl and propargyl derivatives from **6a**.



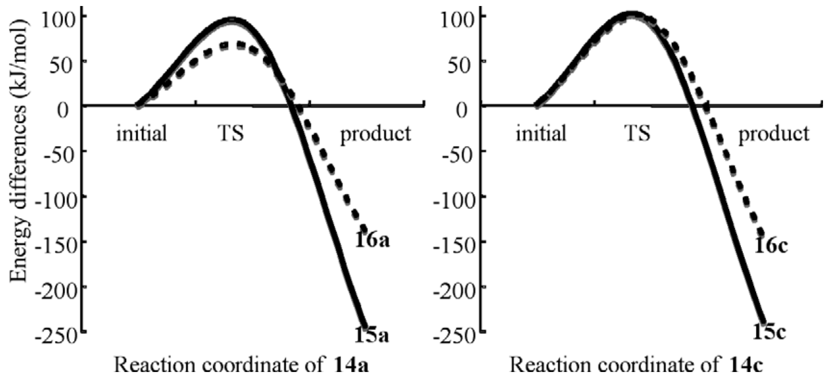
	Yield	**15/16** Ratio
15a : **16a** (X = NMe)	66%	1 : 24
15b : **16b** (X = O)	30%	3 : 1
15c : **16c** (X = S)	65%	1 : 0

Scheme 6. Enyne metathesis and subsequent Diels–Alder reaction.

of allylation product **8a** through intramolecular enyne metathesis[9] using second generation of Grubbs catalyst[10] (ambient temperature for 15 h) gave unstable diene **14a** in a good yield judged by crude ^{1}H NMR spectrum, and **14a** was used directly for the following reaction. Thus, the Diels–Alder reaction of **14a** with dimethyl acetylenedicarboxylate (DMAD) in CH_2Cl_2 at ambient temperature for 10 h gave compound **16a** as a major product (**15a**/**16a** = 1/24) (Scheme 6).[11,12]

Other allylation products **9**, **10** were also converted to diene derivatives **14b**,**c** as in the same procedure described for **14a**, and the Diels–Alder reaction was examined as well. The Diels–Alder reactions of **14** did not show notable solvent effect in yields, the ratio of **15**/**16** and reaction rate (monitored by reverse phase HPLC) by the use of polar solvent such as, MeOH/DMF (10/1).[13] However, it is interesting to note that the ratio of **15**/**16** is heavily dependent on the heteroatom X of **14**. Thus, indole compound **14a** showed a preferable formation of **16a** over **15a** (24/1), and benzothiophene derivatives **14c**, in contrast, gave **15c** as the sole product (Scheme 6). The ratio of **15**/**16** was unaffected by the reaction period (1 or 96 h) at ambient temperature or by the heating of the reaction mixture to reflux in THF. Although we have to await a further study to gain a clear explanation about the notable site selectivity of the reactions of **14** with DMAD, the effect of the atomic orbital coefficiency of the diene HOMO orbital of **14** due to the each heteroatoms X in **14a**,**b** and **14c** might be responsible for the site selectivity. In order to obtain rationalization about the site selectivity in the Diels–Alder reactions of **14** with DMAD, density functional theory (DFT) calculations for the transition state were carried out by employment of B3LYP/6-31G(d) level of theory.[14] Energy profiles for the Diels–Alder reactions of **14a** and **14c** are shown in Figure 1. The reaction coordinate for the Diels–Alder reactions of **14a** and DMAD indicates that **16a** is a kinetic product, and **15a** is a thermodynamic product (E_{act}**15a** = 84.8 kJ/mol, E_{act}**16a** = 62.9 kJ/mol; ΔH**15a** = −246.7 kJ/mol, ΔH**16a** = −140.3 kJ/mol). However, the same calculation for the formations of **15c** and **16c** from **14c** showed very little difference between the activation energies (E_{act}**15c** = 92.2 kJ/mol, E_{act}**16c** = 95.4 kJ/mol; ΔH**15c** = −240.5 kJ/mol, ΔH**16c** = −146.6 kJ/mol). Thus, it is considered to be reasonable that the sole formation of **15c** from **14c** was observed under the present reaction conditions. These theoretical studies would support the preferential formations of **16a** and **15c**, respectively.

In conclusion, we demonstrated that the generation of heteroaromatic zirconocene intermediates and their acylation and allylation under copper catalyzed conditions. The allylation products were converted to polycyclic heteroaromatic compounds through enyne metathesis and subsequent site selective Diels–Alder reaction of the formed diene intermediate. Mechanistic details for the peculiar site selectivity of the diene intermediates with dienophile would be reported in due course.



Reaction coordinate of **14a** Reaction coordinate of **14c**

Figure 1. Energy profiles for the Diels–Alder reactions of **14a** and **14c**.

Acknowledgement

The authors thank Sankyo Co., Ltd, for financial support.

References and notes

1. (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Servien, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 207–258; (b) Sundberg, R. J. Indoles; Academic: San Diego, 1996; (c) McKay, M. J.; Carroll, A. R.; Quinn, R. J.; Hooper, J. N. A. *J. Nat. Prod.* **2002**, *65*, 595; (d) Verpoorte, R. *Alkaloids* **1998**, 397; (e) Sundberg, R. J. *Prog. Heterocycl. Chem.* **1989**, *1*, 111; (f) Saxon, J. E. *Nat. Prod. Rep.* **1986**, *3*, 357; (g) Sundberg, R. J. Indoles. *Best Synthetic Methods*; Academic Press: San Diego, 1996; (h) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
2. For recent references, see: (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037; (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652; (c) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689; (d) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546; (e) Kamijo, S.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 4764; (f) Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2002**, *43*, 7135; (g) Rodriguez, A. L.; Koradin, D.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488; (h) Pete, B.; Toke, L. *Tetrahedron Lett.* **2001**, *42*, 3373; (i) Yasuhara, A.; Takeda, Y.; Suzuki, N.; Sakamoto, T. *Chem. Pharm. Bull.* **2002**, *50*, 235; (j) Rossiter, S. *Tetrahedron Lett.* **2002**, *43*, 4671; (k) Zhou, T.; Chen, Z. C. *Synth. Commun.* **2002**, *32*, 903.
3. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
4. (a) Hanzawa, Y.; Ikeuchi, Y.; Nakamura, T.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 6503; (b) Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2004**, *45*, 3717; (c) Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2004**, *45*, 4495; (d) Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *J. Org. Chem.* **2005**, *70*, 756; Recently, preparation of a steroid framework has been reported through our benzylzirconocene chemistry. Herrmann, P.; Kotora, M.; Budesinsky, M.; Saman, D.; Cisarova, I. *Org. Lett.* **2006**, *8*, 1315.
5. Due to the considerable contamination of the reaction mixture, the reaction was terminated after being heated at reflux temperature for 10 h.
6. Similar observation has been made in the reaction of 'Cp$_2$Zr' with (*o*-MeO-phenyl)acetylene derivative.
7. As examples of the synthesis of polycyclic indole compounds, indolosteroid and/or indolocholestane derivatives have been reported. Indolosteroid, see: Sladkov, V. I.; Shner, V. F.; Alekseeva, L. M.; Turchin, K. F.; Anisimova, O. S. *Doklady Akademii nauk SSSR* **1971**, *198*, 605; Indolocholestane, see: Harvey, D. J.; Reid, S. T. *Tetrahedron* **1972**, *28*, 2489.
8. Pauson–Khand reaction of 2-butenyl-3-ethynyl-1-methyl-1*H*-indole derivative was reported: Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* **2004**, *69*, 5413.
9. For recent reviews on enyne metathesis, see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317; (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1; (c) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133; (d) For reviews on olefin metathesis, see: *Olefins metathesis; a powerful and versatile instrument for organic synthesis* Martin, S. F.; Wasserman, H. H., Eds., Symposia-in-Print, *Tetrahedron* 2004, Vol. 60, 7099; (e) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592; (f) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900; (g) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013; For recent examples on intramolecular enyne metathesis, see: (h) Hansen, E. C.; Lee, D. *Org. Lett.* **2004**, *6*, 2035; (i) Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1329; (j) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2003**, *125*, 9582; (k) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161; (l) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543.
10. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
11. Recently, tandem enyne metathesis/Diels–Alder reactions for the construction of natural product framework were reported: Rosillo, M.; Domínguez, G.; Casarrubios, L.; Amador, U.; Pérez-Castells, J. *J. Org. Chem.* **2004**, *69*, 2084.
12. Diels–Alder reactions of vinyl indole derivatives, see: (a) Zhang, Y. *Tetrahedron* **2006**, *62*, 3917; (b) Le Strat, F.; Maddaluno, J. *Org. Lett.* **2002**, *4*, 2791; (c) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 7586; (d) Gonzalez, E.; Pindur, U.; Schollmeyer, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1767; (e) Noland, W. E.; Xia, G.-M.; Kyle, R.; Konkel, M. J.; Wahlstrom, M. J.; Condoluci, J. J.; Rieger, D. L. *Tetrahedron* **1996**, *52*, 4555; (f) Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1996**, *52*, 3029.
13. Although no solvent effect has been observed, we cannot rigorously rule out the possibility of the intervention of an ionic process leading to **16a**.
14. We used GAUSSIAN 03 and GaussView for the DFT calculations. All DFT calculations were performed at the computer centre of Showa Pharmaceutical University: (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. GAUSSIAN *03, Revision C.02*; Gaussian: Wallingford, CT, 2004; (b) Dennington, Roy, II.; Keith, Todd; Millam, John; Eppinnett, Ken; Lee, Hovell W.; Gilliland, Ray *GaussView, Version 3.09*; Semichem: Shawnee Mission, KS, 2003.