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An NHC-Catalyzed Cross-Benzoin–Esterification Sequential Reaction for the Synthesis of Trifluoromethyl-Substituted α,β-Unsaturated Esters

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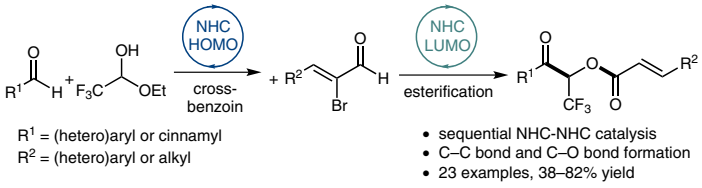

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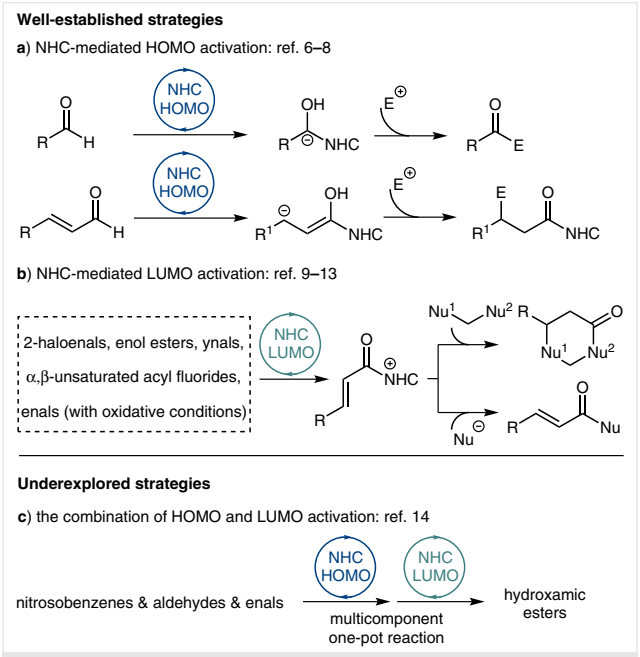
Abstract Efficient preparation of synthetically important CF_3-containing α,β-unsaturated esters is described using an NHC-catalyzed multicomponent reaction. This approach combines sequential NHC-mediated HOMO and LUMO activation to produce a C–C bond and C–O bond in a one-pot operation.

Key words organocatalytic reaction, multicomponent reaction, NHC catalysis, trifluoromethylated compounds, cross-benzoin, esterification

Multicomponent one-pot reactions have developed enormously in recent years and remain one of the hottest areas in organic chemistry.[2] The one-pot approach is often much more efficient, faster, and less expensive than the traditional 'stop-and-go' approach.[3] It also often avoids the need to isolate reaction intermediates. The expanding applications of one-pot reactions mean that developing novel catalytic systems for them remains an important goal.

One potentially useful catalyst class for one-pot reactions are N-heterocyclic carbenes (NHC),[4] first reported in stable form by Arduengo et al. in 1991.[5] NHC-mediated HOMO activation already plays an important role in organic synthesis: it reverses the polarity of the *ipso* position in saturated aldehydes or the β-position in α,β-unsaturated aldehydes (Scheme 1, a).[6] The resulting increase in HOMO energy can be exploited in reactions with carbon- and heteroatom-based electrophiles to generate a diverse range of synthetically valuable compounds. Prominent examples of such reactions include benzoin condensation[7] and the Stetter reaction.[8]



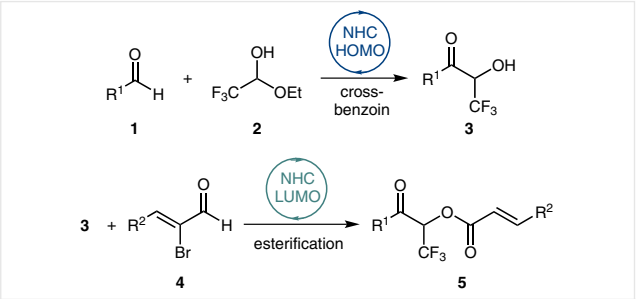
Scheme 1 Synthetic strategies based on NHC-mediated HOMO and/or LUMO activation

NHC can also catalyze reactions by reducing LUMO energy. This strategy has been exploited to generate α,β-unsaturated acylazolium (Scheme 1, b) from 2-haloenals,[9] enals (under oxidative conditions),[10] enol esters,[11] ynals,[12] or α,β-unsaturated acyl fluorides.[13] Several groups have used NHC-mediated LUMO activation to achieve the [3+3] annulation of α,β-unsaturated acylazoliums using 1,3-nucleophiles; this approach has been used to synthesize many important molecules.[9–13]

The ability of NHC to catalyze reactions via both HOMO and LUMO activation raises the possibility that both activation modes might be harnessed in a single multicomponent one-pot reaction. Indeed, Enders and co-workers reported an NHC-catalyzed one-pot reaction involving an aza-benzoin-type reaction between nitrosobenzenes and various aldehydes followed by redox esterification, affording hydroxamic esters (Scheme 1, c).[14] Our group aimed to build on this success by developing one-pot reactions based on NHC-mediated HOMO and LUMO activation that utilize other types of aldehydes or aldehyde equivalents.

Our approach was to start from the system described by Anand's group, who achieved an NHC-catalyzed cross-benzoin reaction of aromatic aldehydes with trifluoroacetaldehyde ethyl hemiacetal to afford trifluoromethyl-containing acyloins.[15] Drawing on our recent success in developing organocatalytic one-pot reactions to assemble multiple substrates into synthetically important molecules,[16] we wondered whether the trifluoromethylated acyloins could serve as the basis for a one-pot reaction combining NHC-mediated HOMO and LUMO activation.

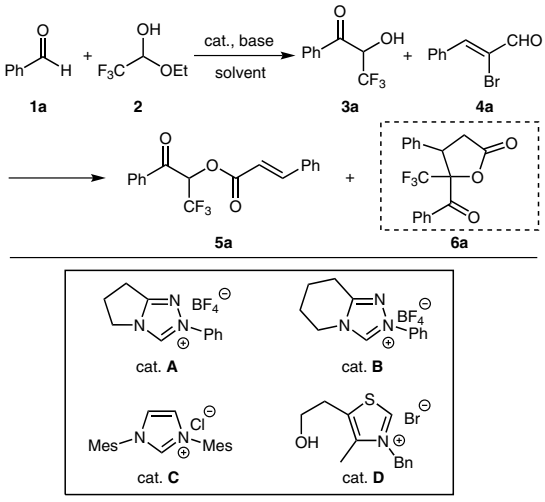
We envisioned a two-step NHC-catalyzed sequential reaction to synthesize trifluoromethyl-substituted α,β-unsaturated ester derivatives (Scheme 2). Synthesis of diverse CF_3-containing compounds is one of the most fascinating areas of organofluorine chemistry, since the added CF_3 groups can significantly improve the chemical, physical, and biological properties of the parent compounds.[17] Our protocol began with a cross-benzoin condensation between aromatic aldehyde **1** and $CF_3CH(OH)OEt$ (**2**). The resulting trifluoromethylated α-hydroxyketone **3** would then participate as the nucleophile in the next step. Subsequent intermolecular esterification with an α,β-unsaturated acylazolium intermediate would generate the final product **5**.



Scheme 2 Synthetic strategy

Initial experiments were carried out with benzaldehyde (**1a**) and $CF_3CH(OH)OEt$ (**2**) in the presence of triazolium salt **A** and DBU in MeCN. Cross-benzoin condensation proceeded quickly. After most benzaldehyde (**1a**) was consumed, we added α-bromocinnamic aldehyde (**4a**) directly to the reaction mixture. To our gratification, the sequential reaction proceeded smoothly to afford the desired product **5a** (Table 1, entry 1). The [3+2] annulation product **6a**, however, was not obtained. We then screened conditions to optimize the reaction (Table 1). We first tested various precatalysts (Table 1, entries 1–4), with precatalyst **A** showing the

Table 1 Optimization of Reaction Conditions[a]



Entry	Cat.	Base	Solvent	Time 1 (h)[b]	Time 2 (h)[c]	Yield (%)[d]
1	**A**	DBU	MeCN	6	6	50
2	**B**	DBU	MeCN	12	6	40
3	**C**	DBU	MeCN	–	–	n.r.
4	**D**	DBU	MeCN	–	–	n.r.
5	**A**	DBU	CH_2Cl_2	24	12	36
6	**A**	DBU	DMF	–	–	n.r.
7	**A**	DBU	toluene	12	8	30
8	**A**	DBU	THF	6	6	60
9	**A**	Et_3N	THF	–	–	n.r.
10	**A**	Cs_2CO_3	THF	6	6	40
11	**A**	*t*-BuOK	THF	6	6	45
12[e]	**A**	DBU	THF	2	2	65

[a] Reaction conditions: Base (0.1 mmol) was added to a solution of benzaldehyde **1a** (0.5 mmol), $CF_3CH(OH)OEt$ (**2**, 1.0 mmol), and precatalyst (0.05 mmol) in solvent (2 mL) at room temperature under argon. After benzaldehyde (**1a**) had been consumed based on TLC monitoring, α-bromocinnamic aldehyde (**4a**, 0.3 mmol) was added.
[b] Time for step 1.
[c] Time for step 2.
[d] Yield of the isolated product **5a**.
[e] Reaction was performed at 60 °C, r.t. = 20–25 °C; n.r. = no reaction; DBU = 1,8-diazabicyclo [5.4.0]undec-7-ene.

best activity (Table 1, entry 1). Replacing MeCN with other solvents substantially changed the yield (Table 1, entries 5–8), with THF giving the highest yield (Table 1, entry 8). Replacing DBU with Et_3N, Cs_2CO_3, or *t*-BuOK did not improve yield (Table 1, entries 9–11). Increasing reaction temperature slightly improved yield (Table 1, entry 12).

With the optimized reaction conditions in hand, we evaluated the substrate scope and limitations of the one-pot sequential reaction (Table 2).[18,19] We explored cross-benzoin condensation of $CF_3CH(OH)OEt$ (**2**) with various aldehydes **1**, followed by addition of α-bromo cinnamaldehyde (**4a**, Table 2, entries 2–11). Most electron-withdrawing-group substitutions generated the desired unsaturated ester in good yield (Table 2, entries 2–7), which varied in the trend *para* > *ortho* ≈ *meta*. Using an aromatic aldehyde carrying an electron-donating group gave the product **5h** in moderate yield (Table 2, entry 8). Heteroaromatic aldehydes and cinnamaldehyde also participated in the reaction (Table 2, entries 9–11), generating the corresponding products **5i**–**k** in slightly lower yield. This lower yield likely reflects the inefficient cross-benzoin condensation involving heteroaromatic aldehydes or cinnamaldehyde. The aliphatic aldehydes, such as 2-phenylacetaldehyde and 3-phenylpropanal, were also screened. Unfortunately, complex mixtures were obtained in the first cross-benzoin step, suggesting that the one-pot reaction is compatible only with (hetero)aromatic aldehydes and aromatic enals.

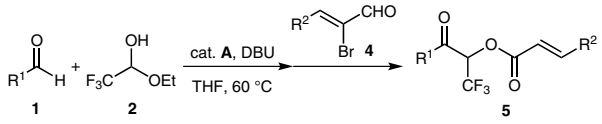
Next we examined various substitutions on the α-bromocinnamic aldehyde in this tandem reaction (Table 2, entries 12–21). Intriguingly, the position of the substitution barely affected reaction efficiency, whereas the electronic properties of substituents on the aromatic ring system markedly affected it. In general, product yield was greater with electron-poor enals (Table 2, entries 12–19) than with electron-rich enals (Table 2, entries 20 and 21). The reaction proceeded with 2-bromo-3-furanyl-acrylaldehyde, but yield of the final product **5v** was low (Table 2, entry 22). We were pleased that even the less reactive α-bromocrotonaldehyde participated in the one-pot reaction, giving product **5w** in moderate yield (Table 2, entry 23).

We propose a mechanism for this multicomponent one-pot sequential reaction (Scheme 3). NHC-mediated HOMO activation leads to transformation of the aromatic aldehyde **1** into the nucleophilic intermediate **M1**. Cross-benzoin condensation between **M1** and $CF_3CH(OH)OEt$ (**2**) generates trifluoromethylated acyloin **3**. Next, NHC-mediated LUMO activation initiates intermolecular esterification of the electrophilic α,β-unsaturated acylazolium intermediate **M2** with nucleophilic α-hydroxyketone **3**, affording the final product **5**. The same catalyst drives both the HOMO and LUMO cycles.

To illustrate the synthetic utility of this one-pot reaction, we showed that the CF_3-containing unsaturated ester **5a** is easily converted into other medicinally interesting building blocks. Treating **5a** with thiourea in DMF at 150 °C for 16 hours generated a high yield of the corresponding multifunctionalized oxazole **7** bearing phenyl, trifluoromethyl, and styryl groups (Scheme 4).[20]

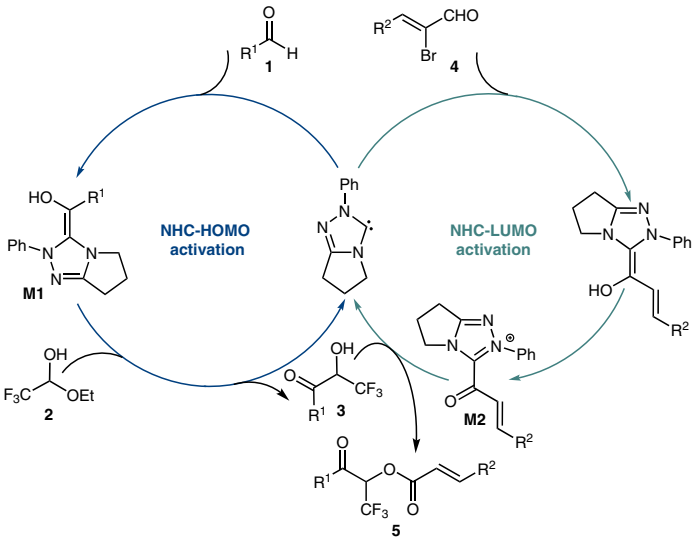
In conclusion, we have developed an NHC-catalyzed multicomponent sequential reaction involving a cross-benzoin–esterification relay to assemble aromatic aldehydes, trifluoroacetaldehyde ethyl hemiacetal, and α-bromoenals into synthetically important CF_3-containing α,β-unsaturated esters in moderate to high yields of up to 82%. This process combines, into a one-pot operation, sequential NHC-mediated HOMO and LUMO activation leading to the pro-

Table 2 Substrate Scope under Optimized Conditions[a]



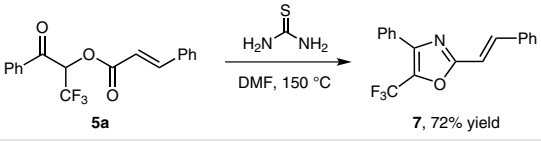
Entry	R^1	R^2	Time 1 + Time 2 (h)[b]	Product	Yield (%)[c]
1	Ph	Ph	2 + 2	**5a**	65
2	3-ClC_6H_4	Ph	2 + 2	**5b**	74
3	4-ClC_6H_4	Ph	2 + 2	**5c**	80
4	3-BrC_6H_4	Ph	2 + 2	**5d**	73
5	4-BrC_6H_4	Ph	2 + 2	**5e**	82
6	2-FC_6H_4	Ph	4 + 2	**5f**	70
7	4-FC_6H_4	Ph	4 + 2	**5g**	76
8	4-*i*-PrC_6H_4	Ph	4 + 2	**5h**	58
9	2-furyl	Ph	8 + 2	**5i**	50
10	2-thienyl	Ph	8 + 2	**5j**	53
11	cinnamyl	Ph	4 + 2	**5k**	55
12	Ph	2-ClC_6H_4	2 + 1	**5l**	67
13	Ph	3-ClC_6H_4	2 + 1	**5m**	70
14	Ph	4-ClC_6H_4	2 + 1	**5n**	73
15	Ph	2-FC_6H_4	2 + 1	**5o**	66
16	Ph	3-FC_6H_4	2 + 1	**5p**	71
17	Ph	3-BrC_6H_4	2 + 1	**5q**	72
18	Ph	4-BrC_6H_4	2 + 1	**5r**	75
19	Ph	4-$O_2NC_6H_4$	2 + 1	**5s**	63
20	Ph	4-MeC_6H_4	2 + 4	**5t**	60
21	Ph	4-$MeOC_6H_4$	2 + 4	**5u**	54
22	Ph	2-furyl	2 + 8	**5v**	38
23	Ph	Me	2 + 4	**5w**	51

[a] Reaction conditions: Base (0.1 mmol) was added to a solution of aromatic aldehyde **1** (0.5 mmol), $CF_3CH(OH)OEt$ (**2**, 1.0 mmol), and precatalyst **A** (0.05 mmol) in THF (2 mL) at 60 °C under argon. After aldehyde **1** had been consumed based on TLC monitoring, α-bromoenal **4** (0.3 mmol) was added.
[b] Time for step 1 and 2.
[c] Yield of the isolated product **5**.



Scheme 3 Proposed reaction mechanism

duction of C–C and C–O bonds. The α,β-unsaturated esters produced using this approach are readily converted into biologically interesting oxazole scaffolds bearing multiple functional groups. Further study of multicomponent one-pot reactions involving consecutive NHC catalysis is under way in our laboratory.



Scheme 4 Synthetic transformation downstream of the one-pot reaction

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Supporting Information

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Primary Data

for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083 and can be cited using the following DOI: 10.4125/pd0078th.

References and Notes

(1) These authors contributed equally.
(2) For recent reviews on multicomponent one-pot reactions, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (b) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8492. (c) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. (d) Pellissier, H. *Tetrahedron* **2013**, *69*, 7171.
(3) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477.
(4) For recent reviews on NHC catalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (c) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (d) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617. (e) Févre, M.; Pinaud, J.; Gnanou, Y.; Vignolle, J.; Taton, D. *Chem. Soc. Rev.* **2013**, *42*, 2142. (f) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (g) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485.
(5) Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.
(6) For selected reviews on NHC-mediated HOMO activation, see: (a) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (b) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336.
(7) For recent reviews on benzoin condensation, see: (a) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, *291*, 118. (b) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (c) Menon, R. S.; Biju, A. T.; Nair, V. *Beilstein J. Org. Chem.* **2016**, *12*, 444.
(8) For recent reviews on Stetter reaction, see: (a) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3. (b) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (c) Yetra, S. R.; Patra, A.; Biju, A. T. *Synthesis* **2015**, *47*, 1357.
(9) (a) Sun, F.-G.; Sun, L.-H.; Ye, S. *Adv. Synth. Catal.* **2011**, *353*, 3134. (b) Zhang, B.; Feng, P.; Cui, Y.; Jiao, N. *Chem. Commun.* **2012**, *48*, 7280. (c) Yao, C.; Jiao, W.; Xiao, Z.; Liu, R.; Li, T.; Yu, C. *Tetrahedron* **2013**, *69*, 1133. (d) Yetra, S. R.; Kaicharla, T.; Kunte, S. S.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2013**, *15*, 5202. (e) Yetra, S. R.; Roy, T.; Bhunia, A.; Porwal, D.; Biju, A. T. *J. Org. Chem.* **2014**,

79, 4245. (f) Jiang, D.; Dong, S.; Tang, W.; Lu, T.; Du, D. *J. Org. Chem.* **2015**, *80*, 11593. (g) Zhang, C.-L.; Wang, D.-L.; Chen, K.-Q.; Ye, S. *Org. Biomol. Chem.* **2015**, *13*, 11255. (h) Chen, K.-Q.; Li, Y.; Zhang, C.-L.; Sun, D.-Q.; Ye, S. *Org. Biomol. Chem.* **2016**, *14*, 2007. (i) Xu, J.; Zhang, W.; Liu, Y.; Zhu, S.; Liu, M.; Hua, X.; Chen, S.; Lu, T.; Du, D. *RSC Adv.* **2016**, *6*, 18601.

(10) (a) De Sarkar, S.; Studer, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9266. (b) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080. (c) Biswas, A.; De Sarkar, S.; Tebben, L.; Studer, A. *Chem. Commun.* **2012**, *48*, 5190. (d) Samanta, R. C.; De Sarkar, S.; Fröhlich, R.; Grimme, S.; Studer, A. *Chem. Sci.* **2013**, *4*, 2177. (e) Bera, S.; Samanta, R. C.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 9622. (f) Hu, S.; Wang, B.; Zhang, Y.; Tang, W.; Fang, M.; Lu, T.; Du, D. *Org. Biomol. Chem.* **2015**, *13*, 4661. (g) Liang, Z.-Q.; Wang, D.-L.; Zhang, H.-M.; Ye, S. *Org. Lett.* **2015**, *17*, 5140. (h) Mao, J.-H.; Wang, Z.-T.; Wang, Z.-Y.; Cheng, Y. *J. Org. Chem.* **2015**, *80*, 6350. (i) Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T. *Angew. Chem. Int. Ed.* **2016**, *55*, 268.

(11) (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176. (b) Cheng, J.; Huang, Z.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8592. (c) Xu, J.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 5028. (d) Chauhan, P.; Enders, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 1485. (e) Candish, L.; Levens, A.; Lupton, D. W. *J. Am. Chem. Soc.* **2014**, *136*, 14397. (f) Kowalczyk, M.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 5314. (g) Zhang, Z.; Zeng, X.; Xie, D.; Chen, D.; Ding, L.; Wang, A.; Yang, L.; Zhong, G. *Org. Lett.* **2015**, *17*, 5052.

(12) (a) Zeitler, K. *Org. Lett.* **2006**, *8*, 637. (b) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (c) Zhu, Z.-Q.; Xiao, J.-C. *Adv. Synth. Catal.* **2010**, *352*, 2455. (d) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun.* **2011**, *47*, 8670. (e) Romanov-Michailidis, F.; Besnard, C.; Alexakis, A. *Org. Lett.* **2012**, *14*, 4906. (f) Du, D.; Hu, Z.; Jin, J.; Lu, Y.; Tang, W.; Wang, B.; Lu, T. *Org. Lett.* **2012**, *14*, 1274. (g) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.* **2012**, *2*, 494. (h) Zhou, B.; Luo, Z.; Li, Y. *Chem. Eur. J.* **2013**, *19*, 4428. (i) Han, R.; Qi, J.; Gu, J.; Ma, D.; Xie, X.; She, X. *ACS Catal.* **2013**, *3*, 2705. (j) Qi, J.; Duan, X.-Y.; Cao, L.-L.; Wang, W.-Y. *Asian J. Org. Chem.* **2015**, *4*, 1254.

(13) (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2011**, *133*, 4694. (b) Ryan, S.; Candish, L.; Lupton, D. W. *Synlett* **2011**, 2275. (c) Ryan, S. J.; Stasch, A.; Paddon-Row, M. N.; Lupton, D. W. *J. Org. Chem.* **2012**, *77*, 1113. (d) Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2013**, *135*, 58.

(14) Song, X.; Ni, Q.; Grossmann, A.; Enders, D. *Chem. Asian J.* **2013**, *8*, 2965.

(15) Ramanjaneyulu, B. T.; Mahesh, S.; Anand, R. V. *Org. Lett.* **2015**, *17*, 6.

(16) (a) Xie, X.; Peng, C.; He, G.; Leng, H.-J.; Wang, B.; Huang, W.; Han, B. *Chem. Commun.* **2012**, *48*, 10487. (b) Li, X.; Yang, L.; Peng, C.; Xie, X.; Leng, H.-J.; Wang, B.; Tang, Z.-W.; He, G.; Ouyang, L.; Huang, W.; Han, B. *Chem. Commun.* **2013**, *49*, 8692. (c) He, G.; Wu, F.; Huang, W.; Zhou, R.; Ouyang, L.; Han, B. *Adv. Synth. Catal.* **2014**, *356*, 2311. (d) Han, B.; Xie, X.; Huang, W.; Li, X.; Yang, L.; Peng, C. *Adv. Synth. Catal.* **2014**, *356*, 3676. (e) Han, B.; Huang, W.; Ren, W.; He, G.; Wang, J.-H.; Peng, C. *Adv. Synth. Catal.* **2015**, *357*, 561. (f) Zhou, R.; Wu, Q.; Guo, M.; Huang, W.; He, X.; Yang, L.; Peng, F.; He, G.; Han, B. *Chem. Commun.* **2015**, *51*, 13113. (g) Leng, H.-J.; Peng, F.; Zingales, S.; Huang, W.; Wang, B.; Zhao, Q.; Zhou, R.; He, G.; Peng, C.; Han, B. *Chem. Eur. J.* **2015**, *21*, 18100.

(17) For recent reviews on the synthesis of trifluoro-methylated compounds and the applications in medicinal chemistry, see: (a) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (d) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (e) Barata-Vallejo, S.; Lantaño, B.; Postigo, A. *Chem. Eur. J.* **2014**, *20*, 16806. (f) Bizet, V.; Besset, T.; Ma, J.-A.; Cahard, D. *Curr. Top. Med. Chem.* **2014**, *14*, 901. (g) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (h) Huang, Y.-Y.; Yang, X.; Chen, Z.; Verpoort, F.; Shibata, N. *Chem. Eur. J.* **2015**, *21*, 8664. (i) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.

(18) **General Procedure for the Synthesis of CF_3-Substituted α,β-Unsaturated Esters**

The reaction was carried out with aromatic aldehyde **1** (0.5 mmol), $CF_3CH(OH)OEt$ (**2**, 1.0 mmol), precatalyst **A** (0.05 mmol, 13.7 mg), and DBU (0.1 mmol, 15 μL) in THF (2.0 mL) at 60 °C under argon to afford the acyloin **3**, after which α-bromoenal **4** (0.3 mmol) was added in one-pot. The reaction mixture was stirred at 60 °C for a specified reaction time until the reaction completed. Then the reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (PE–EtOAc = 40:1) to give the final product.

(19) **Analytical Data for Compound 5a**

Obtained as a white solid in 65% yield (65.3 mg) for two steps after flash chromatography; mp 58–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 2 H), 7.82 (d, *J* = 16.0 Hz, 2 H), 7.57–7.51 (m, 4 H), 7.44–7.38 (m, 3 H), 6.57 (d, *J* = 16.0 Hz, 1 H), 6.45 (q, *J* = 6.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.6, 164.8, 148.2, 134.6, 133.7, 131.2, 129.0, 128.9, 128.5, 121.9 (d, J_{CF} = 280 Hz), 115.2, 70.9 (q, J_{CF} = 31 Hz) ppm. ESI-HRMS: *m*/*z* calcd for $C_{18}H_{13}F_3O_3$ + Na: 357.0714; found: 357.0717.

(20) Loner, C. M.; Luzzio, F. A.; Demuth, D. R. *Tetrahedron Lett.* **2012**, *53*, 5641.