

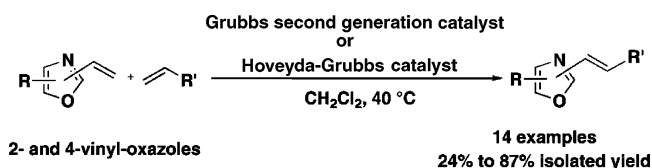
Synthesis of Vinyl-Functionalized Oxazoles by Olefin Cross-Metathesis

Thomas J. Hoffman,^{†,‡} James H. Rigby,[‡]
Stellios Arseniyadis,[†] and Janine Cossy^{*,†}

Laboratoire de Chimie Organique, ESPCI, CNRS,
10 rue Vauquelin, 75231 Paris Cedex 05, France, and
Department of Chemistry, Wayne State University,
Detroit, Michigan 48202-3489

janine.cossy@espci.fr

Received October 24, 2007



A ruthenium-based catalyzed olefin cross-metathesis reaction involving 2- and 4-vinyl-functionalized oxazoles was developed. A wide range of olefinic partners was coupled in good to excellent yields and high stereoselectivities under mild conditions. This methodology offers new opportunities for the synthesis of a plethora of biologically active natural products.

During the last two decades, the isolation of a wide range of natural products containing the oxazole subunit has stimulated considerable synthetic efforts. This interest has arisen from the fact that many of these compounds, among them ulapualide A,¹ mycalolide A,² phorbioxazole A,³ and calyculin A,⁴ have been found to possess significant biological activities as cytotoxic, antifungal, antibacterial, antitumor, and antiviral agents (Figure 1).⁵

Olefin cross-metathesis (CM) catalyzed by ruthenium carbene complexes has been widely utilized as an advantageous method in synthesizing various alkenes that would be otherwise difficult to obtain. In addition, the relative ease of running such reactions

and the commercial availability of several well-defined catalysts, such as [Ru]-I (Grubbs first-generation catalyst),⁶ [Ru]-II (Grubbs second-generation catalyst),⁷ and [Ru]-III (Hoveyda–Grubbs catalyst)⁸ (Figure 2), has brought olefin metathesis to the forefront of one of the most widely used synthetic methods in carbon–carbon bond construction.⁹

Recent studies in our group have focused on developing an efficient CM process applied to vinyl-functionalized thiazoles. Our initial findings in the field were reported as a communication¹⁰ earlier this year and later resulted in the convergent total synthesis of melittiazole C, a powerful fungicide isolated from *Melittangium lichenicola*.¹¹ Herein, we report the results of our endeavor toward extending the substrate scope to 2- and 4-vinyl-functionalized oxazoles.

The initial study focused on the development of an effective CM process applied to 2- and 4-vinyl-functionalized thiazoles.¹⁰ Hence, by subjecting these two compounds to various CM experiments, it was found that the efficiency of the coupling was highly catalyst-dependent as [Ru]-II and [Ru]-III appeared to be more effective than [Ru]-I. Moreover, the CM reactions were highly stereoselective in favor of the (*E*)-isomer as, for most of the substrates engaged, the (*Z*)-isomer could barely be detected by either ¹H or ¹³C NMR.

Following these promising results, we subsequently turned our attention toward the CM of 2- and 4-vinyl-functionalized oxazoles, which, to the best of our knowledge, had never been previously reported (Scheme 1).

The requisite 2-vinyl-functionalized oxazole **1** was readily prepared from ethyl bromopyruvate (**6**) and acrylamide (**7**) by using Holzapfel's modified Hantzsch procedure¹² as outlined in Scheme 2. Under these reaction conditions, compound **1** was isolated in 72% yield.

In order to validate the methodology on 2-vinyl-oxazoles, we initially performed a series of test experiments on two types of olefins we suspected would display very different reactivity patterns. The two coupling partners chosen were type I^{7b} olefin **3e** and type II^{7b} olefin **3j**, while initial conditions involved the

(6) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (c) Belderrain, T. R.; Grubbs, R. H. *Organometallics* **1997**, *16*, 4001–4003.

(7) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.

(8) Kingbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(9) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4490–4527.

(10) Dash, J.; Arseniyadis, S.; Cossy, J. *Adv. Synth. Catal.* **2007**, *349*, 152–156.

(11) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 3425–3427.

(12) (a) Ahmed, F.; Donaldson, W. A. *Synth. Commun.* **2003**, *33*, 2685–2693. (b) Schmidt, U.; Utz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 725–726. (c) Schmidt, U.; Gleich, P. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 569–571. (d) Schmidt, U.; Utz, R.; Lieberknecht, A.; Griesser, H.; Potzli, B.; Bahr, J.; Wagner, K.; Fischer, P. *Synthesis* **1987**, 233–236. (e) Bredenkamp, M. W.; Holzapfel, C. W.; Zyl, W. J. V. *Synth. Commun.* **1990**, *20*, 2235–2249. (f) Deng, S.; Taunton, J. J. *J. Am. Chem. Soc.* **2002**, *124*, 916–917. (g) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826–831. (h) Wang, W.; Nan, F. J. *J. Org. Chem.* **2003**, *68*, 1636–1639.

[†] ESPCI.

[‡] Wayne State University.

(1) (a) Roesner, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846–847. (b) Matsunaga, S.; Fusetani, K.; Hashimoto, K.; Koseki, K.; Norma, M. J. *Am. Chem. Soc.* **1986**, *108*, 847–848. (c) Allingham, J. S.; Tanaka, J.; Marriott, G.; Rayment, I. *Org. Lett.* **2004**, *6*, 597–599. (d) Pattenden, G.; Ashweek, N. J.; Baker-Glenn, C. A. G.; Walker, G. A.; Yee, J. G. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4359–4363.

(2) Fusetani, N.; Yasumuro, K.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1989**, *30*, 2809–2813.

(3) (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126–8131. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422–9423.

(4) (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780–2781. (b) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930–3932.

(5) (a) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196–229. (b) de Souza, M. V. N. *J. Sulf. Chem* **2005**, *26*, 429–449.

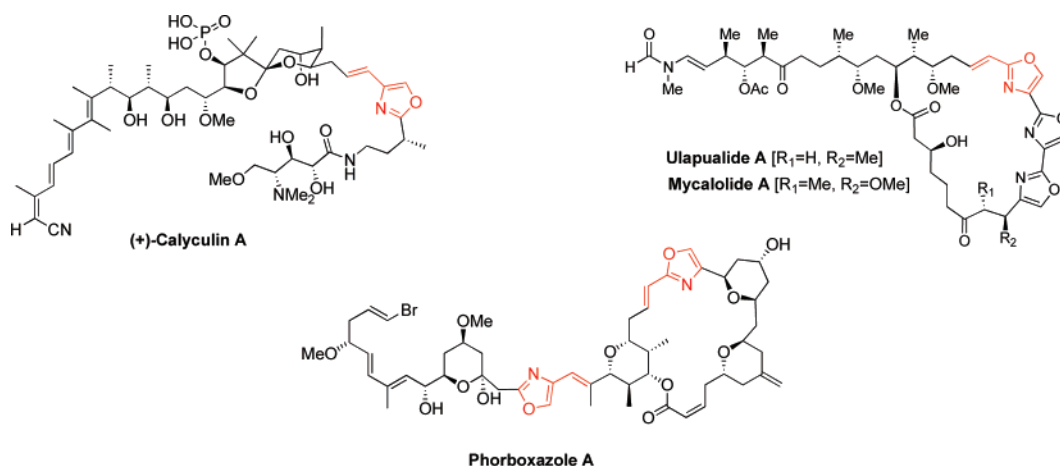


FIGURE 1. Natural products containing the oxazole/thiazole subunit.

use of [Ru]-II and [Ru]-III as the ruthenium carbene catalyst (10 mol %) in refluxing CH₂Cl₂ (Table 1).

Interestingly, under these reaction conditions, both substrates appeared to couple smoothly. While CM between *p*-methoxybenzyl-protected homoallylic alcohol **3e** and 2-vinyloxazole **1** afforded the corresponding coupled product **4e** in 67% and 87% yield when using [Ru]-II and [Ru]-III (Table 1, entries 5 and 6), ethyl vinyl ketone (**3j**) led to disubstituted vinyloxazole **4l** in up to 65% yield after purification (Table 1, entries 13 and 14). Moreover, [Ru]-III appeared to be superior to [Ru]-II as shorter reaction times along with greater yields and conversions were obtained under otherwise identical conditions. These interesting yet unexpected results set the ground rules for our

study to broaden the substrate scope of the reaction. As a consequence, a series of CM experiments was performed exclusively using [Ru]-III as the carbene catalyst (10 mol %) and 1.5 equiv of the appropriate olefinic coupling partner in refluxing CH₂Cl₂.¹² The results are depicted in Table 1.

2-Vinyloxazole **1** appeared to readily undergo CM when coupled to 4-methylpent-1-ene (**3a**), as the desired coupled product **4a** was isolated in both high yield (68%) and high stereoselectivity (*E/Z* = 11/1) (Table 1, entry 1). For olefins such as allyltrimethylsilane (**3b**), allyl bromide (**3c**), and allyl dimethylmalonate (**3d**), CM afforded the corresponding products **4b**, **4c**, and **4d** with chemical yields ranging from 43% to 73%, while the *E/Z* ratio varied from 6/1 to 10/1 in favor of the (*E*)-isomer (Table 1, entries 2–4). Likewise, when olefin **3f** was used, the coupled product **4f** was isolated in 59% yield as an 8/1 mixture of stereoisomers (Table 1, entry 7). High yields were also accessed for substrates such as **3g** (72%, Table 1, entry 8) and **3h** (77%, Table 1, entry 9) with selectivities ranging from 7/1 to 11/1 in favor of the (*E*)-isomer in both cases.

The coupling efficiency of oxazole **1** with a series of styrene derivatives showed a high dependency on the type of substituent at the para position of the phenyl ring. Hence, *p*-fluoro-substituted styrene (**3i**) gave the best yields (80%) (Table 1, entry 10) when compared to styrene (**3j**) and *p*-methoxystyrene (**3k**), which afforded the corresponding coupled products in 37% and 26% yield, respectively (Table 1, entries 11 and 12). These results suggest that electron-poor styrene derivatives such as **3i** are more prone to undergo CM with **1** in comparison to more electron-rich styrene derivatives.

Finally, the reactions between 2-vinyloxazole **1** and electron-deficient olefins such as methyl acrylate (**3m**) and *tert*-butyl acrylate (**3n**) were also investigated. In both cases, CM appeared to be very sluggish as only 52% of **4m** and 24% of **4n** were isolated after 48 h (Table 1, entries 15 and 16). However, the reactions did proceed to afford the desired coupled products in contrast to the thiazole series tested previously which did not undergo any CM, and the ratio of (*Z*)-isomer increased compared to all the other olefins (*E/Z* = 3/1, Table 1, entries 15 and 16).

Along with investigating the CM of 2-vinyloxazole **1**, the utility of the reaction was extended to oxazoles featuring a vinyl group at the 4 position of the ring. The substrate examined, **2**, was readily prepared in 57% overall yield in two steps starting from benzamide (**8**). The synthesis involved a one-pot trimethylsilyldiazomethane addition to the acyl isocyanate prepared in

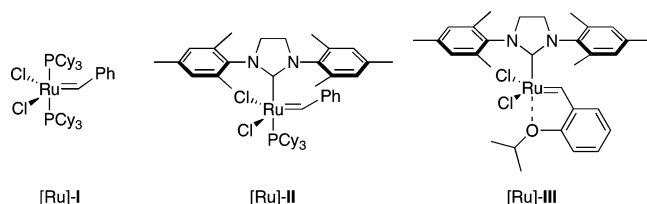
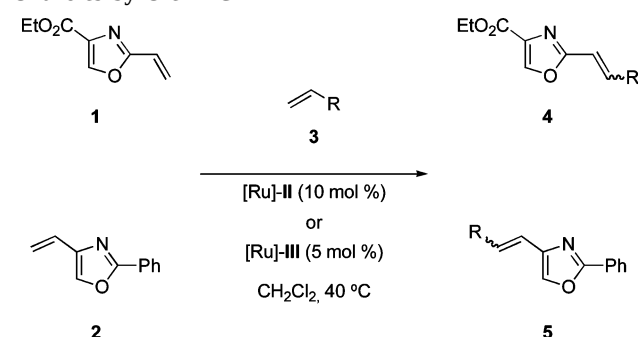


FIGURE 2. Commonly used metathesis catalysts.

SCHEME 1. Synthesis of 2- and 4-Vinyl-Functionalized Oxazoles by Olefin CM



SCHEME 2. Synthesis of 2-Vinyl-Functionalized Oxazole 1

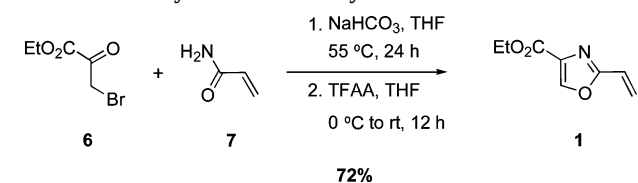
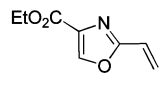
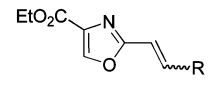
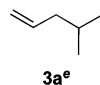
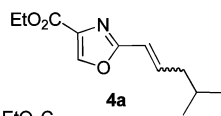
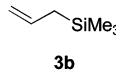
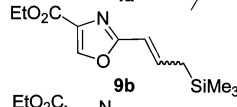
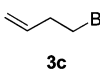
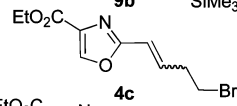
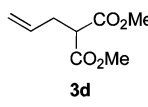
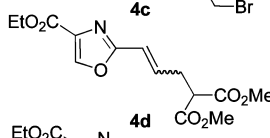
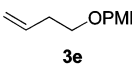
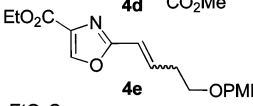
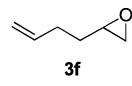
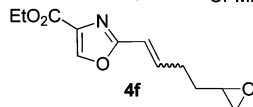
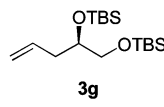
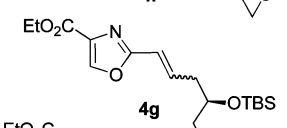
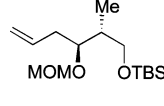
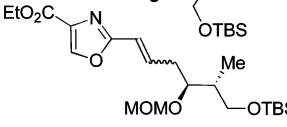
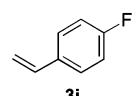
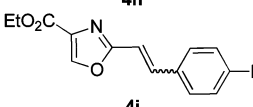
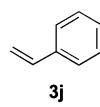
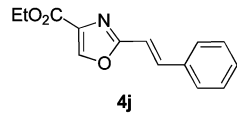
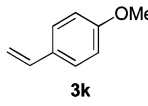
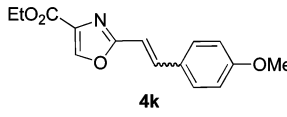
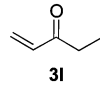
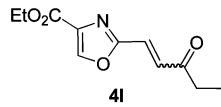
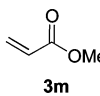
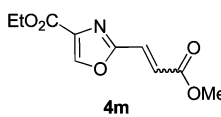
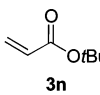
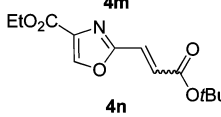
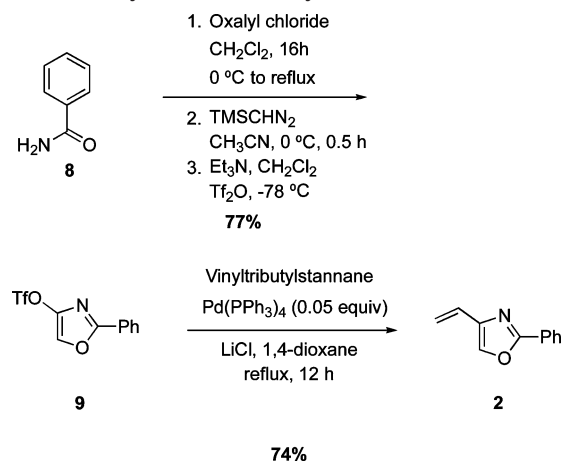


TABLE 1. Olefin Cross-Metathesis Reaction of 2-Vinyloxazole 1^a

 1 $\xrightarrow[\text{CH}_2\text{Cl}_2, 40^\circ\text{C}]{[\text{Ru}]\text{-II or } [\text{Ru}]\text{-III (10 mol\%)}}$  4a-n							
Entry	Olefin	Catalyst	Time [h]	Conversion ^b	Product	Yield ^c [%]	E/Z ^d
1	 3a^e	[Ru]-III	36	94	 4a	68	11/1
2	 3b	[Ru]-III	24	84	 9b	73	6/1
3	 3c	[Ru]-III	24	80	 4c	56	9/1
4	 3d	[Ru]-III	16	100	 4d	43	10/1
5	 3e	[Ru]-II	18	90	 4e	67	8/1
6		[Ru]-III	18	100		87	8/1
7	 3f	[Ru]-III	16	90	 4f	59	8/1
8	 3g	[Ru]-III	36	85	 4g	72	7/1
9	 3h	[Ru]-III	18	90	 4h	77	11/1
10	 3i	[Ru]-III	24	94	 4i	80	15/1
11	 3j	[Ru]-III	36	50	 4j	37	>20/1
12	 3k	[Ru]-III	36	52	 4k	26	11/1
13	 3l	[Ru]-II	24	60	 4l	46	10/1
14		[Ru]-III	24	100		65	10/1
15	 3m	[Ru]-III	48	67	 4m	52	3/1
16	 3n	[Ru]-III	48	30	 4n	24	3/1

^a All reactions were carried out on a 0.11 mmol scale using 1.5 equiv of the selected olefin (unless otherwise specified) in CH₂Cl₂ at 40 °C. ^b Conversion determined by ¹H NMR of the crude reaction mixture. ^c Isolated yield in major isomer. ^d E/Z ratio determined by ¹H NMR of the crude reaction mixture. ^e Reaction performed using 3 equiv of the olefinic partner.

SCHEME 3. Synthesis of 4-Vinyl-Functionalized Oxazole 2



situ¹³ leading to an oxazolidinone, which was converted to the corresponding enol triflate **9**. The latter was then coupled with vinyltributyltin under Stille conditions to introduce the vinyl moiety and thus generate 4-vinyloxazole **2** in 57% yield overall yield (Scheme 3).

4-Vinyloxazole **2** was then subjected to an initial CM experiment using [Ru]-III as the ruthenium carbene catalyst (10 mol %) and 4-methylpent-1-ene (**3a**) (3 equiv) as the olefinic coupling partner in refluxing CH₂Cl₂. Surprisingly, under these reaction conditions, the corresponding coupled product, **5a**, was isolated in low yield (36%) as a single stereoisomer (Table 2, entry 1). The same result was observed with allyldimethylmalonate (**3d**), which upon coupling with **2** led to only 27% yield of the desired coupled product **5d** (Table 5, entry 2). However, electron-poor olefins such as ethyl vinyl ketone (**3l**) and methyl acrylate (**3m**) both coupled suitably well in comparison to activated olefins, as after 36 h, **5l** and **5m** were both isolated in 72% and 60% yield, respectively, as single stereoisomers (Table 2, entries 3 and 4).

By closely examining the results obtained in the CM involving thiazoles¹⁰ and oxazoles, both similarities and contrasts in terms of reactivity and selectivity were observed. This was typically the case for the 2-phenyl-4-vinyl systems, which could be directly compared. First, the oxazoles appeared to be less reactive than the thiazoles as higher yields/conversions along with shorter reaction times were observed with the latter. This feature may well be due to the fact that homodimerization of the oxazole system was prevalent (type I olefin), while homodimerization was not observed with the 4-vinylthiazole system. Another striking aspect was the discrepancies observed in the reactivity toward deactivated type II olefins such as acrylates and enones. Indeed, in the case of vinyloxazoles **1** and **2**, CM proceeded satisfactorily with enone **3l** and tolerably well with acrylates **3m** and **3n**, whereas vinylthiazoles failed to provide any coupling product under similar conditions. Hence, however closely related the two structures are, they both appear to have a completely different reactivity pattern.

Overall, the use of the CM reaction has proven its potential as a versatile method for coupling vinyl-functionalized oxazole

TABLE 2. Olefin Cross-Metathesis Reaction of 4-Vinyloxazole 2^a

Entry	Olefin	Time [h]	Conversion ^b	Product	Yield ^c [%]	E/Z ^d
1	3a^e	36	63	5a	36	>20/1
2	3d	36	55	5d	27	>20/1
3	3l	36	94	5l	72	>20/1
4	3m	36	90	5m	60	>20/1

^a All reactions were carried out on a 0.11 mmol scale using 1.5 equiv of the selected olefin (unless otherwise specified) in CH₂Cl₂ at 40 °C.

^b Conversion determined by ¹H NMR of the crude reaction mixture.

^c Isolated yield. ^d E/Z ratio determined by ¹H NMR of the crude reaction mixture. ^e Reaction performed using 3 equiv of the olefinic partner.

systems with a variety of olefinic coupling partners. The fact that many known biological active molecules exhibit motifs of this type aroused interest in the use of this method toward new synthetic targets. Implementation of this methodology in this field is currently underway in our laboratory.

Experimental Section

General Procedure for the CM of Vinyl-Functionalized Oxazoles with Various Olefins. To a stirred solution of 2- or 4-vinyl-functionalized oxazole (0.11 mmol) and the selected olefin (0.17 mmol, 1.5 equiv) in CH₂Cl₂ (1 mL) was added either [Ru]-II or [Ru]-III (0.01 mmol, 10 mol %). The reaction mixture was heated under an argon atmosphere at 40 °C until completion (the reactions were monitored by TLC). The solvent was then removed under reduced pressure, and the crude residue was purified by flash column chromatography on silica gel using a gradient of eluent (Et₂O/*n*-pentane: 1/9 to 5/5) or (EtOAc/hexanes: 5/95 to 5/5) to provide the corresponding products (see Tables 1 and 2).

Acknowledgment is made to the Ministère de l'Enseignement Supérieur et de la Recherche for a grant to T.J.H.

Note Added after ASAP Publication. Hoveyda–Grubbs catalyst was misspelled in the version published ASAP February 22, 2008; the corrected version was published February 25, 2008.

Supporting Information Available: General methods, experimental procedures, and reproductions of ¹H and ¹³C NMR data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO702305G

(13) (a) Hari, Y.; Iguchi, I.; Aoyama, T. *Synthesis* **2004**, 1359–1362. (b) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495–2498.