

## Accepted Manuscript

### Friedel-Crafts Alkylation of Benzo[b]furan with Activated Cyclopropanes Catalyzed by a Calcium(II) Complex

T. Parker Maloney, Kristen L. Murphy, Tafon L. Mainsah, Kristine A. Nolin

PII: S0040-4039(17)31368-0  
DOI: <https://doi.org/10.1016/j.tetlet.2017.10.064>  
Reference: TETL 49426

To appear in: *Tetrahedron Letters*

Received Date: 23 September 2017  
Revised Date: 17 October 2017  
Accepted Date: 26 October 2017

Please cite this article as: Maloney, T.P., Murphy, K.L., Mainsah, T.L., Nolin, K.A., Friedel-Crafts Alkylation of Benzo[b]furan with Activated Cyclopropanes Catalyzed by a Calcium(II) Complex, *Tetrahedron Letters* (2017), doi: <https://doi.org/10.1016/j.tetlet.2017.10.064>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

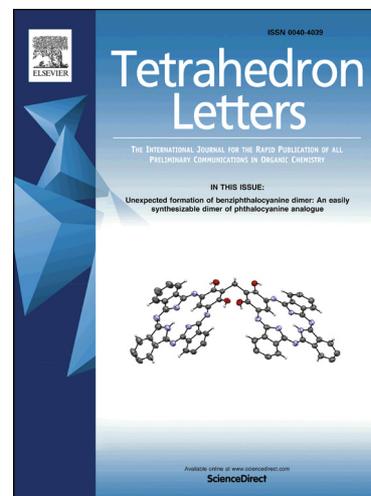


Table 1. Catalyst Screen and Reaction Optimization



Tetrahedron Letters  
journal homepage: [www.elsevier.com](http://www.elsevier.com)

## Friedel-Crafts Alkylation of Benzo[b]furan with Activated Cyclopropanes Catalyzed by a Calcium(II) Complex

T. Parker Maloney, Kristen L. Murphy, Tafon L. Mainsah, and Kristine A. Nolin\*

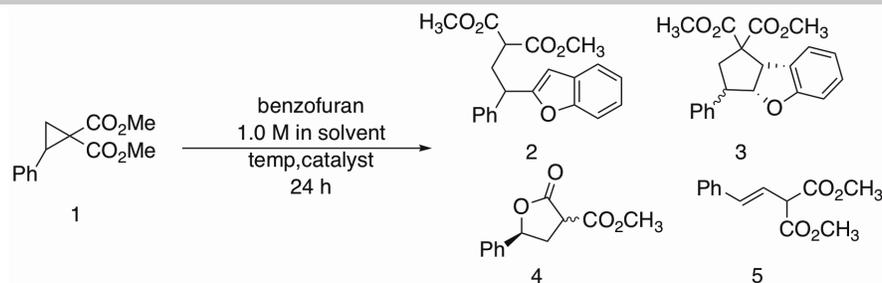
University of Richmond, 28 Westhampton Way, Richmond, Virginia 23173, United States

**KEYWORDS** *cyclopropane, benzo[b]furan, calcium, Friedel-Crafts, Lewis acid catalysis*

**ABSTRACT:** The synthesis of  $\gamma$ -benzo[b]furan malonates was achieved through the addition of benzo[b]furan to activated cyclopropanes. These Friedel-Crafts reactions were catalyzed by calcium bis(trifluoromethanesulfonimide),  $\text{Ca}(\text{NTf}_2)_2$  with tetrabutylammonium hexafluorophosphine as a co-catalyst. The additions proceeded with complete regioselectivity and in good to excellent yield. Optimization of the reaction conditions and investigation into the scope of the methodology with regards to substitution on the cyclopropane are reported.

The Friedel-Crafts reaction has been a key strategy for making C–C bonds in syntheses carried out from the small laboratory scale to manufacturing levels.<sup>1</sup> In contrast to the multitude of studies reported on the reactivity of benzene, its derivatives, and, to a lesser extent, indole, the activity of benzo[b]furan in Friedel-Crafts reactions has been largely unexplored. Kobayashi and coworkers have shown that  $\text{Ga}(\text{OTf})_3$  and  $\text{Sc}(\text{OTf})_3$  catalyzed the addition of benzo[b]furan to acetic anhydride as a mixture of the 2-, and 3-acetylated benzo[b]furan.<sup>2</sup> In a similar acylation reaction, Kantam and coworkers reported that, in presence of beta zeolite, benzo[b]furan is quantitatively converted to 2-acyl benzo[b]furan.<sup>3</sup> Friedel-Crafts phthaloylation of 3-methylbenzo[b]furan has been achieved in the presence of 1.5 equivalents of  $\text{AlCl}_3$ .<sup>4</sup> The addition of benzo[b]furan to 1,4-epoxy-1,4-dihydronaphthalene was achieved in the presence of  $\text{FeCl}_3$ .<sup>5</sup>

Activated cyclopropanes have been substrates in Friedel-Crafts reactions with substituted indoles<sup>6</sup> and aniline derivatives.<sup>7</sup> To the best of our knowledge, *there have been no reported examples of catalytic additions of benzo[b]furan to activated cyclopropanes.* In their recent communication, Chagarovskiy *et al* reported that activated cyclopropanes are reactive with substituted furans to produce [3+2]-cycloaddition products in the presence of catalytic amounts of  $\text{SnCl}_4$  or  $\text{Yb}(\text{OTf})_3$ .<sup>8</sup> Previous studies from our laboratory have shown the ability of Ca(II) complexes to activated cyclopropanes as electrophiles in a number of reactions including the Friedel-Crafts reaction with N-methylindole.<sup>9</sup> We next turned our attention to the analogous reaction with benzo[b]furan and the results are summarized below.



Entry	Catalyst Complex	Catalyst Loading (%)	Co-Catalyst	Co-Catalyst Loading (%)	Temp. (°C)	Solvent	Conversion (%) <sup>a</sup>			
							2	3	4	5
1 <sup>c</sup>	Ca(acac) <sub>2</sub>	5	–	–	90	toluene	0	0	0	0
2 <sup>c</sup>	Ca(OAc) <sub>2</sub>	5	–	–	90	toluene	0	0	0	0
3 <sup>c</sup>	Ca(OH) <sub>2</sub>	5	–	–	90	toluene	0	0	0	0
4 <sup>c</sup>	Ca(OMe) <sub>2</sub>	5	–	–	90	toluene	0	0	0	0
5 <sup>c</sup>	Ca(tartrate)	5	–	–	90	toluene	0	0	0	0
6 <sup>c</sup>	Ca(NTf <sub>2</sub> ) <sub>2</sub>	5	–	–	90	toluene	0	0	0	0
7 <sup>c</sup>	Ca(NTf <sub>2</sub> ) <sub>2</sub>	5	NBu <sub>4</sub> PF <sub>6</sub>	5	90	toluene	40	13	19	14
8 <sup>c</sup>	Ca(NTf <sub>2</sub> ) <sub>2</sub>	10	NBu <sub>4</sub> PF <sub>6</sub>	10	90	toluene	40	20	26	14
9 <sup>c</sup>	Mg(NTf <sub>2</sub> ) <sub>2</sub>	10	NBu <sub>4</sub> PF <sub>6</sub>	10	90	toluene	0	0	0	0
10 <sup>d</sup>	Ca(NTf <sub>2</sub> ) <sub>2</sub>	10	NBu <sub>4</sub> PF <sub>6</sub>	10	50	toluene	24	46	30	0
11 <sup>d</sup>	Ca(NTf <sub>2</sub> ) <sub>2</sub>	10	NBu <sub>4</sub> PF <sub>6</sub>	10	50	DCE <sup>b</sup>	45	33	15	8
12 <sup>d</sup>	Ca(NTf <sub>2</sub> ) <sub>2</sub>	10	NBu <sub>4</sub> PF <sub>6</sub>	10	50	hexanes	37	39	24	0
13 <sup>d</sup>	Ca(NTf <sub>2</sub> ) <sub>2</sub>	10	NBu <sub>4</sub> PF <sub>6</sub>	10	50	THF	3	18	9	0
14 <sup>d</sup>	Ca(NTf <sub>2</sub> ) <sub>2</sub>	10	NBu <sub>4</sub> PF <sub>6</sub>	10	70	toluene	46	18	22	14

<sup>a</sup>Conversion determined by <sup>1</sup>H NMR of the unpurified reaction mixture and based on remaining cyclopropane. <sup>b</sup>In addition to the identified products, the reaction mixture contains approximately 10% of unidentified products. <sup>c</sup>1.2 equiv of benzo[b]furan. <sup>d</sup>2.0 equiv of benzo[b]furan

A number of commercially available calcium(II) complexes were tested as potential catalysts in the Friedel-Crafts addition of benzo[b]furan to dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1**). A representative sample is shown in Table 1. At 90 °C in toluene, no reaction of cyclopropane **1** with benzo[b]furan was observed in the presence of numerous of calcium(II) complexes (entries 1-6). However, a combination of 5 mol% of bis(trifluoromethanesulfoniimide) (Ca(NTf<sub>2</sub>)<sub>2</sub>) and 5 mol% of NBu<sub>4</sub>PF<sub>6</sub> catalyzed the reaction with 86% conversion of **1** with the alkylation product **2** as the major product (entry 7). The remainder of the mass balance was annulation product **3**, and cyclopropane decomposition products **4** and **5**.<sup>10</sup> Alkylation proceeded with 100% regioselectivity with addition occurring at the C2 or the benzo[b]furan. Full conversion was obtained by increasing catalyst loading to 10 mol%. It has been suggested that Ca(NTf<sub>2</sub>)<sub>2</sub> and NBu<sub>4</sub>PF<sub>6</sub> undergo ligand exchange to form Ca(NTf<sub>2</sub>)(PF<sub>6</sub>), which, in previous studies, has been proposed to be the active catalyst.<sup>11</sup> It is of note that Mg(NTf<sub>2</sub>)<sub>2</sub>, with and without co-catalyst, did not facilitate the reaction.

Having identified a suitable catalyst/co-catalyst combination, efforts then turned to optimization of the Friedel-Crafts addition of benzo[b]furan to cyclopropane **1**. The conversion and product distribution were examined for every new set of reaction conditions and select results are summarized in Table 1. In the presence of Ca(NTf<sub>2</sub>)<sub>2</sub> and NBu<sub>4</sub>PF<sub>6</sub>, a small amount polymerization of benzo[b]furan was observed. Therefore, the equivalency of benzo[b]furan was increased to two. At 50 °C in the presence of 10 mol% Ca(NTf<sub>2</sub>)<sub>2</sub> and NBu<sub>4</sub>PF<sub>6</sub> in toluene (entry 10), full conversion of the cyclopropane was achieved; however, the reaction conditions favored the formation annulation product **3** and decomposition product **4**. Dichloroethane (DCE) and hexanes led to similar results (entries 11 & 12). Interestingly, tetrahydrofuran (THF) led to very low conversion (entry 13). Heating the reaction to 70 °C in toluene minimized formation the annulation and decomposition products (entry 14). Using the optimized reaction conditions of 1.0 M in toluene at 70 °C with two equivalents of benzo[b]furan, the Friedel-Crafts reaction of differentially substituted dimethyl arylcyclopropane-1,1-dicarboxylates was carried out.

Figure 1 shows the products from Friedel-Crafts reaction of benzo[b]furan and a wide range of cyclopropyl electrophiles. Cyclopropanes bearing electron-rich aryl substitutions underwent addition to provide Friedel-Crafts products **6-10** in good yield (51- 65%). It is of note that no decomposition of the acetal was observed in the formation of **7**. Several other aromatic and heteroaromatic substrates were excellent electrophiles. Cyclopropanes bearing electron-deficient aryl substitutions proved to be equally reactive as their electron-rich counterparts. Friedel-Crafts products **11-13** were formed and isolated in good yield (48-68%). A naphthyl ring on the cyclopropane did not inhibit the formation of **14** and **15**, which was isolated in 55 and 61% yield respectively. Cyclopropane bearing a 3-indolyl substituent underwent alkylation of benzo[b]furan to provide **16** in excellent yield (89%).

The 2-thiophenyl substituted cyclopropane proceeded with full conversion; however, attempts to isolate the product were plagued with decomposition and **17** was isolated in 36% yield. Changing to the larger ethyl esters had no deleterious effect on reactivity and **18** was isolated in 63%. Unfortunately, attempts to react alkyl-substituted cyclopropanes under the optimized reaction conditions were unsuccessful.

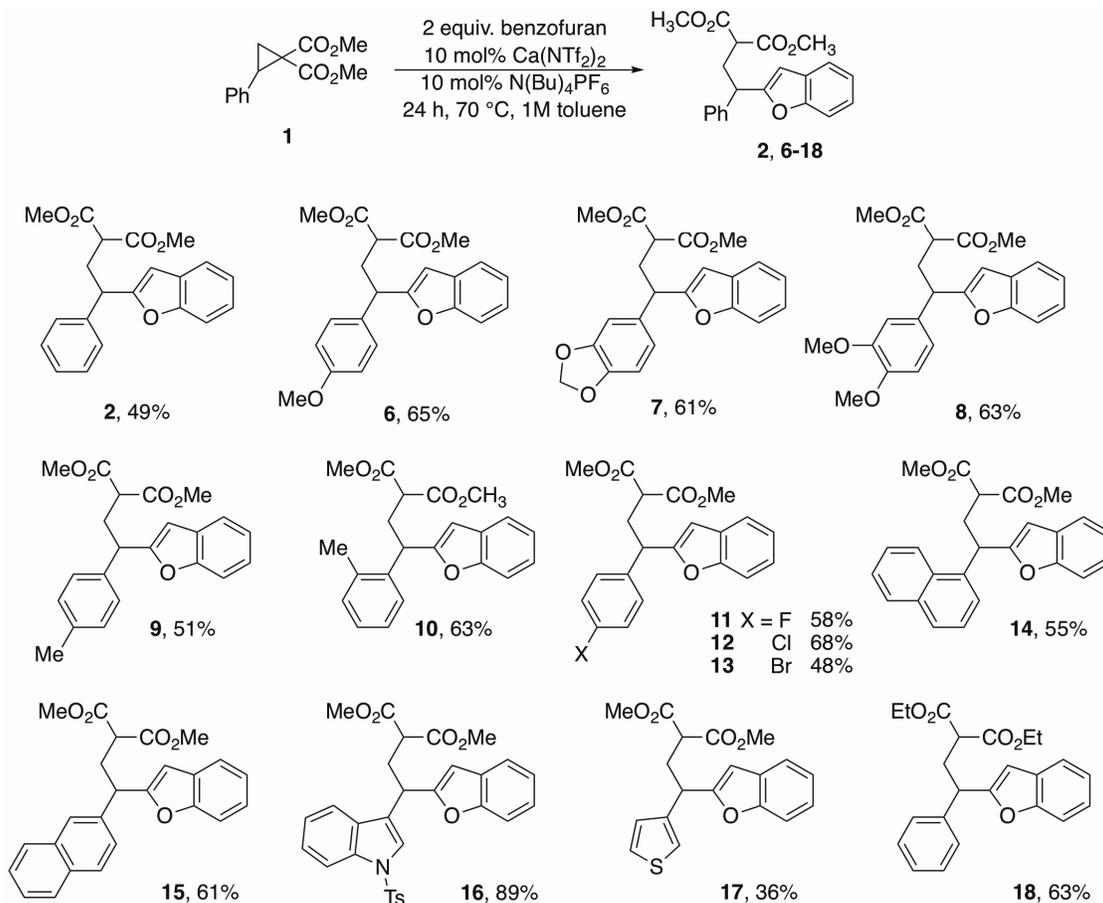
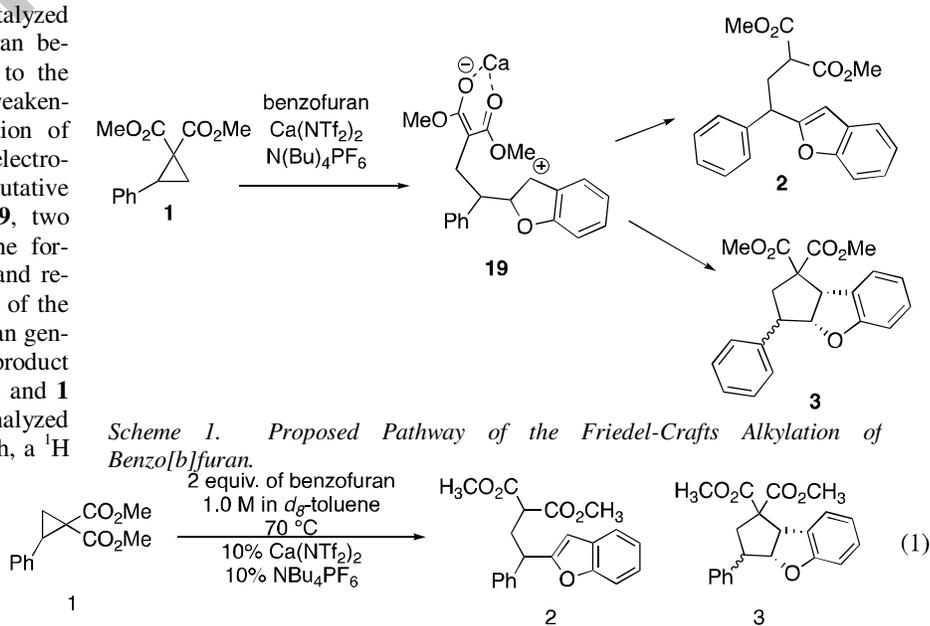


Figure 1. Scope of Friedel-Crafts Alkylation Reaction

We propose that the calcium-catalyzed Friedel-Crafts alkylation of benzo[b]furan begins with coordination of the calcium to the esters of the cyclopropanes causing a weakening the C-C cyclopropyl bond. Addition of benzo[b]furan to the newly generated electrophile leads to the formation putative zwitterionic intermediate **19**. From **19**, two competitive pathways would lead to the formation of **2** and **3**: 1) proton transfer and re-aromatization forms **2** while 2) addition of the calcium enolate to C3 of the benzo[b]furan generates **3**. To test the reversibility of product formation, the reaction of benzo[b]furan and **1** was performed at 70 °C in  $d_8$ -toluene analyzed by  $^1\text{H}$  NMR spectroscopy (eq 1). At 21 h, a  $^1\text{H}$  NMR spectrum of the unpurified reaction mixture showed that the reaction was complete and no cyclopropane remained. The reaction solution contained a mixture of **2** and **3** in a 2.5:1.0 ratio. The reaction was allowed to continue for an additional 47 hours after which time no change in the distribution of **2** and **3** was observed. Additionally, the 4:1



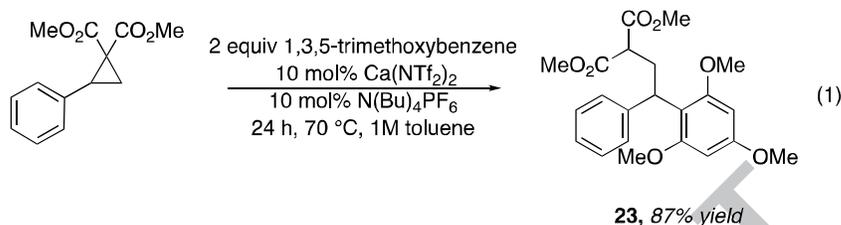
Scheme 1. Proposed Pathway of the Friedel-Crafts Alkylation of Benzo[b]furan.

(1)

continue for an additional 47 hours after which time no change in the distribution of **2** and **3** was observed. Additionally, the 4:1

(cis:trans) diastereometric ratio was unchanged over the course of the reaction. In a second experiment, a pure sample of *cis*-**3** in which phenyl is *cis* to the neighboring oxygen was subjected to the reaction conditions and, after 24 hours, there was no change to the sample. Therefore, it is concluded that the pathways leading to **2** and **3** are not reversible under the reaction conditions.

Having shown  $\text{Ca}(\text{NTf}_2)_2$  is a robust catalyst to the Friedel-Crafts alkylation of 1-methylindole and benzo[b]furan, we next tested the catalysts ability to facilitate the reaction of electron-rich benzene derivatives.  $\text{Yb}(\text{OTf})_3$ ,  $\text{Sc}(\text{OTf})_3$ ,  $\text{Mg}(\text{ClO}_4)_2$  have been previously identified as catalysts in Friedel-Crafts alkylation of electron-rich arenes. We were pleased to find that the combination of  $\text{Ca}(\text{NTf}_2)_2$  and  $\text{NBu}_4\text{PF}_6$  was able to facilitate the alkylation of 1,3,5-trimethoxybenzene (eq 1). Under the similar reaction conditions as describe above for the reactions with benzo[b]furan, 1,3,5-trimethoxybenzene added to cyclopropane **1** to produce alkylation product **20** in 87% yield.



In conclusion, we have developed a new Friedel-Crafts alkylation reaction that couples benzo[b]furan with activated cyclopropanes. The transformation is catalyzed by  $\text{Ca}(\text{NTf}_2)_2$ , in the presence of  $\text{NBu}_4\text{PF}_6$ . Dimethyl aryl- and heteroarylcyclopropane-1,1-dicarboxylates of varying electronic structure were effective coupling partners. The reactions proceeded with good to excellent yield with complete regioselectivity for the C-2 on the benzo[b]furan.

## AUTHOR INFORMATION

### Corresponding Author

\* Email: knolin@richmond.edu

## ACKNOWLEDGMENT

This research was supported by the National Science Foundation (CHE-1559886) and the University of Richmond.

## REFERENCES

- Selected reviews: (a) Calloway, N. O. *Chem. Rev.* 1935, 17 (3), 327–392. (b) Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* 2010, 43 (3), 440–454. (c) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* 2012, 45 (8), 1278–1293. (d) Riguet, E. *J. Org. Chem.* 2011, 76 (20), 8143–8150. (e) Fleming, F. F.; Wei, G.; Steward, O. W. *J. Org. Chem.* 2008, 73 (10), 3674–3679. (f) Tudge, M.; Savarin, Cecile G.; DiFelice, K.; Maligres, P.; Humphrey, G.; Reamer, B.; Tellers, D. M.; Hughes, D. *Org. Process Res. Dev.* 2010, 14 (4), 787–798. (g) Aelterman, W.; Lang, Y.; Willemsens, B.; Vervest, I.; Leurs, S.; De Knaep, F. *Org. Process Res. Dev.* 2001, 5 (5), 467–471. (h) Shirakawa, E.; Uchiyama, N.; Hayashi, T. *J. Org. Chem.* 2011, 76 (1), 25–34.
- Komoto, I.; Matsuo, J.; Kobayashi, S. *Topics in Catalysis* 2002, 19 (1), 43–47.
- Kantam, M. L.; Ranganath, K.; Sateesh, M. *J. Mol. Catal. A: Chem.* 2005, 225, 15–20.
- Clement, J. A.; Gunasekaran, P.; Mohanakrishnan, A. K. *Tetrahedron* 2009, 65, 4113–4123.
- Sawama, Y.; Asai, S.; Kawajiri, T.; Monguchi, Y.; Sajiki, H. *Chem. Eur. J.* 2015, 21 (5), 2222–2229.
- (a) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* 2013, 15 (10), 2558–2562. (b) de Nanteuil, F.; Loup, J.; Waser, J. *Org. Lett.* 2013, 15 (14), 3738–3741. (c) Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* 1997, 38 (34), 5949–5952. (d) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* 2007, 129 (31), 9631–9634. (e) Emmett, M. R.; Kerr, M. A. *Org. Lett.* 2011, 13 (16), 4180–4183. (f) England, D. B.; Kuss, T.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* 2001, 66, 4704–4709. (g) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* 2013, 135 (21), 7851–7854.
- Kim, A.; Kim, S.-G. *Eur. J. Org. Chem.* 2015, 2015 (29), 6419–6422.
- Chagarovskiy, A. O.; Budynina, E. M.; Ivanova, O. A. *Tetrahedron* 2009, 65, 5385–5392.
- We reported that the calcium-catalyzed Friedel-Crafts alkylation of 1-methylindole and **1** initially led to a mixture of alkylation product and an annulation product, which formed reversibly. Dulin, C. C.; Murphy, K. L.; Nolin, K. A. *Tetrahedron Lett.* 2014, 55, 5280–5282.
- (a) Chagarovskiy, A. O.; Ivanova, O. A.; Budynina, E. M.; Trushkov, I. V.; Melnikov, M. Y. *Tetrahedron Lett.* 2011, 52, 4421–4425. (b) Ivanova, O.A.; Budynina, E.M.; Grishin, Y.K.; Trushkov, I.V.; Verteletskii, P.V. *Angew. Chem., Int. Ed.*, 2008, 47, 1107–1110.
- (a) Davies, J.; Leonori, D. *Chem Commun* 2014, 50 (96), 15171–15174. (b) Begouin, J.-M.; Niggemann, M. *Chem. Eur. J.* 2013, 19, 8030–8041. (c) Morcillo, S. P.; Passet, M.; Floquet, S.; Coeffard, V.; Greck, C.; Bour, C.; Gandon, V. *Eur. J. Org. Chem.* 2016, (15), 2688–2694.

12. (a) Kaicharla, T.; Roy, T.; Thangaraj, M. *Angew. Chem. Int. Ed.* 2016, 55, 10061–10064. (b) Luo, Y.-C.; Ma, H.; Hu, X.-Q.; Xu, P.-F. *J. Org. Chem.* 2017, 82 (2), 1013-1023.
13. Sim, J.-T., Kim, J. *Korean. Chem. Soc.* 2016, 60, 374-377.
14. Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, 61, 4439–4449.
15. Goering, B. K. Ph.D. Dissertation, Cornell University, 1995.
16. Haslam, E. *Shikimic Acid Metabolism and Metabolites*, John Wiley & Sons: New York, 1993.
17. Buchanan, J. G.; Sable, H. Z. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 2, pp 1–95.
18. Lyle, F. R. U.S. Patent 5 973 257, 1985; *Chem. Abstr.* **1985**, 65, 2870.

ACCEPTED MANUSCRIPT

- A new Friedel-Crafts alkylation reaction that couples benzo[b]furan with activated cyclopropanes has been developed.
- The substitutions proceeded with complete regioselectivity and in good to excellent yield.
- Synthesis of  $\gamma$ -benzo[b]furanyl malonates.

ACCEPTED MANUSCRIPT

