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Citation	Tetrahedron Letters, 2005, v. 46 n. 15, p. 2709-2712
Issued Date	2005
URL	http://hdl.handle.net/10722/48525
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Tetrahedron Letters
Tetrahedron Letters xxx (2005) xxx–xxx

Metal-catalyzed cyclopropanation on the 8-oxabicyclo-[3.2.1]oct-6-ene template

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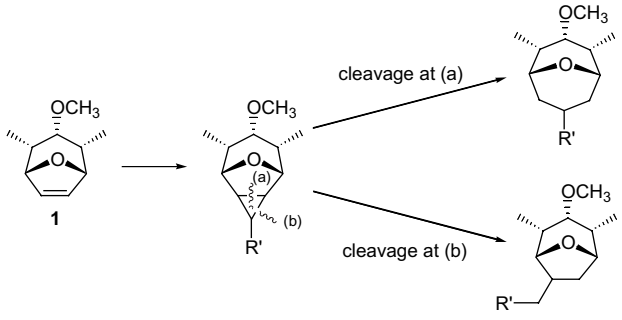
Received 19 November 2004; revised 19 January 2005; accepted 21 January 2005

Abstract—Cyclopropanations of an 8-oxabicyclo[3.2.1]octene substrate using diazocarbonyl compounds provided *exo*, *exo*-cyclopropanated products as the sole or major diastereomeric oxatricyclic products. Reductive cleavage of a *meso*-oxatricyclic ketone by samarium iodide resulted in desymmetrization without concomitant oxygen bridge cleavage.

Oxabicyclic compounds are useful substrates with tremendous synthetic potential for the preparation of functionalized carbocycles and arrays.[1] Selective synthetic elaborations occur with high and predictable stereoselectivity on the basis of the steric bias provided by the rigid template of the oxabicyclic framework.[2] Subsequent ring cleavage provide access to stereochemically-defined cyclic and acyclic compounds.

Among various synthetic transformations, the cyclopropanation reaction, in particular, via the well-established transition metal-catalyzed decomposition of diazocarbonyl compounds, which has seen wide utilization and applications in organic synthesis, has not been examined in the context of oxabicyclic alkenes.[3] Reaction of diazoalkanes with oxabicycloheptenes have yielded intermediate pyrazolines, which have been transformed into cyclopropanated products via photolysis.[4] Dichlorocarbenes and chromium carbenes in the presence of 7-oxabicyclo[2.2.1]heptene templates have resulted in the cyclopropanation of these systems.[5] Other than these examples, few other instances of cyclopropanation of oxabicyclic frameworks have appeared in the literature.[6,7] In particular, there have been no reports on the cyclopropanation of 8-oxabicyclo[3.2.1]octenes.

Other than the apparent lack of data concerning the cyclopropanation of oxabicyclooctenes, we were also interested to examine this reaction because the resultant strained cyclopropanated products could provide interesting synthetic intermediates via a subsequent ring cleavage (Scheme 1). The cyclopropane moiety could conceivably undergo fragmentation in two ways. The scission of bond (a) in this system would result in a ring-enlargement to give an eight-membered ring and would constitute a synthesis for functionalized medium-sized carbocycles. The cleavage of bond (b) would result in a desymmetrization of the *meso*-oxatricyclic molecules. To this end, cyclopropanation reactions, which install functionality at R′ could be particularly useful for inducing subsequent ring opening (Scheme 1). Moreover, in the context of the oxabicyclic system, concomitant oxygen cleavage is also conceivable. Herein we report the preliminary results in the metal-catalyzed cyclopropanation of oxabicyclic template **1** by diazocarbonyl compounds, and the manner by which these functionalized cyclopropanated products undergo ring opening.



Scheme 1. Ring cleavage of cyclopropanated oxabicyclic compounds.

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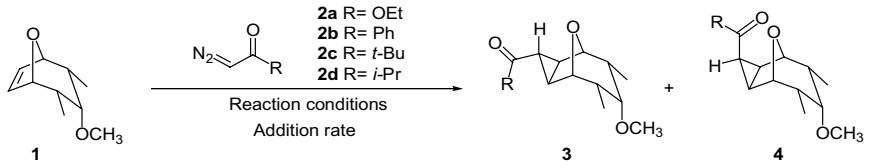
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.01.182

Table 1. Cyclopropanation of **1**



Entry	Diazo compounds **2** (equiv)	Reaction conditions[a]	Concentration of **1** [M]	Addition rate of **2** (equiv/min)	Yield of cyclopropanation %		Recovered **1** (%)
					3	**4**	
1	**2a** (2.5)	A	0.30	0.016	42	12	18
2	**2a** (2.5)	B	0.29	0.010	63	17	—
3	**2a** (2.5)	A	1.54	0.021	70	15	—
4	**2a** (5)	C	0.16	0.20	66	3	—
5	**2b** (4)	A	0.70	0.007	40	—	42
6	**2b** (6)	A	0.11	0.20	68	—	—
7	**2b** (4)	C	0.03	0.016	—	—	72
8	**2c** (2)	A	0.19	0.003	31	—	47
9[c]	**2c** (4)	A	0.26	0.007	68	—	—
10	**2c** (4)	C	0.20	0.20	52	—	—
11	**2d** (4)	A	0.19	0.007	16	—	57
12	**2d** (7)	A	0.19	0.10	35	—	45
13	**2d** (6)	C	0.20	0.062	10	—	44

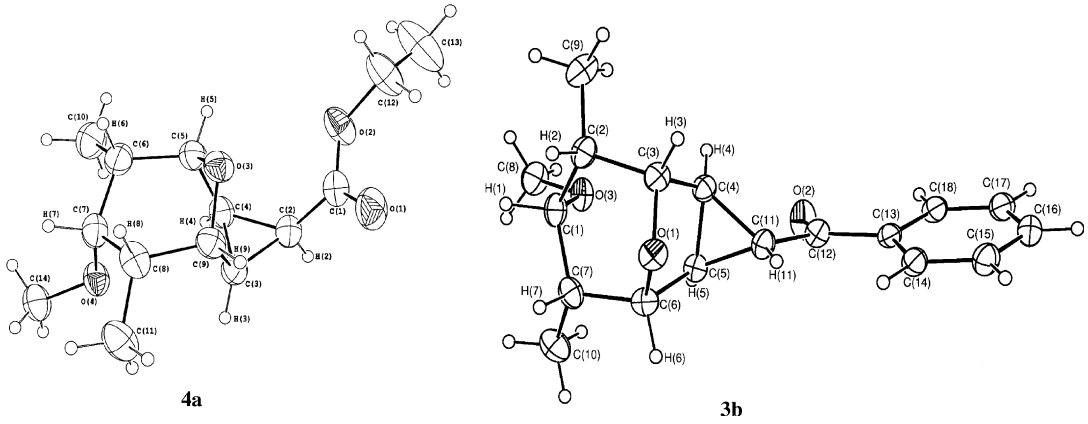
[a] Reaction conditions A: cat. $Rh_2(OAc)_4$,CH_2Cl_2, room temperature; conditions B: cat. $Rh_2(OAc)_4$, CH_2Cl_2, reflux; conditions C: cat. $Cu(acac)_2$, PhH, reflux.

With **1** as the limiting reagent, cyclopropanations by metal carbenes generated from diazocarbonyl compounds **2a–d** and transition metals were examined (Table 1). A very slow addition of the diazocarbonyl compound was imperative to facilitate the cyclopropanation reaction and discourage carbene dimerization.[8] Controlling the rate of addition of **2a** by a syringe pump, the cyclopropanation of **1** in the presence of catalytic $Rh_2(OAc)_4$ occurred in 54% yield, with unreacted **1** being recovered (Table 1, entry 1). The reaction conditions were examined to optimize the yield of cyclopropanation. It was found that the substrate could be fully consumed either by reaction under reflux (Table 1, entry 2), or at room temperature starting with **1** at a higher initial concentration, whereupon an 85% yield was achieved in the cyclopropanation (Table 1, entry 3).[9] Using the less reactive $Cu(acac)_2$ catalyst, cyclopropanation proceeded at an acceptable rate at the temperature of refluxing benzene (Table 1, entry 4).

We expected that cyclopropanation on the rigid template provided by **1** would proceed with high diastereofacial selectivity, as observed in other reactions on similar substrates.[2] In the event, two cyclopropanated products **3a** and **4a** were isolated from the reaction.[10] The major isomer **3a** was an *exo* cyclopropane resulting from carbene attack syn with respect to the oxygen bridge, which is expected due to the facial bias of the oxabicyclic template. The sterically more demanding carboethoxy group was *exo* with respect to the substrate framework and thus avoided interaction with the oxygen bridge. The coupling constant of the cyclopropane protons in the ^1H NMR spectrum of **3a** was 3.2 Hz, within the expected range for trans vicinal protons.[11] The data conformed very well to other compounds having the same relative stereochemistry (vide infra). The minor diastereomer **4a** was also an *exo* cyclopropane from reaction on the same face of the olefin; however, the carboethoxy group was *endo* with respect to the oxygen bridge. With the carboethoxy group proximate to the substrate framework, the cyclopropane protons of isomer **4a** showed coupling constants of 7.2–7.7 Hz, in the range expected for cis vicinal protons. The structure of **4a** was unambiguously determined by X-ray crystallographic analysis (Scheme 2).[12] The lowest energy conformation of isomer **4a** was calculated to be 5.276 kcal/mol less stable than that of **3a**. The formation of this more congested and less stable cyclopropane could be attributed to the high reactivity of the metal carbene, which initiates bond formation at distances relatively removed from the oxabicyclic alkene, resulting in a diminished sensitivity to the steric demands of the substrate.[13]

The cyclopropanation of **1** was further examined using diazoketones **2b–d**. Intermolecular cyclopropanation reactions with diazoketones as carbene precursors would afford cyclopropyl ketones, but these reactions are much less studied than those of diazoesters.[14] In fact, cyclopropanations using **3c** or **d** as carbene precursors have never been described.

Compared with the reaction using **2a**, larger excesses of the diazoketones were required to give satisfactory yields of cyclopropanated products, and the reactions were not clear (Table 1, entries 5–13). Cyclopropanation yielded **3b–d** as the sole diastereomeric products. Presumably, the approach of the metal carbene with the R group *endo* to the substrate has become a much less favourable trajectory with the increased steric demands of the R groups of **2b–d** over the ethoxy group of **2a**; thus the analogous cyclopropane isomers **4b–d** were not generated. The structure of **3b** was unambiguously determined by X-ray crystallography.[12,15] This served to affirm the structure of **3a** as well as other

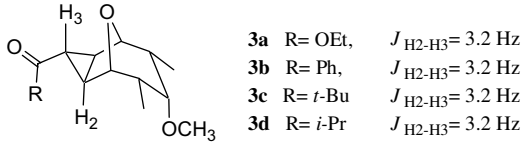


Scheme 2. ORTEP diagrams of **4a** and **3b**.

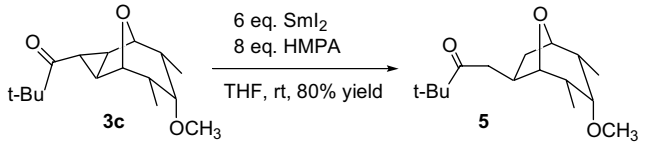
cyclopropanated compounds having the same relative stereochemistry. Due to the extremely rigid oxatricyclic framework, the values of J_{H2-H3} for the series of compounds **3a**–**d** were found to be exactly 3.2 Hz regardless of the identity of R (Scheme 3). However, cyclopropanation of **1** using ethyl diazoacetoacetate failed under all reaction conditions tried.

The cyclopropanation of **1** by diazocarbonyl compounds resulted in oxatricyclic compounds as products, in which the cyclopropane ring is functionalized and inherently strained. Attempted cleavage of the cyclopropanated oxabicyclic compounds **3a**–**d** using Bu_3SnH/AIBN uniformly failed. Treatment with SmI_2/HMPA also failed to effect reaction of cyclopropyl ester **3a**, but was successful in inducing the reductive cleavage of the more reactive cyclopropyl ketone **3c** to afford desymmetrized oxabicyclic compound **5** in 80% yield (Scheme 4). No concomitant cleavage of the oxygen bridge was observed.

Herein we have demonstrated the first metal-catalyzed cyclopropanations by diazocarbonyl compounds on the functionalized 8-oxabicyclo[3.2.1]oct-6-ene template of **1**. Both diazoketones or diazoesters as carbene precursors yielded *exo*, *exo*-cyclopropanated products **3a**–**d** as the sole or major diastereomeric products, although an *exo*, *endo*-cyclopropanated product **4a** was a minor product in the reaction of **2a** with **1**.



Scheme 3. Coupling constants of **3a**–**d**.



Scheme 4. Desymmetrization of **3c** by SmI_2.

Acknowledgements

The authors thank Dr. N. Zhu of the Department of Chemistry at the University of Hong Kong for the crystallographic analyses. Miss L. Hu and Dr. G. H. Chen of the Department of Chemistry at The University of Hong Kong are thanked for performing the computations. The work described in this paper was supported by The University of Hong Kong, and by a grant from The Research Grants Council of Hong Kong SAR, SAR PR China (Project No. HKU 7103/00P). SKL thanks the University of Hong Kong for a conference grant.

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7. (a) Cyclopropanated oxabicyclo[2.2.1] compounds have been obtained from Diels–Alder reactions between cyclopropenes and furan derivatives. Examples: (a) La

Rochelle, R.; Trost, B. M. *J. Chem. Soc. Chem. Commun.* **1970**, 135; (b) Martin, H. D.; Kaudy, L.; Stusche, D. *Tetrahedron Lett.* **1977**, *40*, 3561; (c) Pitt, I. G.; Rusell, R. A.; Warrener, R. N. *J. Am. Chem. Soc.* **1985**, *107*, 7176; (d) Rendall, W. A.; Torres, M.; Strausz, O. P. *J. Org. Chem.* **1985**, *50*, 3034; (e) Binder, P.; Wedemann, P.; Goddard, R.; Brinker, U. H. *J. Org. Chem.* **1996**, *61*, 6462; (f) Leivers, M.; Tam, I.; Groves, K.; Leung, D.; Xie, Y.; Breslow, R. *Org. Lett.* **2003**, *5*, 3407.

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9. *Representative procedure for cyclopropanation:* to a solution of $Rh_2(OAc)_4$ (17.1 mg, 0.039 mmol) and **1** (67.1 mg, 0.399 mmol) in 0.2 mL CH_2Cl_2 was added **2a** (0.10 mL, 0.998 mmol) in 1.3 mL CH_2Cl_2 by syringe pump over 2 h at room temperature. After stirring for 1 h, the reaction mixture was filtered and concentrated in vacuo. Flash chromatography of the residue (0–20% EtOAc/hexane) gave **3a** (70.9 mg, 70%) and **4a** (15.2 mg, 15%).
10. Compound **3a:** a colourless oil; R_f (30% EtOAc/hexane): 0.55; IR (CH_2Cl_2): 2980, 2965, 2935, 2877, 1716, 1254, 1093, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$); δ 4.11 (2H, q, J = 7.1 Hz), 3.81 (2H, d, J = 3.2 Hz), 3.35 (3H, s), 3.10 (1H, t, J = 4.2 Hz), 2.05 (2H, d, J = 3.2 Hz), 2.03 (2H, m), 1.70 (1H, t, J = 3.2 Hz), 1.26 (3H, t, J = 7.1 Hz), 0.99 (6H, d, J = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 81.7, 77.7, 62.3, 60.4, 39.5, 26.2, 22.0, 14.3, 12.2 ppm; LRMS (20 eV): m/z 254 [M^+, 70], 209 (14), 185 (100), 181 (22), 126 (15), 111 (13); EI-HRMS: calcd for $C_{14}H_{22}O_4$ [M^+]: 254.1518. Found: 254.1518. **4a:** white crystals; mp 76 °C, R_f (20% EtOAc/hexane): 0.45; IR (CH_2Cl_2): 2979, 2937, 2903, 2878, 2832, 1720, 1222, 1211, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.08 (2H, q, J = 7.2 Hz), 3.91 (2H, d, J = 3.3 Hz), 3.34 (3H, s), 3.11 (1H, t, J = 4.1 Hz), 2.04 (2H, m), 1.75 (2H, d, J = 6.9 Hz), 1.69 (1H, t, J = 8.3 Hz), 1.24 (3H, t, J = 7.2 Hz), 1.01 (6H, d, J = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 81.9, 76.5, 62.3, 60.4, 39.1, 22.1, 20.1, 14.2 12.3 pm; LRMS (20 eV): m/z 254 [M^+, 22], 209 (10), 185 (100), 157 (28), 125 (15), 111 (5); EI-HRMS: calcd for $C_{14}H_{22}O_4$ [M^+]: 254.1518. Found: 254.1516.
11. Typical vicinal proton coupling constants for cyclopropanes are J = 3–5 Hz (*trans*) and J = 4–9 Hz (*cis*): Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.
12. Crystal data for **4a** and **3b** have been deposited in the Cambridge Crystallographic Data Center, as CCDC 259525 and 259526, respectively.
13. (a) *endo* Products are also observed in the metal-catalyzed cyclopropanation of norbornene using **2a**: Salomon, R. G.; Salomon, M. F.; Kachinski, J. L. C. *J. Am. Chem. Soc.* **1977**, *99*, 1043; (b) Doyle, M. P.; Loh, K. L.; DeVries, K. M.; Chinn, M. S. *Tetrahedron Lett.* **1987**, *28*, 833.
14. (a) There are far fewer examples of cyclopropanations using diazoketones compared to diazoesters, see Refs. 3d,e. The majority of such cyclopropanations are in the context of electron-rich alkenes such as vinyl ethers, rather than simple alkenes. Exceptions: (a) Tsuge, O.; Kanemasa, S.; Suzuki, T.; Matsuda, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2851; (b) House, H. O.; Fischer, W. F.; Gall, M.; McLaughlin, T. E.; Peet, N. P. *J. Org. Chem.* **1971**, *36*, 3429; (c) Smeets, F. L. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1980**, *36*, 3269; (d) Gefflaut, T.; Perie, J. *Synth. Commun.* **1994**, *24*, 29.
15. Compound **3b**: yellow crystals; mp 82–84 °C; R_f (20% EtOAc/hexane): 0.39; IR (CH_2Cl_2): 3070, 2981, 2963, 2936, 2900, 2879, 2832, 1665, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.3 Hz, 2H), 7.52 (m, 1H), 7.45 (m, 2H), 3.90 (d, J = 3.3 Hz, 2H), 3.36 (s, 3H), 3.12 (t, J = 4.1 Hz, 1H), 2.77 (t, J = 3.2 Hz, 1H), 2.29 (d, J = 3.2 Hz, 2H), 2.09–2.07 (m, 2H), 1.01 (d, J = 7.3 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 137.9, 132.7, 128.4, 128.1, 81.6, 78.0, 62.3, 39.6, 29.4, 26.4, 12.2 ppm; LRMS (20 eV): 286 [M^+, 59], 254 (26), 186 (17), 157 (100), 105 (58); EI-HRMS: calcd for $C_{18}H_{22}O_3$ [M^+]: 286.1563. Found: 286.1569.