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[4+3] Cycloaddition of Aromatic α,β-Unsaturated Aldehydes and Ketones with Epoxides: One-Step Approach to Synthesize Seven-Membered Oxacycles Catalyzed by Lewis Acid

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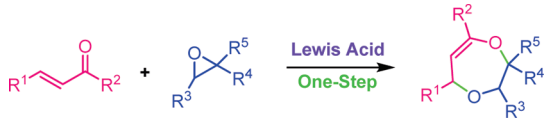
Received February 4, 2010



A novel intermolecular [4 + 3] cycloaddition method to construct 1,4-dioxide seven-membered oxacycles was developed. This one-step method was carried out in the presence of catalytic amount of $(C_2H_5)_2OBF_3$ under mild conditions. Seven-membered oxacycles and some natural compounds could be easily synthesized via this protocol. Control experiments were carried out and possible mechanism for the reaction was proposed. Asymmetric reactions were proceeded and **3e** was obtained with moderate *ee* value.

Search for new methodologies for the selective synthesis of 1,4-dioxide seven-membered oxacycles continues to be of great interest for organic chemists because of the presence of these skeletons in natural products, as well as functionalized organic molecules, such as, marcfortine,[1] paraherquamide,[2] and some other compounds.[3] Unfortunately, unlike methods for the synthesis of five- and six-membered oxacycles, which are known and widely applied, the synthesis of seven-membered oxacycles, especially 1,4-dioxide seven-membered oxacycles, has evolved a smaller array of methods because of the unusual molecular architecture, entropy reasons, ring strain, and the transannular interaction of such compounds.[4] Traditional synthesis of these seven-membered oxacycles are reported usually by intramolecular ring closure reactions,[5] with intricate procedures, complicated byproducts, extreme conditions, and low yields. Therefore, the development of efficient methodologies that enables simple and more concise approaches to generate this kind of oxacycles remains a preeminent challenge in modern organic chemistry. The [4 + 3] cycloaddition reaction is a powerful approach to construct both seven-membered carbocycles[6] and seven-membered nitrogen-containing heterocycles;[7] however, seven-membered oxacycles are rarely synthesized by [4 + 3] cycloaddition method. Herein, we would like to report a novel method to synthesize seven-membered oxacycles via intermolecular [4 + 3] cycloaddition. To the best of our knowledge, it is the first time to report the synthesis of 1,4-dioxide seven-membered oxacycles from epoxides and α,β-unsaturated carbonyls by intermolecular reaction.

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(2) For selected examples, see: (a) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 786–789. (b) Williams, R. M.; Cao, J.; Tsujishima, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2540–2544. (c) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1296–1298. (d) Lee, B. H.; Clothier, M. F.; Johnson, S. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 553–554. (e) López-Gresa, M. P.; González, M. C.; Ciavatta, L.; Ayala, I.; Moya, P.; Primo, J. *J. Agric. Food Chem.* **2006**, *54*, 2921–2925. (f) Stocking, E. M.; Williams, R. M.; Sanz-Cervera, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9089–9098. (g) Williams, R. M.; Cao, J. H.; Tsujishima, H.; Cox, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 12172–12178. (h) Domingo, L. R.; Zaragozá, R. J.; Williams, R. M. *J. Org. Chem.* **2003**, *68*, 2895–2902.

(3) For selected examples, see: (a) Conejo-García, A.; Núñeza, M. C.; Marchal, J. A.; Rodríguez-Serrano, F.; Aránega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Eur. J. Med. Chem.* **2008**, *43*, 1742–1748. (b) Fall, Y.; Vidal, B.; Alonso, D.; Gómez, G. *Tetrahedron Lett.* **2003**, *44*, 4467–4469.

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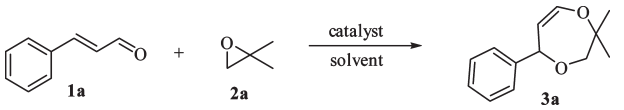
DOI: 10.1021/jo101669t Published on Web 12/30/2010

TABLE 1. Optimized Conditions for [4 + 3] Cycloaddition of Cinnamaldehyde with Isobutylene Oxide[a]



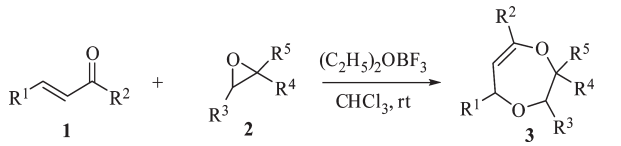
entry	solvent	catalysts	time (h)	yield (%)[b]
1	THF	SmI_2	72	trace
2	CH_2Cl_2	$CuBr_2$	72	9
3	CH_2Cl_2	$ZnCl_2$	72	15
4	CH_2Cl_2	$AlCl_3$	72	32
5	CH_2Cl_2	$SnCl_2$	72	41
6	CH_2Cl_2	$SnCl_4$	72	45
7	CH_2Cl_2	$FeCl_3$	72	55
8	CH_2Cl_2	$(C_2H_5)_2OBF_3$	8	63
9	CH_3OH	$(C_2H_5)_2OBF_3$	8	NR[c]
10	toluene	$(C_2H_5)_2OBF_3$	8	45
11	THF	$(C_2H_5)_2OBF_3$	8	42
12	Et_2O	$(C_2H_5)_2OBF_3$	8	50
13	$CHCl_3$	$(C_2H_5)_2OBF_3$	8	67
14	$CHCl_3$	$(C_2H_5)_2OBF_3$	16	65
15[d]	$CHCl_3$	$(C_2H_5)_2OBF_3$	8	62
16[e]	$CHCl_3$	$(C_2H_5)_2OBF_3$	8	65

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), Lewis acid (5 mol %), solvent (2 mL), room temperature. [b]Isolated yields. [c]NR = no reactions. [d]Reaction was performed at 60 °C. [e]$(C_2H_5)_2OBF_3$ (20 mol %).

Initially, this work was inspired by the original synthesis of 1,3-oxazolidines from imines and epoxides reported by Ishii.[8] It was very interesting that the product was not a five-membered ring compound like Ishii reported[8] when we used cinnamaldehyde as a standard substrate to react with epoxide. According to data of ^{1}H NMR, ^{13}C NMR, IR, and HRMS and the literature,[4a,b,5h,i] we are sure that the product is a seven-membered heterocycle.

With this unexpected detection, our starting point for catalyst screening was carried out. On the basis of the reaction of cinnamicaldehyde **1a** with isobutylene oxide **2a**, some Lewis acids were tried as catalysts. An initial experiment, using Ishii's conditions (SmI_2), was tried, unfortunately, only trace of the target compounds could be obtained (Table 1, entry 2). The use of $CuBr_2$ gave an isolated yield of 9% (Table 1, entry 2). A little bit higher yield was obtained when we changed the catalyst to $ZnCl_2$ (Table 1, entry 3). Although $AlCl_3$ led to a sudden color change, it gave the product in only a 32% yield (Table 1, entry 4). On the contrary, $SnCl_2$ could afford a moderate yield of 41% (Table 1, entry 5), and $SnCl_4$ could afford a higher yield of 45% (Table 1, entry 6). It seems that $FeCl_3$ is an appropriate catalyst with a higher yield of 55%, but long reaction time is needed (Table 1, entry 7). To our delight, $(C_2H_5)_2OBF_3$ gave the highest yield of 63% in a short time (Table 1, entry 8). Thus, $(C_2H_5)_2OBF_3$ is the suitable Lewis acid with moderate acidity neither strong as $AlCl_3$ nor weak as $CuBr_2$ and could sharply short the reaction time. The solvents were subsequently explored (Table 1, entries 8−13). And we found that $CHCl_3$ was the most efficient one among the various solvents. Whether employing higher catalyst loadings or raising the reaction temperature did not lead to any improvement for the reaction, we could conclude that the amount of catalyst and reaction temperature had no significant effect on this reaction (Table 1, entries 14, 15, and 16). Protonic acids, such as sulfuric acid, phosphoric acid and hydrochloric acid, could also be used in this reaction yet with low efficience and failed to give products with yields highter than 10%.

TABLE 2. Expansion of [4 + 3] Cycloaddition of α,β-Unsaturated Carbonyls with Epoxides under Optimized Conditions[a]



entry	R^1	R^2	R^3	R^4	R^5	product	yield (%)[b]	ratio[c]
1	Ph	H	H	Me	Me	**3a**	67	
2	2-furyl	H	H	Me	Me	**3b**	69	
3	4-MePh	Ph	H	M e	Me	**3c**	42	
4	Ph	4-ClPh	H	Me	Me	**3d**	40	
5	Ph	Me	H	Me	Me	**3e**	65	
6	Ph	Me	Me	Me	H	**3f**	68	5:3
7	Ph	Me	H	CH_2Cl	H	**3g**	73	5:2
8	Ph	Me	H	Ph	H	**3h**	66	5:3
9	Ph	Me	-$(CH_2)_4$-		H	**3i**	58	
10	2-furyl	H	Me	Me	H	**3j**	69	1:1
11	Ph	H	Me	Me	H	**3k**	62	3:2

[a]Unless otherwise specified, reaction were carried out in $CHCl_3$ with 1 mmol of **1** and 1 mmol of **2** in the presence of 5 mol % of $(C_2H_5)_2OBF_3$ for 2−8 h. For a detail, see Supporting Information. All the epoxides used are nonoptically pure. [b]**3f**, **3g**, **3h** could be isolated as an isomer, **3j** and **3k** are isolated as the mixture of the isomers. Yields are calculated by the combination of all the isolated products. The absolute configuration was not determined. [c]Determined by ^{1}H NMR.

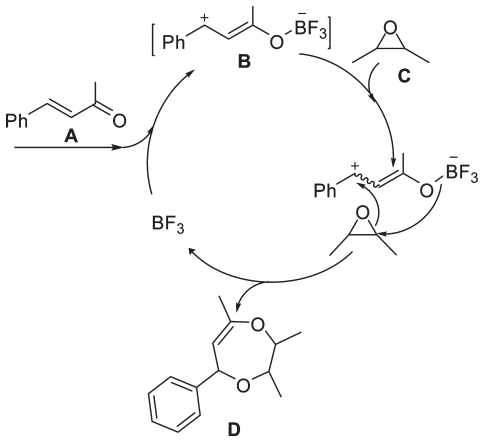
An examination of substrates scope revealed that $(C_2H_5)_2OBF_3$ could tolerate a range of substrates (Table 2). First, several aromatic α,β-unsaturated carbonyls were chosen to react with isobutylene oxide. As can be seen from Table 2, carbonyls with small substituents delivered the products with good yields (Table 2, entries 1, 2, and 5). Lower yields were obtained when these carbonyls bearing bulky hindrance (Table 2, entries 3 and 4). Three different epoxides generated from oxirane were also employed and provided the corresponding cycloaddition adducts efficiently (Table 2, entries 6, 7, and 8). Delightedly, the adduct with the highest yield of 73% was achieved by benzylideneacetone with (±) 2-(chloromethyl)-oxirane (Table 2, entry 7). Even the cyclohexene oxide can provide a 58% yield product (Table 2, entry 9). Unlike **3f**, **3g**, and **3h** could be successfully separated from the isomers, both **3j** and **3k** were isolated only as mixture of isomers in different ratio (Table 2, entries 10 and 11).[9] Interestingly, **3i** is a pure compound that is quite different from **3f**, **3g**, **3h**, **3j**, and **3k**, perhaps the aliphatic six-membered ring, as an important factor, is responsible for this. In general, substituents on epoxides have no significant effect on the reactions, while substituents on the aromatic α,β-unsaturated aldehydes and aromatic α,β-unsaturated ketones do have great influence on the reactions.

When aromatic α,β-unsaturated acids and aromatic α,β-unsaturated esters were used as substrates to react with epoxides, no seven-membered oxacycles could be obtained, indicating that this reaction was not applicable to these substrates. This is probably because of the instability of the seven-membered oxacycles generated from the aromatic α,β-unsaturated acids and aromatic α,β-unsaturated esters.

(8) Nishitani, T.; Shiraishi, H.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2000**, *41*, 3389–3393.

(9) For details of the spectroscopic data, see Supporting Information.

SCHEME 1. Plausible Mechanism



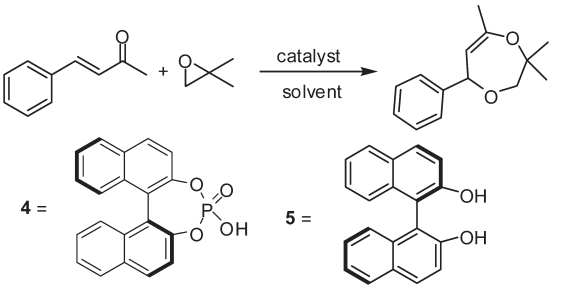
It is worth mentioning that aliphatic α,β-unsaturated aldehyde and aliphatic α,β-unsaturated ketones were also used as substrates to examine the [4 + 3] cycloaddition. Unfortunately, neither of them could provide corresponding seven-membered oxacycles. Probably because of the higher reactivity of these enolizable aldehydes.

To understand the reaction, control experiments were carried out. Addition of benzylideneacetone to a $CHCl_3$ solution containing $(C_2H_5)_2OBF_3$ led to the system with an immediate color change from light yellow to brown, then 2,3-dimethyoxirane was subsequently added and 1,4-dioxepine derivative **3f** was obtained successfully. But when 2,3-dimethyoxirane was first added to the $CHCl_3$ solution containing $(C_2H_5)_2OBF_3$ and then benzylideneacetone was added, no product was detected. This suggests that the reaction is initiated by BF_3 and α,β-unsaturate carbonyl but not by epoxide. A possible mechanism is proposed as following (Scheme 1). α,β-Unsaturate carbonyl **A** reacts with BF_3 to give a reactive intermediate **B**, which could be stabilized by both phenyl and the double bound. Then **B** immediately reacts with epoxide **C**, which not only gets 1,4-dioxepine **D** but also releases the BF_3 at the same time.

It is well-known that the asymmetric reactions attract more and more attention. As part of the examination to this system, we tried to find suitable chiral catalyst to enhance the enantioselectivity and diastereoselectivity, **4** and **5** were used as catalysts. Unfortunately, the use of **4** only gave **3e** in 16% yield and 23% *ee* (Table 3, entry 1). When we changed the catalyst to **5**, no product could be obtained (Table 3, entry 2). Moderate yield **3e** with 27.3% *ee* was obtained when 5% **5** and 5% $Ti(O^iPr)_4$ were employed (Table 3, entry 3). It is delightedly that 53% yield and 43.5% *ee* **3e** could be provided in the present of 5% **5** and 5% $Ti(O^iPr)_4$ when changing the solvent from DCM to toluene (Table 3, entry 4). This is the best result which has been achieved by our group until now, because both changing the ratio of **5** and $Ti(O^iPr)_4$ (Table 3, entries 5 and 6) and lowering the temperature failed to afford higher *ee* (Table 3, entry 7). Studies on the diastereo- and enantioselectivity are proceeding in our group.

In summary, we have developed a novel intermolecular [4 + 3] cycloaddition of α,β-unsaturated carbonyls with epoxides. This one-step reaction is carried out by using $(C_2H_5)_2OBF_3$ as catalyst under mild conditions and gives 1,4-dioxide derivatives with satisfactory yields in a short time. It enriches the methodologies for the synthesis of seven-membered oxacycles. Also, the reaction could be a useful method for the preparation of a great number of natural compounds. Preliminary exploration of the asymmetric synthesis of these seven-membered oxacycles was carried out and product with moderate *ee* value was obtained. Futher studies are currently under investigation and will be presented in a due time.

TABLE 3. Asymmetric Synthesis of 3e Catalyzed by 4 and 5[a]



entry	catalysts	solvent	temperature (°C)	yield (%)[b]	*ee* (%)[c]
1	**4**	DCM	rt	16	23.0
2	**5**	DCM	rt	NR[d]	
3	**5**, $Ti(O^iPr)_4$ (1:1)	DCM	rt	55	27.3
4	**5**, $Ti(O^iPr)_4$ (1:1)	toluene	rt	53	43.5
5	**5**, $Ti(O^iPr)_4$ (2:1)	toluene	rt	47	42.0
6	**5**, $Ti(O^iPr)_4$ (1:2)	toluene	rt	35	14.0
7	**5**, $Ti(O^iPr)_4$ (1:1)	toluene	0	5	43.0

[a]Unless otherwise specified, reactions were performed on a 1 mmol scale in 2.5 mL solvent in the presence of 5% catalyst at room temperature for 4 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. The absolute configuration was not determined. [d]NR = no reaction.

Experimental Section

General Procedure. To a solution of $(C_2H_5)_2OBF_3$ (0.05 mmol) in $CHCl_3$ (2.5 mL), α,β-unsaturated carbonyl (1.0 mmol) was added. The mixture was cooled in an ice bath. Then epoxide (1 mmol) was added dropwise and the resulting mixture was stirred for 2−8 h at room temperature. The reactions were monitored by TLC (1: 5 ethyl acetate: petroleum ether). After evaporation of the solvents, the residue was purified by silica gel column chromatography (1: 40 ethyl acetate: petroleum ether).

2-Dimethyl-5-phenyl-3,5-dihydro-2*H*-1,4-dioxepine (3a): pale yellow oil; R_f = 0.58 (1:5 ethyl acetate/petroleum ether); 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.32 Hz, 2H), 7.33 (m, 2H), 7.27 (d, J = 9.16 Hz, 1H), 6.77 (d, J = 15.96 Hz, 1H), 6.18 (dd, J = 9.60, 6.36 Hz, 1H), 5.53 (d, J = 6.36 Hz, 1H), 3.78 (d, J = 7.76, H_1), 3.69 (d, J = 7.80, H_2), 1.39 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 134.9, 128.6 (2C), 128.4, 127.1(2C), 126.2, 103.6, 79.2, 76.3, 26.8, 25.2; IR (KBr) 3030, 1722,1675, 1495, 1163, 1141, 961, 890, 748 cm^{-1}; HRMS (ESI+) calcd for $C_{13}H_{16}O_2$, 204.1150; Found 204.1151.

5-(Furan-2-yl)-2,2-dimethyl-3,5-dihydro-2*H*-1,4-dioxepine (3b): pale yellow oil; R_f = 0.62 (1:5 ethyl acetate/petroleum ether); 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 1.28 Hz, 1H), 6.56 (d, J = 15.88 Hz, 1H), 6.36 (dd, J = 2.64, 1.76 Hz, 1H), 6.31 (d, J = 3.28, 1H), 6.11 (dd, J = 9.72, 6.16 Hz, 1H), 5.49 (d, J = 6.08, Hz 1H), 3.75 (d, J = 7.76 Hz, H_1), 3.67 (d, J = 7.76 Hz, H_2), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 142.7, 124.7, 122.4, 111.5, 109.7, 103.2, 79.2, 76.2, 26.8, 25.2; IR (KBr) 2924, 1722, 1463,1258, 1138, 1064, 1013, 955, 733 cm^{-1}; HRMS (ESI+) calcd for $C_{11}H_{14}O_3$, 194.0943; Found 194.0903.

2,2,7-Trimethyl-5-phenyl-3,5-dihydro-2*H*-1,4-dioxepine (3e): pale yellow oil; R_f = 0.60 (1:5 ethyl acetate/petroleum ether);

65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.36 Hz, 2H), 7.34−7.30 (m, 2H), 7.25 (d, J = 6.56, 1H) 6.72 (d, J = 15.96 Hz, 1H), 6.21 (d, J = 15.96 Hz, 1H), 3.78 (d, J = 8.08 Hz, H_1), 3.69 (d, J = 8.08 Hz, H_2), 1.56 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 131.5, 129.3, 128.7 (2C), 127.9, 126.8 (2C), 108.3, 79.7, 75.3, 27.6, 27.1, 26.1; IR (KBr) 3060, 1722, 1458, 1369, 1222, 1173, 1099, 1047, 961, 890, 748, 692 cm^{-1}; HRMS (ESI+) calcd for $C_{14}H_{18}O_2$, 218.1307; Found 218.1250.

2,3,7-Trimethyl-5-phenyl-3,5-dihydro-2*H*-1,4-dioxepine (3f$_1$): white oil; R_f = 0.68 (1:5 ethyl acetate/petroleum ether); 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.36 Hz, 2H), 7.34−7.30 (m, 2H), 6.71 (d, J = 15.92 Hz, 1H), 6.17 (d, J = 15.92 Hz, 2H), 4.24 (m, 1H), 4.23 (m, 1H), 1.58 (s, 3H), 1.21 (d, J = 4.52 Hz,3H), 1.18 (d, J = 4.48 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 130.8, 129.3, 128.6 (2C), 127.8, 126.8 (2C), 106.1, 73.9 (2C), 27.2, 15.5 (2C); HRMS (ESI+) calcd for $C_{14}H_{18}O_2$, 218.1307; Found 218.1273.

2-(Chloromethyl)-7-methyl-5-phenyl-3,5-dihydro-2*H*-1,4-dioxepine (3g$_1$): pale yellow oil; R_f = 0.68 (1:5 ethyl acetate/petroleum ether); 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 1.52 Hz, 2H), 7.35 (m, 2H), 7.27 (m, 1H), 6.70 (d, J = 15.96 Hz, 1H), 6.12 (d, J = 15.92 Hz, 1H), 4.34 (m, 1H), 4.05 (m, H_1), 3.95 (m, H_2), 3.62 (m, H_a), 3.52 (m, H_b), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 130.1, 129.3, 128.7(2C), 128.2, 126.9(2C), 109.2, 75.7, 67.4, 44.8, 26.1; HRMS (ESI+) calcd for $C_{13}H_{15}ClO_2$, 238.0761; Found 238.0771.

4-Methyl-2-phenyl-5*a*,6,7,8,9,9*a*-hexahydro-2*H*-benzo[*b*][1,4]-dioxepine(3i): Pale yellow oil; R_f = 0.61 (1:5 ethyl acetate/petroleum ether); 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.41−7.43 (m, 2H), 7.34−7.30 (m, 2H) 7.26−7.24 (m, 1H), 6.76 (d, J = 15.92 Hz, 1H), 6.27 (d, J = 15.96 Hz, 1H), 3.35−3.38 (m,1H), 3.34−3.30 (m, 1H), 2.16−2.15 (m, 2H), 1.83−1.80 (m, 2H), 1.59 (s, 3H), 1.51−1.46 (m, 2H), 1.30−1.26 (m, 2H); ^{3}C NMR (100 MHz, $CDCl_3$) δ 136.5, 130.9, 129.1, 128.6(2C), 127.9,126.9(2C), 107.3, 80.7, 80.2, 29.0, 28.8, 26.3, 23.8(2C); HRMS (ESI+) calcd for $C_{16}H_{20}O_2$, 244.1463; Found, 244.1462.

Acknowledgment. We thank the National 973 Program (NO. 2010CB732202) Foundation for financial support.

Supporting Information Available: General experimental method, ^{1}H NMR, ^{13}C NMR, and MS data for **3a**−**3i**, IR spectra data for **3a**, **3b**, **and 3e**, and copies of ^{1}H and ^{13}C NMR spectra for the all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.