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# Selective Access to Trisubstituted Macrocyclic *E*- and *Z*-Alkenes from the Ring-Closing Metathesis of Vinylsiloxanes

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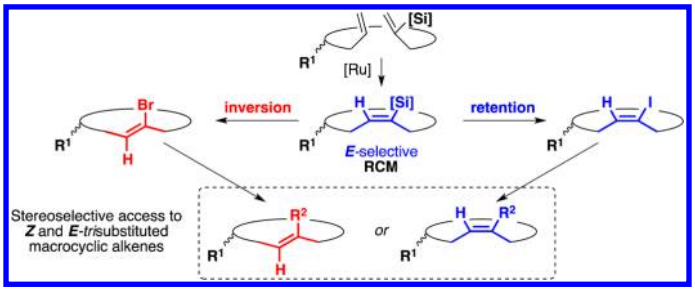
## ABSTRACT




**Macrocyclic (*E*)-alkenylsiloxanes, obtained from *E*-selective ring-closing metathesis reactions, can be converted to the corresponding (*Z*)-alkenyl bromides and (*E*)-alkenyl iodides allowing access to both *E*- and *Z*-trisubstituted macrocyclic alkenes. The reaction conditions and substrate scope of these stereoselective transformations are explored.**

Ring-closing metathesis (RCM) is a powerful transformation that can be used to construct macrocyclic molecules. It has been extensively applied in the total synthesis of natural products,[1] diversity-oriented synthesis,[2] and medicinal chemistry.[3] However, further elaboration of the resulting macrocyclic alkene is usually limited to symmetrical reactions (e.g., hydrogenation) that avoid issues related to regioselectivity. Additionally, due to the flexibility of macrocycles, RCM frequently results in mixtures of *Z*/*E* alkene isomers that may be undesirable or difficult to separate.[1b,4] Finally, in contrast to disubstituted macrocycles, the use of RCM to access trisubstituted variants with control of olefin geometry has not been rigorously explored.[4b,5]

Recently, several groups have made progress in achieving selective olefin geometry in macrocyclic RCM through catalyst control.[6] Nevertheless, these catalyst-controlled approaches are limited to generating *di*substituted alkene products with *Z* geometry. Moreover, the problem of

(1) (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (b) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. (c) Hassan, H. M. A. *Chem. Commun.* **2010**, *46*, 9100. (d) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.

(2) (a) Peng, L. F.; Stanton, B. Z.; Maloof, N.; Wang, X.; Schreiber, S. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6319. (b) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D.; Liu, H. B.; Lowe, J. T.; Marie, J. C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B. C.; Wei, J. Q.; Young, D. W.; Akella, L. B.; Ross, N. T.; Zhang, Y. L.; Fass, D. M.; Reis, S. A.; Zhao, W. N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962. (c) Dandapani, S.; Lowe, J. T.; Comer, E.; Marcaurelle, L. A. *J. Org. Chem.* **2011**, *76*, 8042.

(3) (a) Tsantrizos, Y. S.; Ferland, J.-M.; McClory, A.; Poirier, M.; Farina, V.; Yee, N. K.; Wang, X.-j.; Haddad, N.; Wei, X.; Xu, J.; Zhang, L. *J. Organomet. Chem.* **2006**, *691*, 5163. (b) Abell, A. D.; Jones, M. A.; Coxon, J. M.; Morton, J. D.; Aitken, S. G.; McNabb, S. B.; Lee, H. Y. Y.; Mehrtens, J. M.; Alexander, N. A.; Stuart, B. G.; Neffe, A. T.; Bickerstaffe, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1455. (c) Huber, T.; Manzenrieder, F.; Kuttruff, C. A.; Dorner-Ciossek, C.; Kessler, H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4427.

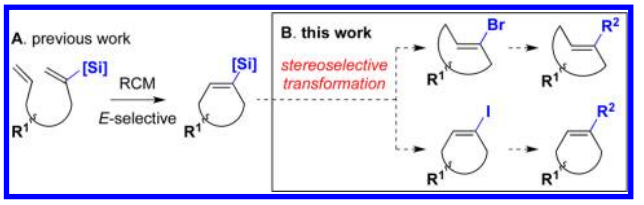
(4) (a) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826. (b) Rivkin, A.; Cho, Y. S.; Gabarda, A. E.; Yoshimura, F.; Danishefsky, S. J. *J. Nat. Prod.* **2004**, *67*, 139.

(5) Macrocyclic RCM reactions to access trisubstituted alkenes were largely limited to alkyl (Me or Et) substituted products with unpredictable stereoselectivity. See: (a) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449. (b) Jin, J.; Chen, Y. L.; Li, Y. N.; Wu, J. L.; Dai, W. M. *Org. Lett.* **2007**, *9*, 2585. (c) Llàcer, E.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2009**, *11*, 3198. (d) May, S. A.; Grieco, P. A. *Chem. Commun.* **1998**, 1597. (e) Sengoku, T.; Uemura, D.; Arimoto, H. *Chem. Lett.* **2007**, *36*, 726. (f) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292. (g) Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926.

10.1021/ol400134d 

further transformation of the alkene in RCM products remains unresolved. There is a need for a comprehensive methodology that overcomes these limitations of macrocyclic RCM, allowing access to both geometric isomers of the more demanding trisubstituted macrocyclic alkenes.[7]

**Scheme 1.** General Concept

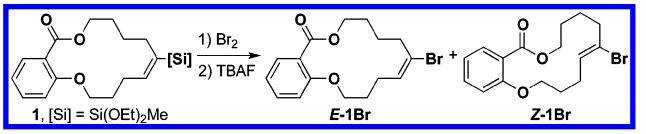



To address these issues, we focused on the introduction of a removable 2-silyl substituent to one of the olefin partners. We have shown previously that the RCM of these vinylsiloxane substrates yields macrocyclic compounds with high *E* selectivity, resulting in *Z*-disubstituted alkenes after protodesilylation[8] (Scheme 1A). Herein, we report a strategy to selectively achieve both geometrical isomers of trisubstituted macrocyclic alkenes from the common (*E*)-alkenylsiloxane intermediate.

Noting early studies on the halogenation of acyclic alkenylsilanes,[9] we envisioned that macrocyclic (*E*)-alkenylsiloxanes could be transformed to the corresponding alkenyl halides with either inversion or retention of stereochemistry (Scheme 1B). Additionally, the resulting alkenyl halides would serve as versatile synthetic intermediates allowing access to trisubstituted alkenes. We first explored conditions that yielded stereochemical inversion of the starting (*E*)-alkenylsiloxanes.

Mild halogenating reagents such as pyridinium tribromide and phenyltrimethylammonium tribromide were examined with substrate **1**.[10] Neither of these reagents led to complete consumption of starting material, and decomposition was also observed. Fortunately, treatment of substrate **1** in DCM at −78 °C with dropwise addition of bromine solution gave complete consumption of starting material and formation of a dibromide intermediate along with a small amount of alkenyl bromide product by LC-MS analysis. It was observed that the dibromide intermediate was converting to the alkenyl bromide on silica gel when conducting TLC analysis. Instead of isolating the intermediate, a two-step one-pot procedure was adopted. Accordingly, TBAF was chosen as the reagent to promote bromodesilylation. Upon addition of up to 4 equiv of TBAF (1 M solution in THF, fresh, containing water), the dibromide intermediate collapsed to the desired alkenyl bromide after warming up to rt. The *Z*/*E* ratio was determined to be 97:3 by $^1$H NMR analysis.

**Table 1.** Influence of Reaction Conditions on the Stereoselectivity of Converting Alkenylsiloxane **1** to Alkenyl Bromides




| entry | solvent[a] | temp (°C) | conversion[b] | *E*/*Z*[d] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 40 | >90% | 15:85 |
| 2 | $CH_2Cl_2$ | 0 | >90% | 8:92 |
| 3 | $CH_2Cl_2$ | −78 | >90% | 3:97 |
| 4 | $CH_2Cl_2$ | −100 | >90% | 2:98 |
| 5 | toluene | 23 | >90% | 17:83 |
| 6 | toluene | 0 | >90% | 13:87 |
| 7 | toluene | −78 | ~80% | 8:92 |
| 8 | $CS_2$ | 23 | >90% | 13:87 |
| 9 | $CS_2$ | 0 | >90% | 15:85 |
| 10 | $CS_2$ | −78 | >90% | 3:97 |
| 11 | THF | 23 | f, md[c] | 31:69 |
| 12 | THF | 0 | f, md | 22:78 |
| 13 | THF | −78 | i, md[c] | 67:33 |
| 14 | THF | −100 | i, md | 84:16 |
| 15 | $Et_2O$ | 23 | >90% | 20:80 |
| 16 | $Et_2O$ | 0 | >90% | 13:87 |
| 17 | $Et_2O$ | −78 | ~30% | 55:45 |
| 18 | DMF | 23 | i, d[c] | 74:26 |
| 19 | DMF | 0 | i, d | 70:30 |
| 20 | DMF | −78 | i, d | 63:37 |
| 21 | MeOH | −78 | d | nd[c] |

[a] $Br_2$ was added as a solution in the indicated solvent. [b] Conversion was calculated based on $^1$H NMR analysis. [c] f: full conversion; md: minor decomposition; i: incomplete conversion; d: decomposition; nd: not determined. [d] *E* to *Z* ratio measured by $^1$H NMR analysis.

With this initial success, we next explored the influence of solvent and temperature on the stereoselectivity of this transformation (Table 1). It was found that nonpolar solvents (DCM, toluene, and $CS_2$, entries 1−10) generally favored inversion of stereochemistry leading to the desired (*Z*)-alkenyl bromide. Using these solvents and lowering the temperature increased the selectivity toward the *Z* isomer, and reactions reached complete conversion in most cases. In contrast, polar nonprotic solvents such as DMF favored the retention of stereochemistry yielding the *E* isomer as the major product independent of reaction

(6) (a) Flook, M. M.; Jiang, A. J.; Schrock, R. R.; Muller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7962. (b) Vougioukalakis, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2008**, *130*, 2234. (c) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88. (d) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 94.

(7) For a method to construct disubstituted macrocycles using alkyne ring-closing metathesis, see: (a) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108. (b) Fürstner, A.; Grela, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1234. (c) Fürstner, A.; Radkowski, K. *Chem. Commun.* **2002**, 2182.

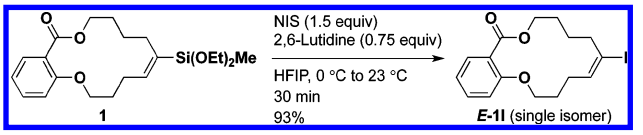
(8) Wang, Y. K.; Jimenez, M.; Hansen, A. S.; Raiber, E. A.; Schreiber, S. L.; Young, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 9196.

(9) (a) Brook, A. G.; Duff, J. M.; Reynolds, W. F. *J. Organomet. Chem.* **1976**, *121*, 293. (b) Chan, T. H.; Lau, P. W. K.; Mychajlowskij, W. *Tetrahedron Lett.* **1977**, *18*, 3317. (c) Fisher, R. P.; On, H. P.; Snow, J. T.; Zweifel, G. *Synthesis* **1982**, 127. (d) Jarvie, A. W.; Holt, A.; Thompson, J. *J. Chem. Soc. B* **1969**, 852. (e) Koenig, K. E.; Weber, W. P. *Tetrahedron Lett.* **1973**, *14*, 2533. (f) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424. (g) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647.

(10) Synthesis of **1** involves hydrosilylation of the alkyne and subsequent RCM of the vinylsiloxane. For details, see ref 8.

temperature, while decomposition became significant (entries 18−20). Interestingly, when the reaction was performed in THF or ether, the reaction proceeded more slowly at lower temperatures (−100 and −78 °C, entries 13, 14, and 17) with higher *E* selectivity. As the temperature was elevated, both the conversion and *Z* selectivity were increased (entries 11, 12, 15, and 16). In MeOH (entry 21), extensive decomposition occurred. Based on these results, we selected DCM and −78 °C as the optimal reaction conditions.

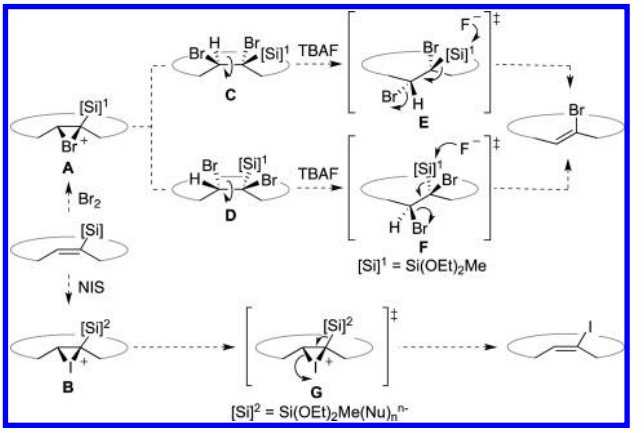
**Scheme 2.** Iodination of **1**




We next explored reaction conditions that gave rise to an alkenyl halide with retention of stereochemistry (*E* isomer). Although bromination with retention of olefin geometry has been reported,[11] we chose to follow an iodination procedure requiring a protic solvent and NIS (Scheme 2).[12] A single *E* isomer ***E*-1I** was obtained from the reaction of **1** with 93% yield.

Based on literature precedent[11,13] and our own results, the reaction mechanisms leading to the products with controlled olefin geometries are proposed in Scheme 3. In the case of inversion, once the bromonium ion **A** is formed, the bromide ion ($Br^-$) undergoes backside attack to generate the *anti*-dibromide (**C** and/or **D**). The issue of which carbon the bromide attacks (**C** or **D**) is inconsequential as long as the relative stereochemistry of the dibromide is *anti*. Upon treatment with TBAF, bromodesilylation occurs more readily when the $\beta$-bromo group is antiperiplanar to the silyl group via rotation about the C−C bond (transition state **E** and **F**) following an $E_2$ mechanism. The product from both intermediates is the same (*Z*)-alkenyl bromide. In contrast, formation of the (*E*)-alkenyl iodide proceeds through a *pseudo*-$E_1$ process in which the iodonium ion **B** rearranges, accompanied by the expulsion of the silicon (penta- or hexavalent silicate may form initially[11]) yielding the *E* product. Retention is favored because it requires the smallest angle of rotation of the C−C bond to achieve elimination.[13] This mechanism is in agreement with the observation that iodination proceeds faster in polar protic solvents that stabilize the iodonium ion and promote silicate formation. Similarly, retention of stereochemistry with bromination in THF at low temperatures (−78 °C and below) and DMF can be rationalized by the fact that a longer-lived bromonium ion exists and may allow formation of the *E* isomer, analogous to the iodination pathway. However, we cannot exclude the possibility of *syn*-dibromination under these conditions that also leads to the *E* product. Further mechanistic studies are warranted to fully understand the factors governing the selectivity of this reaction.

**Scheme 3.** Proposed Reaction Mechanisms

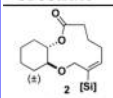
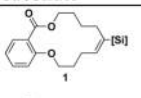
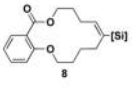
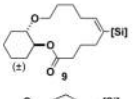
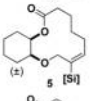
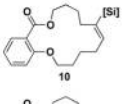
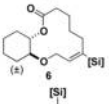
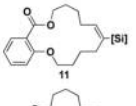
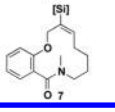
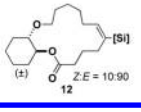



To explore the generality of both transformations we applied the optimized reaction conditions to a variety of substrates with ring sizes from 11 to 15 (Table 2). The iodinations proceeded very efficiently to generate the desired (*E*)-alkenyl iodide with high yield and selectivity except for one case (compound **6**). A moderate yield was obtained even when the reaction was performed in refluxing HFIP with the addition of 10 equiv of NIS. The reluctance of this molecule may result from the position of the silyl group (relative to compound **4**) that limits the flexibility of the macrocycle in undergoing rearrangement leading to product.

In contrast, the bromination reactions were more complex. As shown in Table 2, a general trend is that 11- or 12-membered rings tend to give retention of stereochemistry while compounds with larger ring sizes successfully render high *Z* selectivity. *cis*-Cyclohexanediol derived substrates tend to have higher *Z* selectivity than their *trans* analogues (compound **3** vs **2**, **5** vs **4**). The positions of the silyl group have an influence on reaction outcomes for smaller rings (compound **4**, 87% yield with high *E* selectivity vs **6**, decomposition) but not for larger rings (compound **10** vs **11**), and the positions of the double bond can slightly affect the *Z* selectivity for larger rings (compound **1** vs **8**). The dependency on ring sizes, stereochemistry, and regiochemistry can be tentatively rationalized by two factors: the ability of the substrates to undergo *anti*-dibromination, which may be inaccessible in the smaller rings due to transannular effects, and the flexibility of the macrocycle to accommodate the alkenyl bromide products (especially the *Z* isomer). These results provide a basis for further studies on the differences between macrocyclic substrates that account for the differential outcomes. Efforts to increase the *Z* selectivity of smaller macrocycles are ongoing.

(11) Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100.
(12) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727.
(13) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57.

**Table 2.** Conversion of (*E*)-Alkenylsiloxane Substrates to the Corresponding Alkenyl Bromide and Alkenyl Iodide

| substrate[a] | yield (*E*:*Z*)[b] | substrate[a] | yield (*E*:*Z*)[b] |
|---|---|---|---|
|  | 95% (88:12)<br>88% (>99:1) |  | 89% (3:97)<br>93% (>99:1) |
|  | 82% (56:44)<br>82% (>99:1) |  | 91% (9:91)<br>89% (>99:1) |
|  | 87%[c] (96:4)<br>94% (>99:1) |  | 84%[c] (4:96)<br>88% (>99:1) |
|  | 90% (85:15)<br>89% (>99:1) |  | 92% (2:98)<br>88% (>99:1) |
|  | decomp.<br>60% (>99:1) |  | 97% (2:98)<br>87% (>99:1) |
|  | 79%[c] (98:2)<br>92% (>99:1) |  | 87% (12:88)<br>91% (90:10) |

[a] [Si] = $Si(OEt)_2Me$. [b] Isolated yields for bromination reactions (in blue) and iodination reactions (in black) including both isomers unless otherwise noted. Selectivity (in parentheses) determined by $^1H$ NMR analysis of crude reaction mixtures. [c] Isolated yield for the major isomer.

The synthetic potential of this methodology is demonstrated in Scheme 4. The macrocyclic (*E*)-alkenylsiloxane **1** can be converted to trisubstituted macrocyclic alkene ***E*-14** through a Suzuki coupling between alkenyl iodide ***E*-1I** and 3-acetylphenyl-boronic acid.[14] Compound ***E*-14** can also be obtained directly through a Hiyama-type reaction;[15] however, for the majority of cross-coupling reactions, alkenyl iodides serve as more effective intermediates than the initial alkenylsiloxanes.[16] Conversely, the ***Z*** stereoisomer of **14** can be accessed from ***Z*-1Br**, the product from the stereochemical inversion of **1**.[17] Finally, since vinylsiloxane **1** contains a differentiated alkene it can be regiospecifically oxidized to macrocyclic ketone **13** via

(14) Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, C. M.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Org. Lett.* **2008**, *10*, 3235.

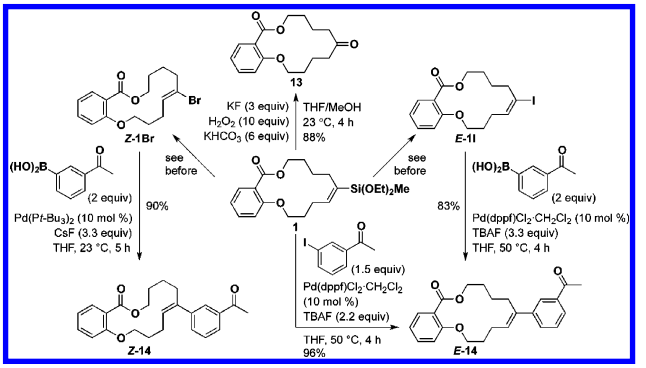
(15) (a) Denmark, S. E.; Pan, W. *Org. Lett.* **2003**, *5*, 1119. (b) Rooke, D. A.; Ferreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3225. (c) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051.

(16) For the synthetic utility of vinylsilanes, see: Denmark, S. E.; Liu, J. H. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2978.

(17) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2002**, *124*, 7376.

(18) Tamao, K.; Kumada, M.; Maeda, K. *Tetrahedron Lett.* **1984**, *25*, 321.

**Scheme 4.** Access to Both Stereoisomers of Trisubstituted Alkene, and Macrocyclic Ketone




Tamao oxidation.[18] Yields from all of these transformations are excellent.

In summary, we have demonstrated a methodology to access trisubstituted macrocyclic (*E*)- and (*Z*)-alkenes from ring-closing metathesis. The strategy employs a substrate-controlled RCM reaction of linear vinylsiloxanes to selectively generate macrocyclic (*E*)-alkenyl siloxanes. Conditions were developed to convert the alkenyl siloxane products into alkenyl halides with retention or inversion of configuration of the alkene geometry. The *E*- and *Z*-alkenyl halides in turn served as effective substrates for palladium-mediated cross-coupling reactions to generate trisubstituted alkenes. The application of this methodology to the construction of biologically relevant macrocycles is currently underway.

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**Supporting Information Available.** Experimental procedures, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.