

Regio- and Stereoselective Synthesis of 2-Amino-1,3-diene Derivatives by Ruthenium-Catalyzed Coupling of Ynamides and Ethylene

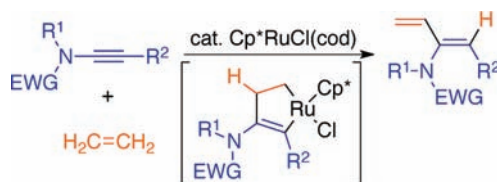
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ABSTRACT



A ruthenium-catalyzed hydrovinylation-type cross-coupling of ynamides and ethylene proceeds via ruthenacyclopentene to give 2-aminobuta-1,3-diene derivatives in a highly regioselective manner. It was also demonstrated that 2-aminobuta-1,3-diene derivatives reacted with various dienophiles or singlet oxygen to give a cyclic enamide derivative.

Amino-1,3-diene derivatives have been recognized as versatile units in synthetic organic chemistry, and many methods for the preparation of amino-1,3-dienes have been reported.¹ Recently, amino-1,3-diene derivatives were synthesized by the transition-metal-mediated transformation of ynamides.^{2–6}

Transition-metal-catalyzed hydrovinylation of alkynes is an attractive and efficient strategy for the stereoselective synthesis of 1,3-dienes from the standpoint of atom economy.⁷ It is known that several ruthenium complexes show high catalytic activity for such hydrovinylation-type direct cross-couplings of alkynes and alkenes.^{8,9}

With this background, we planned to investigate the intermolecular coupling of ynamides and ethylene mediated by a low-valent ruthenium catalyst with the focus of introducing a new protocol for the stereoselective synthesis of amino-1,3-dienes (Scheme 1). Based on our previous investigations of the intramolecular reaction of

(3) For most recent examples of the preparation and reactions of ynamides, see: (a) Gourdet, B.; Lam, H. W. *Angew. Chem., Int. Ed.* **2010**, *49*, 8733. (b) Sato, A.; Yorimitsu, H.; Oshima, K. *Bull. Korean Chem. Soc.* **2010**, *31*, 570. (c) Valenta, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 14179. (d) Poloukhina, A.; Rassadin, V.; Kuzmin, A.; Popik, V. V. *J. Org. Chem.* **2010**, *75*, 5953. (e) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000. (f) Gourdet, B.; Rudkin, M. E.; Lam, H. W. *Org. Lett.* **2010**, *12*, 2554. (g) Banerjee, B.; Litvinov, D. N.; Kang, J.; Bettale, J. D.; Castle, S. L. *Org. Lett.* **2010**, *12*, 2650. (h) Kramer, S.; Madsen, J. L. H.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2010**, *12*, 2758. (i) Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272. (j) Li, H.; Hsung, R. P.; DeKorver, K. A.; Wei, Y. *Org. Lett.* **2010**, *12*, 3780. (k) Wakamatsu, H.; Takeshita, M. *Synlett* **2010**, 2322. (l) DeKorver, K. A.; North, T. D.; Hsung, R. P. *Synlett* **2010**, 2397. (m) Grimster, N. P.; Wilton, D. A. A.; Chan, L. K. M.; Godfrey, C. R. A.; Green, C.; Owen, D. R.; Gaunt, M. J. *Tetrahedron* **2010**, *66*, 6429. (n) Fadel, A.; Legrand, F.; Evano, G.; Rabasso, N. *Adv. Synth. Catal.* **2011**, *353*, 263. (o) Schotes, C.; Mezzetti, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3072. (p) Davies, P. W.; Cremonesi, A.; Martin, N. *Chem. Commun.* **2011**, 47, 379. (q) Mak, X. Y.; Crombie, A. L.; Danheiser, R. *J. Org. Chem.* **2011**, *76*, 1852. (r) Shindoh, N.; Takemoto, Y.; Takasu, K. *Heterocycles* **2011**, *82*, 1133. (s) Xu, C.-F.; Xu, M.; Jia, Y.-X.; Li, C.-Y. *Org. Lett.* **2011**, *13*, 1556. (t) Kramer, S.; Friis, S. D.; Xin, Z.; Odabachian, Y.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 1750. See also: References 2d and 2e.

[†] Hokkaido University.

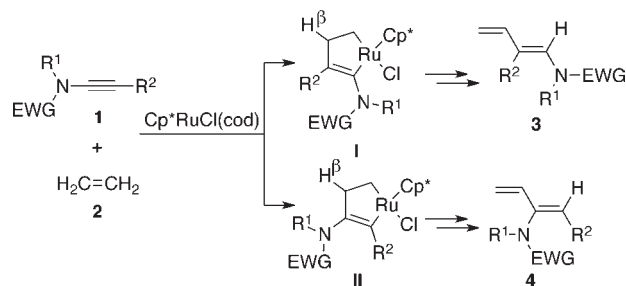
[‡] Rigaku Corporation.

(1) For reviews on preparations and reactions of amino-1,3-diene derivatives, see: (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753 and references cited therein. (b) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421 and references cited therein.

(2) For reviews on the chemistry of ynamides, see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (c) Hsung, R. P., Ed. In *Tetrahedron Symposia-in-Print No. 118*, *Tetrahedron* **2006**, *62*, 3783. (d) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (e) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.

ene-yne^{10a-d} and allene-yne^{10e,f} catalyzed by Cp^{*}RuCl(cod) (cod), the oxidative cycloaddition of ynamides **1** and ethylene **2** to a low-valent ruthenium complex could give the ruthenacyclopentene **I** or **II**. β -Hydride elimination from **I** or **II** followed by reductive elimination would afford the corresponding 1-amino-1,3-diene derivative **3** or 2-amino-1,3-diene derivative **4**.

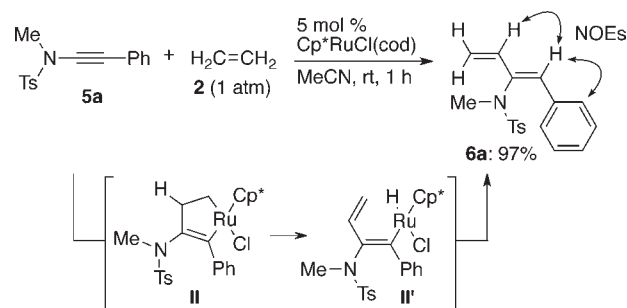
Scheme 1. Strategy for the Synthesis of Amino-1,3-dienes



To examine the feasibility of this strategy, tosylamide-derived ynamide **5a** was reacted with ethylene (**2**, 1 atm) in the presence of Cp^{*}RuCl(cod) (5 mol %) in MeCN. As a result, the desired 2-amino-1,3-diene derivative **6a** was obtained in 97% yield as a single isomer, whose regio- and stereochemistries were determined by NOE experiments (Scheme 2). This result indicated that the oxidative

cycloaddition of **5a** and ethylene to the ruthenium complex occurred regioselectively to give the ruthenacyclopentene **II**. β -Hydride elimination then gave the intermediate **II'** from which reductive elimination proceeded to afford **6a** in a regio- and stereoselective manner.^{11,12}

Scheme 2. Ruthenium-Catalyzed Regioselective Coupling of Ynamide **5a** and Ethylene



Encouraged by these results, the effects of substituents on the alkyne part or nitrogen atom were investigated (Table 1). The coupling reactions of ynamides **5b** and **5c**, with an aromatic group on the alkyne, were studied with ethylene (**2**) and gave the 2-amino-1,3-dienes **6b** and **6c**, respectively, in high yield (runs 1 and 2). When ynamides **5d-f**, bearing an alkyl group on the alkyne moiety, were reacted with ethylene (**2**), the desired coupling products **6d-f** were stereoselectively produced in low to high yield (runs 3–5). On the other hand, the ethylene coupling reaction of the terminal ynamide **5g** or the ynamide having a TMS group on the alkyne part **5h** did not proceed and the starting ynamides were recovered (runs 6 and 7). Ynamides with an *N*-isopropyl group **5i** and an *N*-phenyl group **5j** also reacted with ethylene (**2**) in the presence of a ruthenium catalyst, giving the corresponding 2-amino-1,3-diene derivatives **6i** and **6j** in 48% and 85% yield, respectively (runs 8 and 9).

(9) Recently, Tanaka reported the rhodium-catalyzed hydrovinylolation-type direct cross-coupling of alkynes and alkenes giving 1,3-dienes via a rhodacyclopentene intermediate; see: Shibata, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2829.

(10) (a) Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5606. (b) Mori, M.; Tanaka, D.; Saito, N.; Sato, Y. *Organometallics* **2008**, *27*, 6313. (c) Tanaka, D.; Sato, Y.; Mori, M. *Organometallics* **2006**, *25*, 799. (d) Tanaka, D.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2007**, *129*, 7730. (e) Saito, N.; Tanaka, Y.; Sato, Y. *Organometallics* **2009**, *28*, 669. (f) Saito, N.; Tanaka, Y.; Sato, Y. *Org. Lett.* **2009**, *11*, 4124.

(11) In acetonitrile, a cationic ruthenium species would be generated from Cp^{*}RuCl(cod) accompanied by dissociation of chloride ligands. See: Davies, S. G.; McNally, J. P.; Smallridge, A. J. *Adv. Organomet. Chem.* **1990**, *30*, 1. At the ruthenacycle formation stage, the reaction proceeded as such cationic ruthenium complex would interact with β -carbon atom of the ynamide which has a partial negative charge (see ref 4a). Consequently, ruthenacyclopentene **II** would be formed in a regioselective manner. In this context, when the reaction of **5a** and **2** was carried out in the presence of [Cp^{*}Ru(MeCN)₃]PF₆ (5 mol %) in MeCN at room temperature, 2-amino-1,3-diene **6a** was produced in 63% yield as a single isomer, and no regioisomer of **6a** was observed.

(12) Recently Hsung reported the synthesis of 2-amino-1,3-diene derivatives via isomerization of allenamide; see: (a) Hayashi, R.; Hsung, R. P.; Feltenberger, J. B.; Lohse, A. G. *Org. Lett.* **2009**, *11*, 2125. (a) Hayashi, R.; Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2010**, *12*, 1152.

(4) For our approach to regio- and stereoselective synthesis of enamide derivatives by Ni(0)-catalyzed multicomponent coupling of ynamide, aldehyde, and silane, see: (a) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829. (b) Saito, N.; Katayama, T.; Sato, Y. *Heterocycles* **2011**, *82*, 1181.

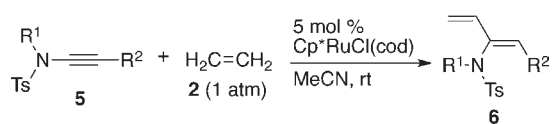
(5) For Pd-catalyzed ene-yne coupling, see: (a) Lindhardt, A. T.; Mantel, M. L. H.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2668. For Rh-catalyzed carbocationic coupling of ynamides, see: (b) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802. (c) Gourdet, B.; Rudkin, M. E.; Watts, C. A.; Lam, H. W. *J. Org. Chem.* **2009**, *74*, 7849. (d) Gourdet, B.; Smith, D. L.; Lam, H. W. *Tetrahedron* **2010**, *66*, 6026. For Ti-mediated reductive coupling of ynamide and simple alkyne, see: (e) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67. (f) Hirano, S.; Fukudome, Y.; Tanaka, R.; Sato, F.; Urabe, H. *Tetrahedron* **2006**, *62*, 3896.

(6) For ruthenium-catalyzed ring-closing metathesis of ene-ynamide leading to cyclic-1,3-dienamide, see: (a) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (b) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (c) Mori, M.; Wakamatsu, H.; Saito, N.; Sato, Y.; Narita, R.; Sato, Y.; Fujita, R. *Tetrahedron* **2006**, *62*, 3872. (d) Wakamatsu, H.; Sakagami, M.; Hanata, M.; Takeshita, M.; Mori, M. *Macromol. Symp.* **2010**, *293*, 5.

(7) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(8) For ene-yne coupling via ruthenacyclopentene formation, see: (a) Mitsudo, T.; Zhang, S.-W.; Nagao, M.; Watanabe, Y. *Chem. Commun.* **1991**, 598. (b) Trost, B. M.; Martos-Redrujo, A. *Org. Lett.* **2009**, *11*, 1071. For ene-yne coupling via hydrotathenation of alkynes, see: (c) Yi, C. S.; Lee, D. W.; Chen, Y. *Organometallics* **1999**, *18*, 2043. (d) Nishimura, T.; Washitake, Y.; Uemura, S. *Adv. Synth. Catal.* **2007**, *349*, 2563. For ene-yne coupling via the formation of ruthenium vinylidene complex, see: (e) Murakami, M.; Ubukata, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 7361. For ene-yne coupling via C–H activation process, see: (f) Kakiuchi, F.; Uetsuhara, T.; Tanaka, Y.; Chatani, N.; Murai, S. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 511. (g) Neisius, N. M.; Plietker, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5752. 1-Amino-1,3-diene derivatives were synthesized by ruthenium-catalyzed direct cross-coupling of alkynes and *N*-vinylamides; see: (h) Tsujita, H.; Ura, Y.; Matsuki, S.; Wada, K.; Mitsudo, T.; Kondo, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5160.

Table 1. Coupling of Tosylamide-Derived Ynamides and Ethylene

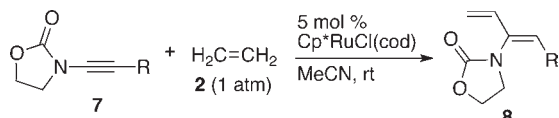


run	ynamide	time (h)	yield (%) ^b
1	5b (R ¹ = Me, R ² = 4-MeO ₂ CC ₆ H ₄)	2	6b : quant
2	5c (R ¹ = Me, R ² = 4-MeOC ₆ H ₄)	3	6c : 99
3 ^a	5d (R ¹ = Me, R ² = ⁿ Bu)	19	6d : 80
4 ^a	5e (R ¹ = Me, R ² = CH ₂ CH ₂ OTBS)	21	6e : 88
5 ^a	5f (R ¹ = Me, R ² = CH ₂ OTBS)	20	6f : 20 (57)
6 ^a	5g (R ¹ = Me, R ² = H)	21	6g : - (45)
7 ^a	5h (R ¹ = Me, R ² = TMS)	18	6h : - (83)
8 ^a	5i (R ¹ = ⁱ Pr, R ² = Ph)	22	6i : 48 (23)
9	5j (R ¹ = R ² = Ph)	4	6j : 85

^aThe reaction was carried out at 60 °C. ^bValues in parentheses are the yields of recovered ynamide **5**.

Next, the coupling reaction using oxazolidinone-derived ynamides with ethylene was investigated (Table 2). When ynamides with an aromatic group on the alkyne moiety **7a–c** were employed for the coupling with ethylene, 2-amino-1,3-diene derivatives **8a–c** were obtained in high yield in a stereoselective manner (runs 1–3). On the other hand, the reaction of an alkyl-group-substituted ynamide **7d** and ethylene (**2**) gave the coupling product in low yield (run 4).

Table 2. Coupling of Oxazolidinone-Derived Ynamides and Ethylene



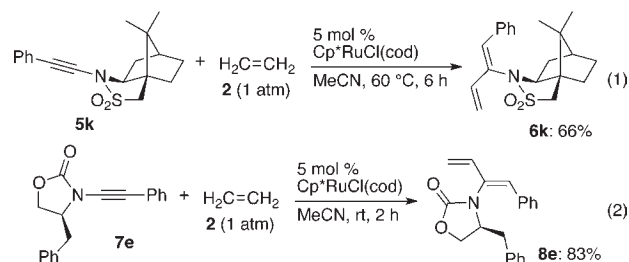
run	ynamide	time (h)	yield (%) ^b
1	7a (R = Ph)	2	8a : 86
2	7b (R = 4-MeO ₂ CC ₆ H ₄)	2	8b : 87
3	7c (R = 4-MeOC ₆ H ₄)	2	8c : 92
4 ^a	7d (R = ⁿ Bu)	25	8d : 10 (89)

^aThe reaction was carried out at 60 °C. ^bValues in parentheses are the yields of recovered ynamide **7**.

Furthermore, chiral ynamides **5k** derived from Oppolzer's sultam¹³ and **7e**, prepared from L-phenylalanine, could be applied in the coupling with ethylene (**2**), and the corresponding 2-amino-1,3-dienes **6k** and **8e** were obtained in optically active form (Scheme 3).

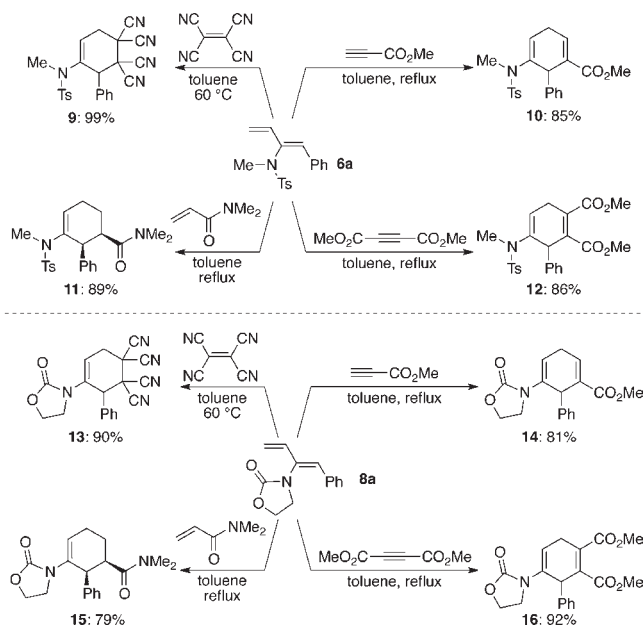
Next, we turned our attention to the utilization of 2-aminobuta-1,3-diene derivatives we had prepared. First, we investigated the Diels–Alder reaction of **6a** and **8a**

Scheme 3. Coupling of Chiral Ynamides and Ethylene



(Scheme 4). Thus, various alkenes and alkynes were employed as dienophiles, giving the corresponding cyclic enamide derivatives **9–16** in good yields and in a regio- and stereoselective manner.

Scheme 4. Diels–Alder Reaction of **6a** and **8a** with Various Dienophiles

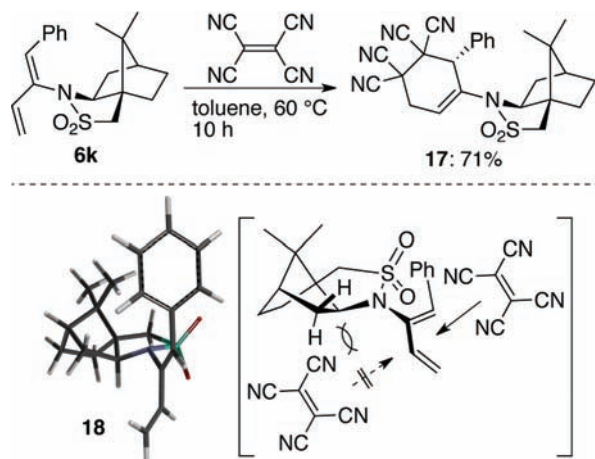


The chiral 2-amino-1,3-diene **6k** was applied to a diastereoselective Diels–Alder reaction with tetracyanoethene (TCNE), and the enamide derivative **17** was obtained as a single diastereomer (Scheme 5).¹⁴ The most stable conformation of **6k** was found by conformational analysis using Spartan'06 (Wavefunction, Inc., Irvine, CA) with the MMFF force field, and the structure was depicted as **18**. Based on this result, it was thought that TCNE would approach the diene part of **6k** to avoid steric repulsion with the camphor ring of **6k**, which might control the stereochemistry of **17**.

(14) The absolute configuration at the methyne carbon in the cyclohexene ring of **17** was determined by X-ray crystallographic analysis. Crystallographic data of **17** have been deposited at the Cambridge Crystallographic Data Center (CCDC 818816).

(13) For reviews on the use of Oppolzer's sultam as a chiral auxiliary in asymmetric synthesis, see: (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.

Scheme 5. Diels–Alder Reaction of **6k** and TCNE

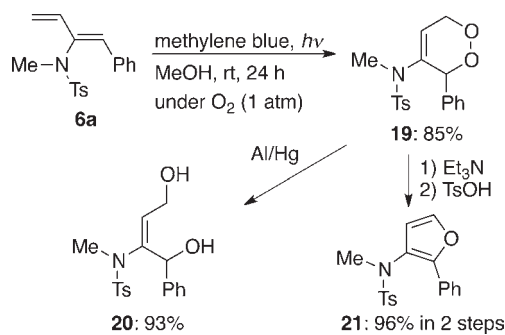


Furthermore, the reaction of **6a** and singlet oxygen was examined (Scheme 6). When a solution of **6a** in MeOH was stirred under oxygen gas (1 atm) in the presence of the catalytic amount of methylene blue for 1 day, the six-membered endoperoxide **19** was produced in 85% yield. The endoperoxide was reduced by Al/Hg^{15a} to give bis-allylic alcohol derivative **20** in 93% yield. On the other hand, when the endoperoxide **19** was treated with Et₃N followed by TsOH, it gave the 3-aminofuran derivative **21** in high yield.^{15b}

In summary, we have succeeded in developing a new method for the synthesis of 2-amino-1,3-diene derivatives

(15) (a) Pearson, A. J.; Lai, Y.-S.; Srinivasan, K. *Aust. J. Chem.* **1992**, *45*, 109. (b) Kondo, K.; Matsumoto, M. *Tetrahedron Lett.* **1976**, *17*, 4363.

Scheme 6. Reaction of **6a** and Singlet Oxygen and Transformations of Endoperoxide **19**



by ruthenium-catalyzed regioselective coupling of ynamides and ethylene via the formation of a ruthenacyclopentene intermediate. We have also shown that 2-amino-1,3-dienes are suitable substrates for the preparation of cyclic enamide derivatives by a Diels–Alder reaction or reaction with singlet oxygen.

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