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Lewis Acid-Catalyzed Cascade Reactions of Arylmethylenecyclopropanes with 1,1,3-Triarylprop-2-yn-1-ols or Their Methyl Ethers

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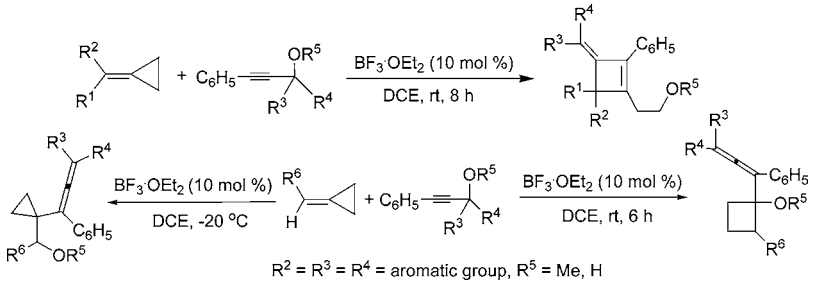
ABSTRACT



Arylmethylenecyclopropanes 1 can react with 3-methoxy-1,3,3-triarylprop-1-yne 2 or 1,1,3-triarylprop-2-yn-1-ol 2-OH to give the corresponding functionalized methylenecyclobutene, cyclobutane, and cyclopropane derivatives in the presence of Lewis acid BF_3·OEt_2 under mild conditions. A plausible Meyer–Schuster rearrangement mechanism has been proposed.

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that serve as useful building blocks in organic synthesis.[1] MCPs undergo a variety of ring-opening/cycloaddition reactions in the presence of transition metals or Lewis acids because the relief of ring strain can provide a powerful thermodynamic driving force.[2,3] Thus far, a number of interesting cycloadditions and ring enlargements of MCPs have been explored. For example, Yamamoto et al. reported cycloaddition reactions of MCPs with aldehydes and imines, using a palladium catalyst, that afforded the corresponding tetrahydrofuran and pyrrolidine skeletons in good yields.[4] In addition, we and others have developed a number of heterocycle-forming reactions from MCPs and

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(1) For recent reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal*. **2002**, *344*, 111. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev*. **2003**, *103*, 1213. (c) Nakamura, E.; Yamago, S. *Acc. Chem. Res*. **2002**, *35*, 867. For the synthesis of MCPs, see: Brandi, A.; Goti, A. *Chem. Rev*. **1998**, *98*, 598.

(2) Selected recent articles about transition metal-catalyzed reactions of MCPs: (a) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem*. **2001**, *66*, 270. (b) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc*. **1996**, *118*, 10676. (c) Lautens, M.; Ren, Y. *J. Am. Chem. Soc*. **1996**, *118*, 9597. (d) Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc*. **2004**, *126*, 10540. (e) Shi, M.; Wang, B.-Y.; Huang, J.-W. *J. Org. Chem*. **2005**, *70*, 5606. (f) Nakamura, I.; Itagaki, H.; Yamamoto, Y. *J. Org. Chem*. **1998**, *63*, 6458. (g) Tsukada, N.; Hibuya, A.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc*. **1997**, *119*, 8123. (h) Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc*. **2000**, *122*, 11015. (i) Scott, M. E.; Bethuel, Y.; Lautens, M. *J. Am. Chem. Soc*. **2007**, *129*, 1482.

(3) Selected recent articles about Lewis acid-mediated reactions of MCPs: (a) Shi, M.; Xu, B. *Org. Lett*. **2002**, *4*, 2145. (b) Xu, B.; Shi, M. *Org. Lett*. **2003**, *5*, 1415. (c) Huang, X.; Zhou, H.-W. *Org. Lett*. **2002**, *4*, 4419. (d) Huang, J.-W.; Shi, M. *Tetrahedron Lett*. **2003**, *44*, 9343 and references cited therein.

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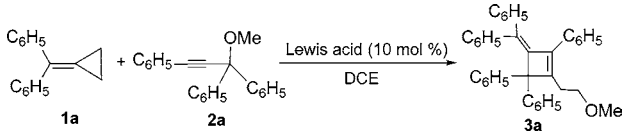
aldehydes or imines as well as ring enlargements of MCPs in the presence of Lewis or Brønsted acids.[5,6] Herein, we wish to report an interesting Lewis acid-catalyzed cascade reaction of MCPs **1** with 3-methoxy-1,3,3-triarylprop-1-yne **2** or 1,1,3-triarylprop-2-yn-1-ol **2**-OH to produce functionalized methylenecyclobutene, cyclobutane, and cyclopropane derivatives **3**, **4**, and **5** in moderate to good yields under mild conditions.

Initial examinations with diphenylmethylenecyclopropane (**1a**, 0.2 mmol) and 3-methoxy-1,3,3-triphenylprop-1-yne (**2a**, 0.2 mmol) as the substrates in the presence of various Lewis acids (10 mol %) in 1,2-dichloroethane (DCE) were aimed at determining the best catalyst for this intermolecular reaction and the results of these experiments are summarized in Table 1. We found that when using $Bi(OTf)_3$ and $Sn(OTf)_2$ (10 mol %) as Lewis acids, an interesting functonalized methylenecyclobutene derivative **3a** was formed in 18% and 13% yields at room temperature, respectively, although no reaction occurred, or complex product mixtures were obtained with use of $Yb(OTf)_3$ or $Sc(OTf)_3$ (10 mol %) as a Lewis acid (Table 1, entries 2−5). In the presence of TfOH, a Brønsted acid, trace of **3a** was produced (Table 1, entry 1). However, in the presence of $BF_3{\cdot}OEt_2$ under identical conditions, **3a** was produced in 34% yield within 6 h (Table 1, entry 6). Increasing the employed amounts of $BF_3{\cdot}OEt_2$ or raising the reaction temperature did not improve the yields of **3a** under identical conditions (Table 1, entries 7−11). Next, we attempted to improve the yield of **3a** by adjusting the ratios of **1a** and **2a** as well as by prolonging the reaction time. The results are shown in Table 2. As can be seen from Table 2, when **1a** (1.0 equiv) and **2a** (1.5 equiv) were used, **3a** was produced in 54% yield within 6 h and when **1a** (1.0 equiv) and **2a** (2.0 equiv) were used, **3a** was produced in 65% yield after 8 h (Table 2, entries 1 and 2). The use of an excess amount of **2a** facilitates this reaction because **2a** itself can rearrange to an allenic product in the presence of Lewis acid. Further increasing the amount of **2a** and prolonging the reaction time did not improve the yield of **3a** (Table 2, entries 3 and 4). Solvent effects have been examined with $BF_3{\cdot}OEt_2$ (10 mol %) at room temperature in dichloromethane (DCM), toluene, acetonitrile, THF, pentane, and ethanol. In THF or ethanol, no reaction occurred (Table 2, entries 8 and 10). In toluene and pentane, a trace of **3a** was formed, and in MeCN, complex product mixtures were obtained (Table 2, entries 6, 7, and 9). We found that DCM is also the solvent of choice to give **3a** in 58% yield under otherwise identical conditions (Table 2, entry 5). Therefore, the optimized reaction conditions are to carry out the reaction in DCE or DCM at room temperature with **1a** (1.0 equiv) and **2a** (2.0 equiv) in the presence of $BF_3{\cdot}OEt_2$ (10 mol %) for 8 h.

Under these optimal reaction conditions, we next carried out this methylenecyclobutene-forming reaction using a variety of starting materials **1** and 3-methoxy-1,3,3-triarylprop-1-ynes **2**. The results are summarized in Table 3. As can be seen from Table 3, the corresponding methylenecyclobutene derivatives **3** were obtained in 40−65% yields (Table 3, entries 1−8). Substituents on the aromatic rings of **1** and **2** have little influence on the reaction. By using

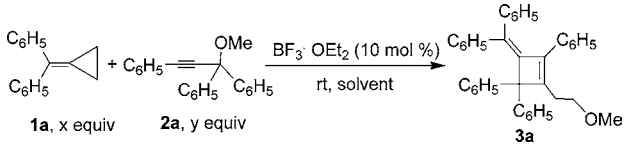
Table 1. Optimization of the Reaction Conditions



entry[a]	Lewis acid	temp (°C)	time (h)	yield of **3a** (%)[b]
1	TfOH	rt	12	trace
2	$Bi(OTf)_3$	rt	8	18
3	$Sc(OTf)_3$	rt	8	complex
4	$Yb(OTf)_3$	rt	24	NR
5	$Sn(OTf)_2$	rt	12	13
6	$BF_3{\cdot}OEt_2$	rt	6	34
7	$BF_3{\cdot}OEt_2$	rt	6	32[c]
8	$BF_3{\cdot}OEt_2$	rt	6	33[d]
9	$BF_3{\cdot}OEt_2$	rt	6	13[e]
10	$BF_3{\cdot}OEt_2$	40	6	34
11	$BF_3{\cdot}OEt_2$	60	6	33

[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (0.2 mmol), and Lewis acid (10 mol %) in various solvents (2.0 mL). [b] Isolated yields. [c] $BF_3{\cdot}OEt_2$ (20 mol %) was used. [d] $BF_3{\cdot}OEt_2$ (100 mol %) was used.

Table 2. Further Optimization of the Reaction Conditions



entry	x	y	solvent	time (h)	yield of **3a** (%)[a]
1	1	1.5	DCE	6	54
2	1	2	DCE	8	65
3	1	2.5	DCE	10	41
4	1	3	DCE	10	52
5	1	2	DCE	10	58
6	1	2	Toulene	12	trace
7	1	2	MeCN	12	complex
8	1	2	THF	24	NR
9	1	2	pentane	24	trace
10	1	2	EtOH	24	NR

[a] Isolated yields.

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(5) (a) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175. (b) Shi, M.; Shao, L.-X.; Xu, B. *Org. Lett.* **2003**, *5*, 579. (c) Shao, L.-X.; Xu, B.; Huang, J.-W.; Shi, M. *Chem. Eur. J.* **2006**, *12*, 510. (d) Huang, J.-W.; Shi, M. *Synlett* **2004**, 2343. (e) Patient, L.; Berry, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1015.

(6) (a) Ma, S.-M.; Zhang, J.-L. *J. Am. Chem. Soc.* **2003**, *125*, 12386. (b) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312. (c) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028. (d) Scott, M. E.; Han, W.; Lautens, M. *Org. Lett.* **2004**, *6*, 3309. (e) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045. Ring enlargement of MCPs: (f) Shi, M.; Liu. L. P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430. (g) Furstner, A.; Aissa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306.

Table 3. Construction of Methylenecyclobutenes from **1** and **2**

entry	R^1/R^2	R^3/R^4	R^5	yield of **3** (%)[a]
1	*p*-ClC_6H_4/C_6H_5, **1b**	**2a**	Me	**3b**, 55
2	*p*-MeC_6H_4/*p*-MeC_6H_4, **1c**	**2a**	Me	**3c**, 56
3	*p*-ClC_6H_4/*p*-ClC_6H_4, **1d**	**2a**	Me	**3d**, 54
4	*p*-FC_6H_4/*p*-FC_6H_4, **1e**	**2a**	Me	**3e**, 59
5	**1a**	*p*-$MeOC_6H_4$/*p*-$MeOC_6H_4$, **2b**	Me	**3f**, 65[b]
6	**1a**	*p*-FC_6H_4/*p*-FC_6H_4, **2c**	Me	**3g**, 40[c]
7	**1a**	*p*-MeC_6H_4/*p*-MeC_6H_4, **2d**	Me	**3h**, 63
8	**1a**	*p*-MeC_6H_4/C_6H_5, **2e**	Me	**3i**, 54[d]
9	**1a**	**2a**-OH	H	**3j**, 36
10	**1a**	**2c**-OH	H	**3k**, 30
11	**1a**	**2d**-OH	H	**3l**, 50

[a] Isolated yields. [b] 15% of **1a** was recovered. [c] 10% of **1a** was recovered. [d] 10% of **1a** was recovered and mixtures of cis- and trans-isomer (1:1) were obtained.

1,1,3-triarylprop-2-yn-1-ols **2a**-OH, **2c**-OH, and **2d**-OH, in which R^5 = H, as the substrates, the corresponding methylenecyclobutene derivatives **3j**, **3k**, and ***3l*** (R^5 = H) were obtained in 30−50% yields (Table 2, entries 9−11). Product structures of **3a**−***l*** were determined by ^1H and ^{13}C NMR spectroscopic data, HRMS, microanalysis. Furthermore, the X-ray crystal structure of **3a** was determined and its CIF data are presented in the Supporting Information (Figure 1).[7]

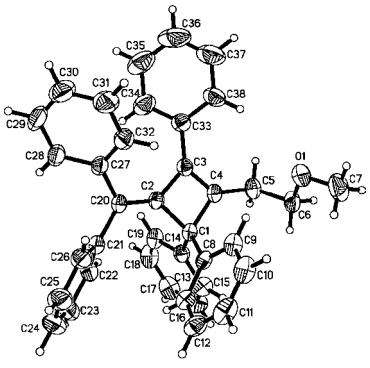
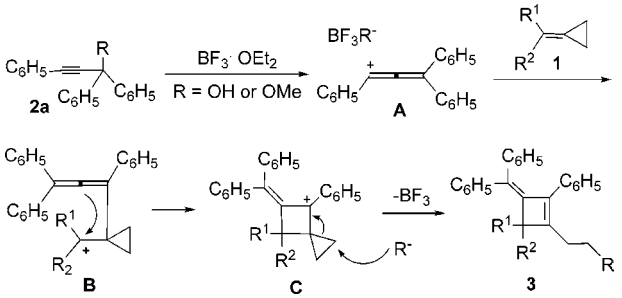


Figure 1. ORTEP drawing of **3a**.

A plausible reaction mechanism is outlined in Scheme 1. In the presence of BF_3·OEt_2, **2a** produces cationic intermediate **A** via a Meyer−Schuster rearrangement,[8] which reacts with MCP **1** to afford intermediate **B** stabilized by two aromatic rings and one cyclopropane group.[9] Intramolecular cyclization gives intermediate **C**, which undergoes nucleophilic attack by the counteranion to provide product **3**.

Scheme 1. Proposed Mechanism for the Formation of **3**



Interestingly, as for monoaromatic group substituted MCP **1f**, an allenic group attached cyclobutane derivative **4a**, which was unambiguously determined by X-ray diffraction (Figure 2),[10] was formed in 40% yield at room temperature (20 °C)

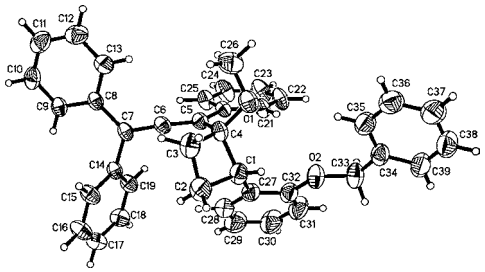


Figure 2. ORTEP drawing of **4a**.

(Table 4, entry 1). For monoaromatic group substituted MCPs **1g**−**j**, similar results were obtained for other 3-methoxy-1,3,3-triarylprop-1-ynes **2** or 1,1,3-triaryl-prop-2-yn-1-ols **2**-OH under identical conditions (Table 4, entries 2−7). As for aliphatic MCP **1k**, a similar adduct **4h** was obtained in 52% yield (Table 4, entry 8).

In addition, under the standard conditions at −20 °C, the corresponding cyclopropane derivatives **5** bearing an allenic moiety were formed in 30−55% yields for MCPs **1f**−**h** and ***1l***, indicating the formation of cationic intermediate **B** shown in Scheme 1 (Table 5).

On the basis of the above results, a plausible reaction mechanism for the formation of **4** and **5** is outlined in Scheme

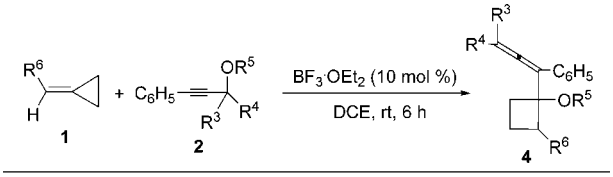
(7) The crystal data of **3a** have been deposited in the CCDC with number 644870. Empirical formula, $C_{38}H_{32}O$; formula weight, 504.64; crystal color/habit, colorless/prismatic; crystal system, triclinic; lattice type, primitive; lattice parameters, a = 10.9684(13) Å, b = 11.1701(14) Å, c = 12.9433(15) Å, α = 87.150(2)°, β = 67.964(2)°, γ = 81.135(2)°, V = 1452.3(3) Å^3; space group, $P\bar{1}$; Z = 2; D_{calc} = 1.154 g/cm^3; F_{000} = 536; diffractometer, Rigaku AFC7R; residuals *R*/*Rw*, 0.0524/0.1271.

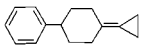
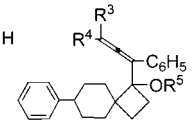
(8) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.

(9) For a review of cyclopropylmethyl cations, see: Richey, H. G., Jr. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1972; Vol. III, Chapter 25.

(10) The crystal data of **4a** have been deposited in the CCDC with number 650905. Empirical formula, $C_{39}H_{34}O_2$; formula weight, 534.66; crystal color/habit, colorless/prismatic; crystal system, monoclinic; lattice type, primitive; lattice parameters, a = 11.9815(12) Å, b = 28.144(3) Å, c = 9.7933(10) Å, α = 90°, β = 111.828(2)°, γ = 90°, V = 3065.6(5) Å^3; space group, $P2(1)/c$; Z = 4; D_{calc} = 1.158 g/cm^3; F_{000} = 1136; diffractometer, Rigaku AFC7R; residuals *R*/*Rw*, 0.0520/0.1163.

Table 4. Construction of Cyclobutane Derivatives from MCPs **1f−j** and Aldehydes

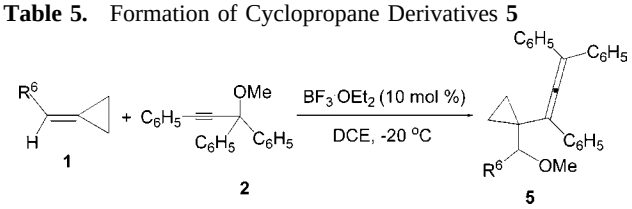


entry[a]	R^6	R^3/R^4	R^5	yield of **4** [%][b]
1	*o*-$BnOC_6H_4$, **1f**	**2a**	Me	**4a**, 40
2	*o*-$MeOC_6H_4$, **1g**	**2a**	Me	**4b**, 54
3	*o*-$TBDPSOC_6H_4$, **1h**	**2a**	Me	**4c**, 30
4	*p*-BrC_6H_4, **1i**	**2a**-OH	H	**4d**, 41
5	**1i**	*p*-ClC_6H_4/*p*-ClC_6H_4, **2f**-OH	H	**4e**, 33
6	*p*-ClC_6H_4, **1j**	**2a**-OH	H	**4f**, 23
7	**1f**	**2d**	Me	**4g**, 30
8	 **1k**	**2a**-OH	H	 **4h**, 52

[a] Ratio of **1**:**2** = 1:2. [b] Isolated yields.

2. The addition of cationic intermediate **A** to monoaromatic group substituted MCP **1** produces intermediate **D**, which undergoes ring expansion to give intermediate **E** at higher temperature (rt, 20 °C). The nucleophilic attack by the counteranion provides product **4**. On the other hand, at lower

Table 5. Formation of Cyclopropane Derivatives **5**



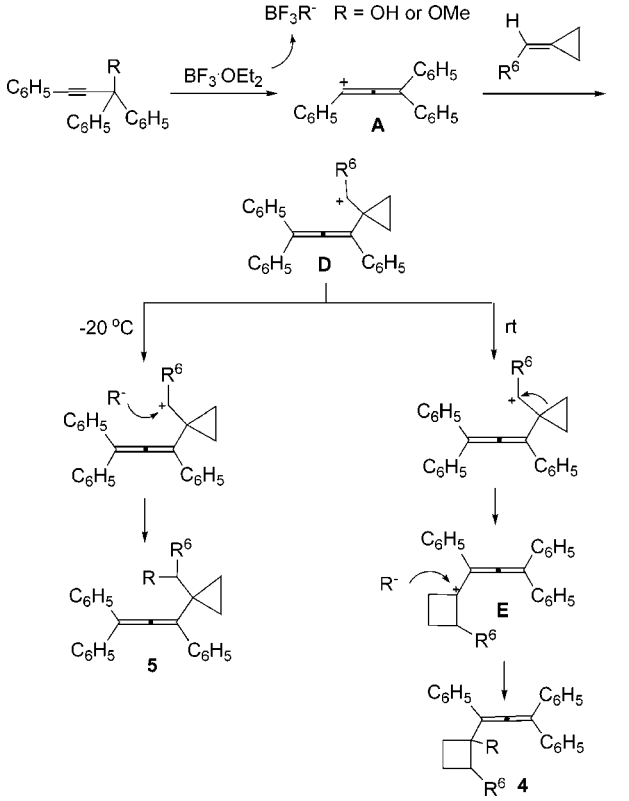
entry[a]	R^6	yield of **5** (%)[b]
1	*o*-$BnOC_6H_4$, **1f**	**5a**, 55
2	*o*-$MeOC_6H_4$, **1g**	**5b**, 40
3	*o*-$TBDPSOC_6H_4$, **1h**	**5c**, 35
4	*p*-$MeOC_6H_4$, **1l**	**5d**, 30

[a] Ratio of **1**:**2** = 1:2. [b] Isolated yields.

temeparture (−20 °C), nucleophilic attack by the counteranion at intermediate **D** takes place to provide product **5** directly, presumably due to the higher reaction temperature perhaps facilitating the ring-expansion process.

The difference in stability and steric bulkiness of cationic intermediates **B** and **D** causes the different reaction pathway between diarylmethylenecyclopropanes **1a−e** and monoaromatic group substituted MCPs **1f−j**. The intramolecular rearrangement of intermediate **D** and the reaction of R^- with intermediate **D** can more easily take place, therefore exclusively affording **4** and **5** in moderate to good yields, respectively (Scheme 2).

Scheme 2. Plausible Mechanism for the Formation of **4** and **5**



In conclusion, we have found an interesting procedure where diarylmethylenecyclopropanes and monoaromatic group substituted methylenecyclopropanes react with 3-methoxy-1,3,3-triarylprop-1-ynes or 1,1,3-triarylprop-2-yn-1-ols to provide functionalized methylenecyclobutene derivatives and cyclobutane or cyclopropane derivatives bearing an allenic moiety catalyzed by Lewis acid under mild conditions. A plausible reaction mechanism has been proposed that is based on a Meyer−Schuster reaction pathway. With use of this procedure, a series of novel functionalized methylenecyclobutene derivatives and cyclobutane or cyclopropane derivatives were obtained selectively, with easily available reagents under mild conditions, in moderate to good yields. Further studies regarding the mechanistic details and scope of this process are in progress.

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Supporting Information Available: Spectroscopic data of all the new compounds in Tables 1−5, the detailed descriptions of experimental procedures, and X-ray data for compounds **3a** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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