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Rauhut–Currier-Type Reaction with Morita–Baylis–Hillman Carbonates of 2-Cyclohexenone and Alkylidenemalononitriles To Access Chromene Derivatives

Jing Peng,[†] Xin Huang,[†] Peng-Fei Zheng,[‡] and Ying-Chun Chen*,[†,‡]

Key Laboratory of Drug-Targeting and Drug Delivery System of the Ministry of Education, Department of Medicinal Chemistry, West China School of Pharmacy and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China, and College of Pharmacy, Third Military Medical University, Shapingba, Chongqing 400038, China

ycchen@scu.edu.cn

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ABSTRACT

An assembly of MBH carbonates of cyclohexen-2-one and alkylidenemalononitriles was investigated by the catalysis of a tertiary amine, which efficiently provides aromatic chromene derivatives with dense functionalities through a domino Rauhut–Currier-type reaction, cyclization, and isomerization process under metal-free conditions.

Direct usage of activated alkenes as enolate precursors under the catalysis of a nucleophilic tertiary phosphine or amine represents an efficient and atom-economical protocol in organic synthesis. While significant progress has been made by using carbonyl compounds or imines as the electrophiles [Morita–Baylis–Hillman (MBH) reaction or aza-version],[1] the related Rauhut–Currier reaction,[2] in which Michael acceptors are utilized as the electrophilic partners, has been much less explored due to the lack of selectivity. Thus, most successful Rauhut–Currier reactions are conducted in an intramolecular manner at the current stage.[3,4]

On the other hand, MBH acetates or carbonates still contain an activated alkene group, which enable an attack by a nucleophilic Lewis base (LB) catalyst, generating either electrophilic salts[5] **I** or nucleophilic zwitterionic ylides[6] **II** after a deprotonation process, as outlined in Scheme 1. While fruitful results have been reported through such latent transformations with MBH derivatives from simple

[†] Sichuan University.
[‡] Third Military Medical University.

(1) For selected reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Ma, G.-N.; Jiang, J.-J.; Shi, M.; Wei, Y. *Chem. Commun.* **2009**, 5496. (c) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. (d) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447. (e) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614. (f) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (g) Mansilla, J.; Saá, J. M. *Molecules* **2010**, *15*, 709.

(2) Rauhut, M. M.; Currier H. (American Cyanamid Co.) U.S. Patent 3, 074, 999, 1963 [*Chem. Abstr.* **1963**, *58*, 11224a].

(3) For reviews on Rauhut–Currier reaction, see: (a) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (b) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069. (c) Xie, P.; Huang, Y. *Eur. J. Org. Chem.* **2013**, 6213.

(4) For selected examples of intermolecular Rauhut–Currier reaction, see: (a) Reynolds, T. E.; Binkley, M. S.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 2449. (b) Zhong, C.; Chen, Y.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 1279. (c) Zhao, Q.-Y.; Pei, C.-K.; Guan, X.-Y.; Shi, M. *Adv. Synth. Catal.* **2011**, *353*, 1973. (d) Shi, Z.; Yu, P.; Loh, T.-P.; Zhong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7825.

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acrylates or vinyl ketones,[7] there are more rare examples with MBH derivatives from β-substituted activated alkenes, such as cyclohexen-2-one,[8] under the above-mentioned catalysis. Since MBH carbonates from cyclohexen-2-one contain a stronger acidic δ'-C−H bond adjacent to carbonyl group, it is feasible that multifunctional zwitterionic dienolates[9] **III** might be generated after S_N2' attack by a tertiary amine followed by a cascade elimination and deprotonation process, rather than the formation of ylide-type intermediates **II** (Scheme 1). Subsequently, a δ'-regioselective[10] extended Rauhut−Currier-type addition to suitable Michael acceptors might be developed in an intermolecular pattern. Here, we would like to present the first chemoselective assembly of MBH carbonates of cyclohexen-2-one and alkylidenemalononitriles catalyzed by a tertiary amine, which efficiently provides aromatic chromene derivatives with dense functionalities through domino reactions under metal-free conditions.[11]

Scheme 1. Alternative Reaction Pathway of MBH Carbonates of Cyclohexen-2-one

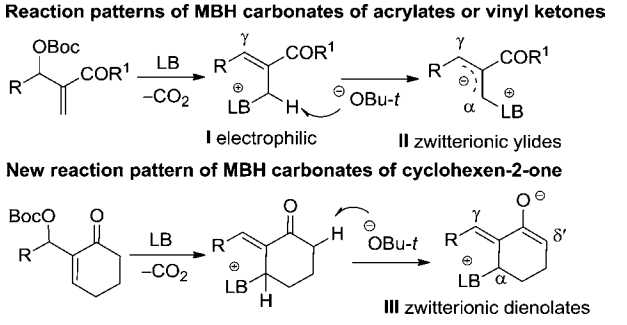
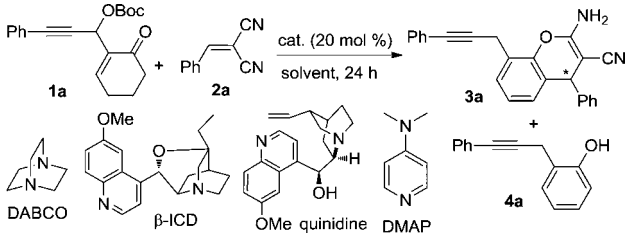


Table 1. Screening Conditions for Assembly of MBH Carbonate **1a** and Benzylidenemalononitrile **2a**[a]



entry	cat.	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	DABCO	CH_3CN	rt	**3a**, 67	/
2	DMAP	CH_3CN	rt	/	/
3	PPh_3	CH_3CN	rt	NR	/
4	quinidine	CH_3CN	50	**3a**, 27	0
5	β-ICD	CH_3CN	50	**3a**, 61	0
6	DABCO	CH_3CN	35	**3a**, 77	/
7	DABCO	CH_3CN	50	**3a**, 76	/
8	DABCO	toluene	50	**3a**, <10	/
9	DABCO	THF	50	**3a**, <10	/
10	DABCO	$CHCl_3$	50	**3a**, 57	/
11[d]	DABCO	CH_3CN	35	**3a**, 76	/

[a] Unless noted otherwise, reactions were performed with **1a** (0.1 mmol), **2a** (0.2 mmol), and a catalyst (20 mol %) in solvent (0.5 mL) for 24 h. [b] Yield of isolated product **3a**. [c] Determined by chiral HPLC analysis. [d] In 0.2 mL of CH_3CN for 12 h.

The initial reaction of MBH carbonate **1a**[8d] and benzylidenemalononitrile **2a** proceeded smoothly under the catalysis of DABCO at room temperature. An unexpected aromatic 2-aminochromene[12] derivative **3a** was isolated in 67% yield after 24 h, resulting from a domino

(5) For selected examples, see: (a) Cho, C.-W.; Krische, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689. (b) van Steenis, D. J. V. C.; Marcelli, T.; Lutz, M.; Spek, A. L.; van Maarseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal.* **2007**, *349*, 281. (c) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202. (d) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737. (e) Cui, H.-L.; Peng, J.; Feng, X.; Du, W.; Jiang, K.; Chen, Y.-C. *Chem.—Eur. J.* **2009**, *15*, 1574. (f) Furukawa, T.; Kawazoe, J.; Zhang, W.; Nishimine, T.; Tokunaga, E.; Matsumoto, T.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 9684. (g) Mao, H.; Lin, A.; Shi, Y.; Mao, Z.; Zhu, X.; Li, W.; Hu, H.; Cheng, Y.; Zhu, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 6288.

(6) For selected examples, see: (a) Du, Y.; Lu, X.; Zhang, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035. (b) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951. (c) Wang, Q.-G.; Zhu, S.-F.; Ye, L.-W.; Zhou, C.-Y.; Sun, X.-L.; Tang, Y.; Zhou, Q.-L. *Adv. Synth. Catal.* **2010**, *352*, 1914. (d) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (e) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (f) Peng, J.; Huang, X.; Jiang, L.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2011**, *13*, 4584. (g) Wang, Y.; Liu, L.; Zhang, T.; Zhong, N.-J.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2012**, *77*, 4143.

(7) For reviews, see: (a) Liu, T.-Y.; Xie, M.; Chen, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4101. (b) Rios, R. *Catal. Sci. Technol.* **2012**, *2*, 267. (c) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659.

(8) For transformations of MBH products of cyclohexen-2-one, see: (a) Park, J. B.; Ko, S. H.; Hong, W.-P.; Lee, K.-J. *Bull. Korean Chem. Soc.* **2004**, *25*, 927. (b) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387. (c) Shafiq, Z.; Liu, L.; Liu, Z.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2007**, *9*, 2525. (d) Park, S. P.; Ahn, S.-H.; Lee, K.-J. *Tetrahedron* **2010**, *66*, 3490. (e) Gendrineau, T.; Genet, J. P.; Darses, S. *Org. Lett.* **2010**, *12*, 308. (f) Reddy, C. R.; Reddy, M. D.; Srikanth, B.; Prasad, K. R. *Org. Biomol. Chem.* **2011**, *9*, 6027. (g) Wang, F.; Li, S.; Qu, M.; Zhao, M.-X.; Liu, L.-J.; Shi, M. *Chem. Commun.* **2011**, *47*, 12813. (h) Ramesh, C.; Lei, P.-M.; Janreddy, D.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *J. Org. Chem.* **2012**, *77*, 8451.

(9) For generation of extended zwitterionic enolates from ynones, see: (a) Kuroda, H.; Tomita, I.; Endo, T. *Org. Lett.* **2003**, *5*, 129. (b) Wilson, J. E.; Sun, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2010**, *98*, 161. (c) Ramachary, D. B.; Venkaiah, C.; Krishna, P. M. *Org. Lett.* **2013**, *15*, 4714.

(10) A side reaction was reported in which a dienol of the MBH product of *p*-nitrobenzaldehyde and cyclohexen-2-one underwent δ'-regioselective addition to another molecular cyclohexen-2-one under the catalysis of $BBr_3 \cdot Me_2S$; see: Iwamura, T.; Fujita, M.; Kawakita, T.; Kinoshita, S.; Watanabe, S.-i.; Kataoka, T. *Tetrahedron* **2001**, *57*, 8455.

(11) For metal-catalyzed dehydrogenation of cyclohexanones or its enones to aromatic compounds, see: (a) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209. (b) Pun, D.; Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 8213. (c) Diao, T.; Pun, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 8205. (d) Simon, M.-O.; Girard, S. A.; Li, C.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7537. (e) Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.-O.; Deng, G.-J.; Li, C.-J. *Org. Lett.* **2012**, *14*, 5606. Under metal-free conditions, see: (f) Zhou, F.; Simon, M.-O.; Li, C.-J. *Chem.—Eur. J.* **2013**, *19*, 7151. (g) Zhao, J.; Huang, H.; Wu, W.; Chen, H.; Jiang, H. *Org. Lett.* **2013**, *15*, 2604.

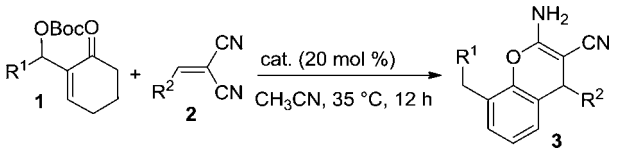
(12) For related chromene derivatives exhibiting diverse biological activity, see: (a) Aryapour, H.; Mahdavi, M.; Mohebbi, S. R.; Reza Zali, M.; Foroumadi, A. *Arch. Pharm. Res.* **2012**, *35*, 1573. (b) Zhang, G.; Zhang, Y.; Yan, J.; Chen, R.; Wang, S.; Ma, Y.; Wang, R. *J. Org. Chem.* **2012**, *77*, 878. (c) Patil, S. A.; Wang, J.; Li, X. S.; Chen, J.; Jones, T. S.; Hosni-Ahmed, A.; Patil, R.; Seibel, W. L.; Li, W.; Miller, D. D. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4458. (d) Ren, Q.; Gao, Y.; Wang, J. *Chem.—Eur. J* **2010**, *16*, 13594. (e) Ren, Q.; Siau, W.-Y.; Du, Z.; Zhang, K.; Wang, J. *Chem.—Eur. J.* **2011**, *17*, 7781.

δ'-regioselective Michael addition–cyclization–isomerization process.[8a,b] The structure of product **3a** has been unambiguously determined by X-ray analysis.[13] In addition, we also detected a phenol compound **4a**,[10] which might be generated from the direct repulsion of an amine catalyst in intermediate **III** followed by subsequent isomerization (Table 1, entry 1). In fact, it was found that **4a** was dominantly produced in the absence of electrophile **2a**. Next, a few Lewis base catalysts were investigated. Only a trace amount of **3a** was delivered by the catalysis of DMAP due to some side reactions (entry 2), and almost no reaction occurred in the presence of triphenylphosphine (entry 3). Since a chiral center was generated in product **3a**, we tested the reactions catalyzed by chiral amines. Unfortunately, no enantioselectivity could be induced though the reaction could be promoted by β-ICD (entry 4) or quinidine (entry 5), probably because the reactive δ'-site is too remote from the chiral amine catalyst.[13] In order to improve the efficacy of this reaction, other parameters were further explored by the catalysis of DABCO. A higher yield could be obtained at 35 °C (entry 6), while similar data were afforded at 50 °C (entry 7). Nevertheless, inferior results were observed in other solvents (entries 8–10). Finally, it was found that the reaction proceeded more efficiently in a higher concentration, and a good yield could be gained after 12 h at 35 °C (entry 11).

Consequently, we explored the generality of this reaction by employing a variety of MBH carbonates **1** of cyclohex-en-2-one and alkylidenemalononitriles **2**. The results are summarized in Table 2. Most of the reactions evaluated were completed within 12 h. For the reactions of MBH carbonate **1a**, an array of alkylidenemalononitriles bearing diverse aryl or heteroaryl groups could be well tolerated, delivering the corresponding heterocycles **3a**–**3l** in moderate to good isolated yields (Table 2, entries 1–12). A β-styryl-substituted substrate could afford the desired product **3m** in a diluted solution (entry 13), but both phenylethynyl or alkyl-substituted acceptors failed to yield the expected products (entries 14 and 15).[14]

On the other hand, further exploration of the substrate scope was focused on MBH carbonates. As shown in Table 2, MBH carbonates derived from other arylpropiolaldehydes could give the products **3n** and **3o** in moderate yield (entries 16 and 17) under the same catalytic conditions. A cinnamaldehyde derived substrate exhibited lower reactivity, but a moderate yield could be obtained for product **3p** after a longer reaction time (entry 18). An alkylacetylenic MBH carbonate also delivered the desired product **3q** while β-ICD was used as the catalyst at higher temperature (entry 20). Moreover, the MBH carbonates derived from a spectrum of arylaldehydes or even an aliphatic aldehyde were tested, and a satisfactory yield could be produced for products **3s**–**3w** by the catalysis of β-ICD, though a higher temperature and a longer time were required (entries 20–25).

Table 2. Substrate Scope and Limitations[a]



entry	cat.	R^1	R^2	yield (%)[b]
1	DABCO	PhC≡C–	Ph	**3a**, 76
2	DABCO	PhC≡C–	4-FC_6H_4	**3b**, 81
3	DABCO	PhC≡C–	2-BrC_6H_4	**3c**, 73
4	DABCO	PhC≡C–	4-$CF_3C_6H_4$	**3d**, 86
5	DABCO	PhC≡C–	3-$NO_2C_6H_4$	**3e**, 74
6	DABCO	PhC≡C–	4-MeC_6H_4	**3f**, 69
7	DABCO	PhC≡C–	3-$MeOC_6H_4$	**3g**, 66
8	DABCO	PhC≡C–	3,4-$(MeO)_2C_6H_3$	**3h**, 60
9	DABCO	PhC≡C–	1-naphthyl	**3i**, 72
10	DABCO	PhC≡C–	2-furyl	**3j**, 65
11	DABCO	PhC≡C–	2-thienyl	**3k**, 74
12	DABCO	PhC≡C–	3-pyridyl	**3l**, 65
13[c]	DABCO	PhC≡C–	2-styryl	**3m**, 55
14	DABCO	PhC≡C–	PhC≡C–	/
15	DABCO	PhC≡C–	*c*hexyl	/
16	DABCO	4-MeOPhC≡C–	Ph	**3n**, 63
17	DABCO	4-Br-PhC≡C–	Ph	**3o**, 56
18[d]	DABCO	2-styryl	Ph	**3p**, 66
19[c,e]	β-ICD	nC_5H_{11}–C≡CH–	Ph	**3q**, 72
20[c,e]	β-ICD	Ph	Ph	**3r**, 70
21[c,e]	β-ICD	4-BrC_6H_4	Ph	**3s**, 67
22[c,e]	β-ICD	4-$MeOC_6H_4$	Ph	**3t**, 82
23[c,e]	β-ICD	2-BrC_6H_4	Ph	**3u**, 76
24[c,e]	β-ICD	*N*-Bs-2-indolyl	Ph	**3v**, 62
25[c,e]	β-ICD	ethyl	Ph	**3w**, 76

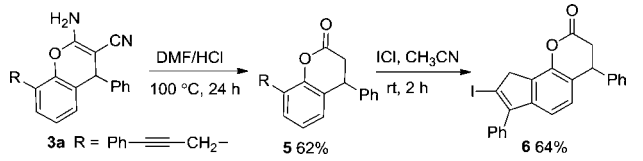
[a] Unless noted otherwiase, reactions were performed with MBH carbonate **1** (0.1 mmol), alkylidenemalononitrile **2** (0.2 mmol), and catalyst DABCO or β-ICD (20 mol %) in CH_3CN (0.2 mL) at 35 °C for 12 h. [b] Yield of isolated product. [c] In 0.5 mL of solvent. [d] For 35 h. [e] At 50 °C for 24 h.

As illustrated in Scheme 2, 2-amino-3-cyanochromene product **3a** could be easily converted to chroman-2-one derivative **5** after acid-promoted hydrolysis and subsequent decarboxylation. Importantly, an intramolecular Friedel–Crafts reaction was smoothly conducted through ICl-mediated activation of the alkyne group,[15] furnishing a tricyclic indene derivative **6**. More structural diversity and complexity might be expected with such multifunctionalities.

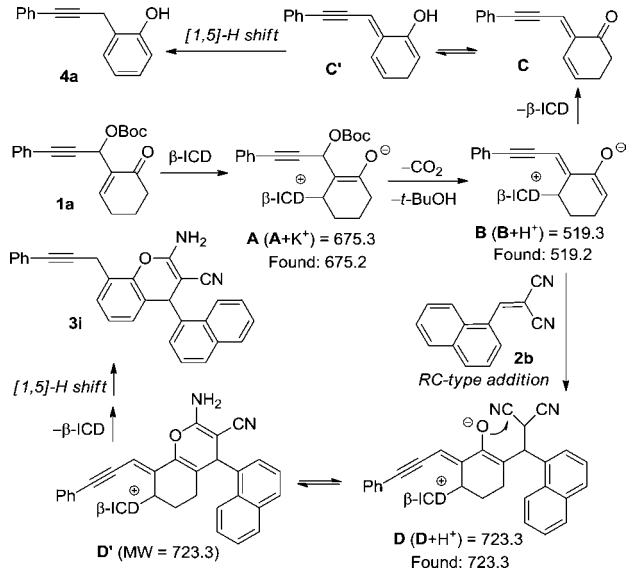
In order to gain some insight into the catalytic reaction mechanism, we proposed a plausible catalytic cycle and conducted a mass spectroscopy study to monitor the potential intermediates.[16] As outlined in Scheme 3, the Rauhut–Currier-type adduct **A** could be smoothly detected after combining MBH carbonate **1a** and catalyst β-ICD for 2 h. Importantly, the key zwitterionic dienolate

(13) For more details, see the Supporting Information.
(14) Alkylidenecyanoacetates or malonates also failed to give the desired products due to lower reactivity.
(15) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.
(16) (a) Regiani, T.; Santos, V. G.; Godoi, M. N.; Vaz, B. G.; Eberlin, M. N.; Coelho, F. *Chem. Commun.* **2011**, *47*, 6593. (b) Yao, Y.; Li, J.-L.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *Chem.—Eur. J.* **2013**, *19*, 9447.

Scheme 2. Synthetic Transformation of 2-Aminochromene **3a**



Scheme 3. A Plausible Catalytic Cycle and MS Study



intermediate **B** was clearly observed after elimination of CO_2 and *t*-BuOH. In addition, a labile intermediate dienone **C** could be isolated albeit in a very low yield. It should be noted that both intermediate **C** and phenol **4a** could not react with alkylidenemalononitriles, indicating that the current work does not proceed in a Friedel–Crafts pathway.[10] Moreover, after adding electrophile **2b** and stirring for another 2 h, we could also detect another key intermediate **D** or **D′**, verifying that zwitterionic dienolate **B** should be the key nucleophilic species in this catalytic cycle. As a result, aromatic product **3i** could be generated by a domino intramolecular cyclization, elimination of β-ICD, and a final [1,5]-H shift process.

In conclusion, we have explored the assembly of MBH carbonates of cyclohexen-2-one and alkylidenemalononitriles catalyzed by a Lewis basic tertiary amine. The reaction proceeds by in situ generation of the key Rauhut–Currier-type zwitterionic dienolates from MBH carbonates and an amine catalyst, which later react with electrophiles in a δ'-regioselective Michael addition pattern to give multifunctional chromene derivatives followed by a domino cyclization–isomerization sequence. Thus, this cascade process provides a formal Friedel–Crafts reaction pathway for phenol compounds. Moreover, a mass spectroscopy study has been conducted to monitor the reaction, and some important intermediates have been smoothly detected to verify the catalytic cycle. This activation mode of MBH carbonates from cyclohexen-2-one by a Lewis base might find more application in organic synthesis including potential asymmetric catalysis. More results will be reported in due course.

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Supporting Information Available. Experimental procedures, structural proofs, NMR spectra and HPLC chromatograms of the products, CIF file of product **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.