Graphical Abstract

Brønsted acid-catalyzed 1,4-addition of 1,3,5-trimethoxybenzene to maleimides and acrylates

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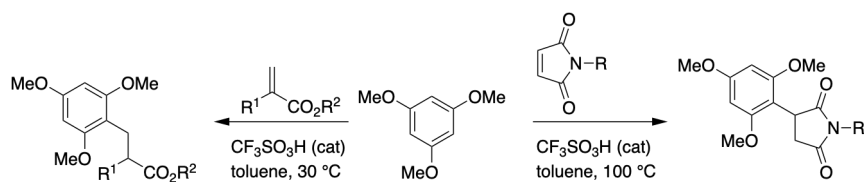Seanghai Hor, Kin-ichi Oyama, Nobuaki Koga, and Masaki Tsukamoto

Brønsted acid-catalyzed 1,4-addition of 1,3,5-trimethoxybenzene to maleimides and acrylates

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| ARTICLE INFO	ABSTRACT
	Several Brønsted acids were investigated as catalysts for 1,4-additions of 1,3,5-trimethoxybenzene to maleimides. Among the acids tested, trifluoromethanesulfonic acid in low polar solvents such as toluene and 1,2-dichloroethane was found to show high reactivity, enabling preparation of 3-(2,4,6-trimethoxyphenyl)succinimides. 1,4-Additions of 1,3,5-trimethoxybenzene to acrylates were also realized by a catalytic amount of trifluoromethanesulfonic acid in toluene.

Succinimide derivatives possessing an aromatic ring at the 3-position have been extensively studied due to their promise as therapeutics, including as anticonvulsants and cancer chemotherapeutics.[1–9] For screening of drug candidates and pharmacological applications, numerous succinimide analogues have been designed and synthesized.[9] Succinimides are also important synthons for transformations to other five-membered heterocycles, including ω-carbinol lactams,[10] maleimides,[11–13] pyrrolidines,[13,14] and pyrroles.[12] This background has prompted researchers to develop a variety of synthetic methods for succinimide derivatives. In the present study, we focused on the synthesis of 3-arylsuccinimides via 1,4-addition to maleimides (Scheme 1). In 1961, aluminum chloride was found to be efficient for unreactive nucleophiles such as benzene.[15] Recently, coupling reactions catalyzed by various transition-metals such as cobalt,[16] titanium,[17] ruthenium[12,18,19] or rhodium[14,20–23] were also reported. On the other hand, there are only two 1,4-addition reactions of aromatic ring to maleimide without a metal promoter. One is the reaction between maleimide and benzene in the presence of an excess amount of trifluoromethanesulfonic acid.[24] In this reaction, 3-phenylsuccinimide was obtained in ca. 10% yield. However, the main product was 5,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-one (ca. 70%) formed via the dicationic maleimide protonated at the two carbonyl oxygen atoms. The other is the 1,4-addition reaction between maleimide and *N,N*-disubstituted anilines using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent.[13] It should be noted that this reaction requires

nucleophiles bearing a nitrogen atom in almost all cases. To develop a straightforward, robust, scalable and ecologically sound synthetic method, we envisioned C–H functionalization by
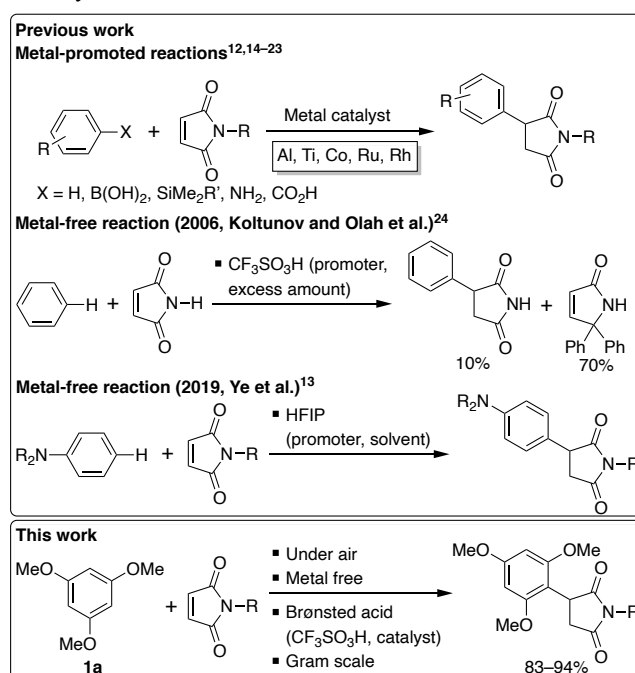
Scheme 1. Synthesis of 3-arylsuccinimides via 1,4-addition.
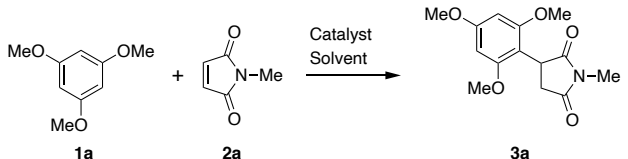
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a non-metal catalyzed reaction and selected alkoxybenzenes as the coupling partner of maleimide. The alkoxybenzenes have been drawing considerable attention due to their high nucleophilicity,[25] high potential as derivatizing agents,[26] and easy availability.[25] In addition, the alkoxybenzenes are eco-friendly and sustainable compounds, because they are components of lignin.[27] Herein, we disclose a novel Brønsted acid-catalyzed 1,4-addition of 1,3,5-trimethoxybenzene (**1a**) to maleimides. As an application of this reaction, 1,4-addition of **1a** to acrylates is also described.

As shown in Table 1, a combination of **1a** and *N*-methylmaleimide (**2a**) was selected to optimize the conditions as a model reaction. First, perchloric acid (pK_a (H$_2$O) = −15)[28,29] as a conventional strong acid in 1,4-dioxane[30] was tested because we have continuously studied reactions using perchlorates.[31,32] To our delight, with a catalyst amount of 10 mol% at 100 °C for 5 h under an argon atmosphere, *N*-methyl-3-(2,4,6-trimethoxyphenyl)succinimide (**3a**) was obtained in 63% conversion (entry 1). A similar result was obtained by using a 12-mL screw vial with a cap and operating under air without an argon atmosphere (entry 2). Therefore, the optimizations were

Table 1. 1,4-Addition of 1,3,5-trimethoxybenzene (**1a**) to *N*-methylmaleimide (**2a**).[a]

Entry	Catalyst (mol%)	Solvent	Convn, %
1[b]	HClO$_4$ (10)	1,4-dioxane	63
2	HClO$_4$ (10)	1,4-dioxane	58
3	MeSO$_3$H (10)	1,4-dioxane	<5
4	CF$_3$CO$_2$H (10)	1,4-dioxane	<5
5	CF$_3$SO$_3$H (10)	1,4-dioxane	57
6	TMSOTf (10)	1,4-dioxane	43
7	BF$_3$•OEt$_2$ (10)	1,4-dioxane	<5
8	Pd(OAc)$_2$ (10)	1,4-dioxane	<5
9	(CF$_3$)$_2$CHOH (10)	1,4-dioxane	<5
10	HClO$_4$ (10)	3:1 toluene–1,4-dioxane	90
11	HClO$_4$ (10)	3:1 DCE–1,4-dioxane	>95 (82)[d]
12	HClO$_4$ (10)	3:1 DMSO–1,4-dioxane	<5
13	HClO$_4$ (10)	3:1 DMF–1,4-dioxane	<5
14[c]	CF$_3$SO$_3$H (10)	DCE	>95
15[c]	CF$_3$SO$_3$H (5)	DCE	>95
16[c]	CF$_3$SO$_3$H (1)	DCE	84
17	CF$_3$SO$_3$H (10)	toluene	94 (84[d], 92[e])
18	CF$_3$SO$_3$H (5)	toluene	87

[a]Unless otherwise stated, the reaction was conducted on a 0.60 mmol scale in a 12-mL screw vial under the following conditions: [**1a**] = [**2a**] = 250 mM, 100 °C, 5 h.

[b]The reaction was conducted in a 20-mL Schlenk tube under argon.

[c]The temperature was set at 80 °C.

[d]Isolated yield.

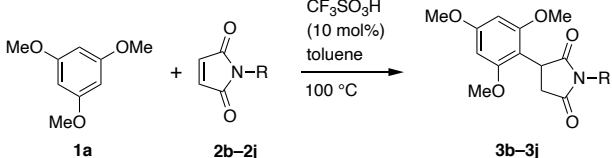[e]Isolated yield on a 1-gram scale after 4 h.

conducted in the vials for fast screening. With these promising results in hand, we next examined Brønsted acids, Lewis acids, and a palladium salt as catalysts (entries 3–8). Brønsted acids weaker than perchloric acid, such as methanesulfonic acid (pK_a (H$_2$O) = −1.9)[33,34] and trifluoroacetic acid (pK_a (H$_2$O) = 0.3),[34] did not practically catalyze the reaction (entries 3 and 4). Trifluoromethanesulfonic acid (pK_a (H$_2$O) = −15)[28,29] in 1,4-dioxane gave moderate conversion (entry 5). Other catalysts such as trimethylsilyl triflate (TMSOTf), boron trifluoride diethyl etherate, and palladium (II) acetate were less efficient than perchloric acid (entries 6–8). Use of HFIP as a catalyst did not afford **3a** at all (entry 9).[13] On the basis of the above results, we concluded that Brønsted acids catalyzed the 1,4-addition reaction and the high acidity was a significant factor.
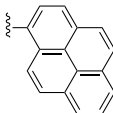
At this stage, perchloric acid was found to be the most active. Next, therefore, we investigated the solvent effect. We found that the use of a less polar solvent such as toluene and 1,2-dichloroethane (DCE) enhanced the reaction conversion and efficiency. Use of a 3:1 mixture of toluene and 1,4-dioxane afforded a higher conversion than 1,4-dioxane itself (entry 10), indicating that toluene was effective as a co-solvent. Furthermore, the conversion using a 3:1 mixture of DCE and 1,4-dioxane reached >95% (entry 11).

In contrast, use of polar solvents such as DMSO or DMF was not effective (entries 12, 13). Because the low polar solvents enhanced the reaction conversion, we re-examined trifluoromethanesulfonic acid as a superacid[35] in both DCE and toluene (entries 14–18). As expected, with a catalyst loading of 10 mol%, reaction in DCE or toluene was almost completed (entries 14 and 17). Remarkably, the reactivity was retained (>95%) even with 5 mol% of acid (entry 15) and was slightly decreased with 1 mol% of acid in DCE (entry 16). In toluene, 5 mol% of catalyst loading afforded 87% conversion (entry 18). It was revealed that trifluoromethanesulfonic acid in DCE or toluene effectively catalyzes the 1,4-addition reaction on a practical level. Because toluene is more ecologically sound than DCE, we selected entry 17 as the optimized conditions and conducted a 1-gram scale reaction to afford 92% yield. With a catalytic amount of the acid, the product is formed probably via a mono-protonated *N*-methylmaleimide. This is in sharp contrast to the report by Koltunov and Olah (Scheme 1).[24]

With the optimized conditions in hand, we changed maleimides **2b**–**2j** with various substituents R as shown in Table 2. The reactions proceeded similarly as judged by the isolated yields. Maleimide (**2b**) could be used as an acceptor (entry 1). A sterically bulky *t*-butyl group did not affect the yield (entry 2). An excellent functional group tolerance was observed for the hydroxy and carboxy groups (entries 3, 4). In the cases of the phenyl group (entry 5) and its para-substituted moieties (entries 6–8), the desired products were isolated easily upon addition of ethanol to the reaction mixture with or without recrystallization. Substituents at the para-position on the benzene ring had no effect on the yields. Pyrene containing succinimide **3j** with a fluorescent property was obtained in a yield of 83% (entry 9).

Next, we investigated the scope and limitation of benzenes with methoxy and/or methyl groups (**1b**–**1e**) in the 1,4-addition to *N*-methylmaleimide (**2a**), as shown in Figure 1 and Scheme 2. In the case of 1,3-dimethoxybenzene (**1b**), the reaction was complicated due to side-reactions and *N*-methyl-3-(2,4-dimethoxyphenyl)succinimide (**3k**) was obtained in less than 10% yield with inseparable impurities. By use of 2 equivalents of **1b** toward **2a** for 24 h, the yield of **3k** increased to 54% (Scheme 2). Using nucleophiles such as 1,2,3-trimethoxybenzene (**1c**), 1,2,3,4-tetramethoxy-5-methylbenzene (**1d**), and 1,2,3,4,5-
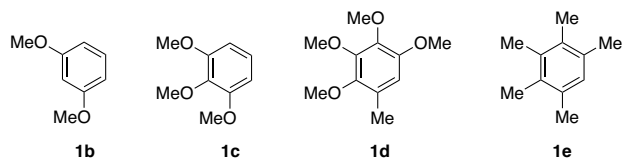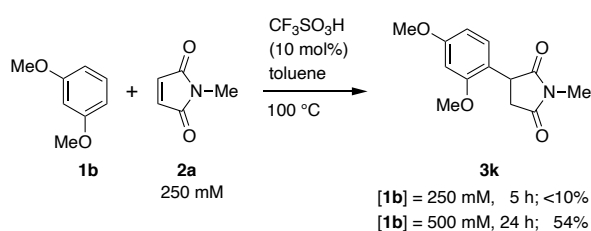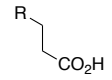
Table 2. 1,4-Addition of 1,3,5-trimethoxybenzene (**1a**) to various maleimides.[a]

Entry	R	Maleimide	Product	Isolated yield, %
1	H	**2b**	**3b**	84
2	*t*-Bu	**2c**	**3c**	83
3	(CH$_2$)$_2$OH	**2d**	**3d**	86
4[b]	(CH$_2$)$_5$CO$_2$H	**2e**	**3e**	86
5	Ph	**2f**	**3f**	89
6	4-MeOPh	**2g**	**3g**	80
7	4-BrPh	**2h**	**3h**	80
8	4-NO$_2$Ph	**2i**	**3i**	87 (94)[c]
9[b]		**2j**	**3j**	83

[a]The reaction was conducted on a 0.60 mmol scale in a 12-mL screw vial under the following conditions: [**1a**] = [maleimide] = 250 mM, 100 °C, 5 h.
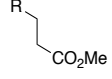
[b][**1a**] = 380 mM.
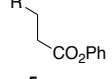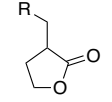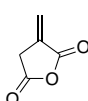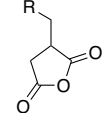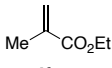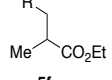
[c]On a 1-gram scale reaction without column chromatography.

Figure 1. Unreactive substituted benzenes in the 1,4-addition to *N*-methylmaleimide (**2a**) under the following conditions: [substituted benzene] = [**2a**] = 250 mM, [CF$_3$SO$_3$H] = 25 mM, toluene, 100 °C, 5 h.

Scheme 2. 1,4-Addition of 1,3-dimethoxybenzene (**1b**) to *N*-methylmaleimide (**2a**).

pentamethylbenzene (**1e**) gave no desired product at all. Unexpectedly, **1d** bearing a higher HOMO level than **1a**,[36] under the influence of four methoxy groups, was totally inactive. The re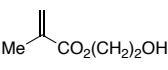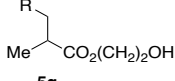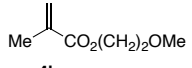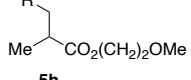sults suggest that high HOMO levels of nucleophiles are not the only governing factor for reactivity. The substitution pattern and number of the electron-donating groups might be crucial factors for both electric and steric effects.

Finally, the 1,4-addition reactions of 1,3,5-trimethoxybenzene (**1a**) to acrylic acid (**4a**) and its derivatives **4b**–**4h** were investigated as shown in Table 3. These reactions were conducted with two equivalents of **1a** at lower temperature (30 °C) in order to capture electrophiles rapidly while

Table 3. 1,4-Addition of 1,3,5-trimethoxybenzene (**1a**) to several acrylates.[a]

Entry	Acrylate	Time, h	Product (R = 2,4,6-trimethoxyphenyl)	Isolated yield, %
1	**4a**	24	**5a**	86
2	**4b**	24	**5b**	85
3	**4c**	24	**5c**	78
4[b]	**4d**	24	**5d**	76
5[b]	**4e**	24	**5e**	73
6	**4f**	1	**5f**	NR[c]
7[d]	**4f**	1	**5f**	NR[c]
8	**4g**	1	**5g**	75
9	**4h**	1	**5h**	NR[c]

[a]Unless otherwise stated, the reaction was conducted in a 12-mL screw vial under the following conditions: [**1a**] = 500 mM, [acrylate] = 250 mM, [CF$_3$SO$_3$H] = 25 mM (10 mol%), toluene, 30 °C.

[b]1-Gram scale reaction in a 100-mL round bottom flask.

[c]No reaction.

[d]The reaction was conducted with an equimolar amount of ethanol to **4f**.

suppressing side reactions, because acrylic acid derivatives are highly reactive and more unstable than maleimides.[37] The reactions of acrylic acid (**4a**), its methyl and phenyl esters afforded 3-substitued propanoic acids **5a**–**5c** in good yields (entries 1–3).[38] α-Methylene-γ-butyrolactone (**4d**) (entry 4) and itaconic anhydride (**4e**) (entry 5) showed a similar yield as above, indicating that α-substituents with a cyclic structure do not decrease the reactivity. In contrast, the reaction with ethyl methacrylate (**4f**) could not proceed and the starting materials remained (entry 6). The steric hindrance of the methyl group at the pivotal reaction point might be influential for the reactivity. Unexpectedly, reaction with 2-hydroxyethyl ester **4g** proceeded smoothly to afford 1,4-adduct **5g** in 75% yield after only 1 h along with two byproducts, **6a** and **6b** (Figure 2), formed via ether formation and transesterification (ca. totally 10% yield) (entry 8). Protecting the hydroxy function of **4g** with a methyl
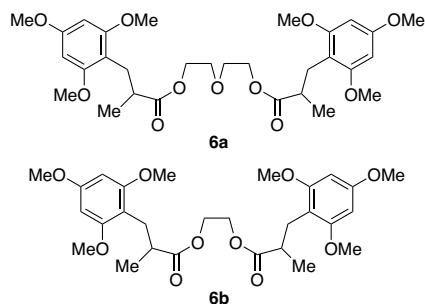
Figure 2. Two byproducts, **6a** and **6b**, formed in the 1,4-addition of 1,3,5-trimethoxybenzene (**1a**) to 2-hydroxyethyl methacrylate (**4g**).

group prevented **1a** from nucleophilic attack (entry 9), indicating that the hydroxy group is essential for this transformation. To gain further insight into the hydroxy group effect, a control experiment using **4f** in the presence of an equimolar amount of ethanol to **4f** was conducted (entry 7). The result clearly showed that ethanol did not activate **4f** intermolecularly. On the basis of the above experiments (entries 6–9), we speculate that the hydroxy group activates the carbonyl group of **4g** in an intramolecular fashion.

In conclusion, we have developed a Brønsted acid-catalyzed 1,4-addition of 1,3,5-trimethoxybenzene to maleimides and acrylates. The reaction proceeded smoothly even when containing carboxylic acid and free alcohol. The solvent effect was a significant factor in this catalytic reaction system. Low polar solvents such as toluene and DCE enhanced the reaction efficiency dramatically. Especially for addition to *N*-methylmaleimide, catalyst loading can be decreased to 1–5 mol%. Furthermore, the reaction operation is quite concise and can be easily scaled up. All synthesized trimethylphloroglucinol-succinimide hybrids (**3a–3j**) and some of the 1,4-adducts (**5c–5e**, **5g**) with acrylates belong to a new class of compounds. Applications of this 1,4-addition are ongoing in our group.

Acknowledgments

References and notes

1. Miller, C. A.; Scholl, H. I.; Long, L. M. *J. Am. Chem. Soc.* **1951**, *73*, 4895–4898.
2. Millichap, J. G. *Lancet* **1952**, *260*, 907–910.
3. Kornet, M. J.; Crider, A. M.; Magarian, E. O. *J. Med. Chem.* **1977**, *20*, 405–409.
4. Crider, A. M.; Kolczynski, T. M.; Yates, K. M. *J. Med. Chem.* **1980**, *23*, 324–326.
5. Rankin, G. O. *J. Toxicol. Environ. Health B* **2004**, *7*, 399–416.
6. Peng, X.; Wang, F.; Li, L.; Bum-Erdene, K.; Xu, D.; Wang, B.; Sinn, A. A.; Pollok, K. E.; Sandusky, G. E.; Li, L.; Turchi, J. J.; Jalal, S. I.; Meroueh, S. O. *Mol. BioSyst.* **2014**, *10*, 581–591.
7. Crosignani, S.; Bingham, P.; Bottemanne, P.; Cannelle, H.; Cauwenberghs, S.; Cordonnier, M.; Dalvie, D.; Deroose, F.; Feng, J. L.; Gomes, B.; Greasley, S.; Kaiser, S. E.; Kraus, M.; Négrerie, M.; Maegley, K.; Miller, N.; Murray, B. W.; Schneider, M.; Soloweij, J.; Stewart, A. E.; Tumang, J.; Torti, V. R.; Van den Eynde, B.; Wythes, M. *J. Med. Chem.* **2017**, *60*, 9617–9629.
8. Wróbel, M. Z.; Chodkowski, A.; Herold, F.; Marciniak, M.; Dawidowski, M.; Siwek, A.; Starowicz, G.; Stachowicz, K.; Szewczyk, B.; Nowak, G.; Belka, M.; Bączek, T.; Satała, G.; Bojarski, A. J.; Turło, J. *Eur. J. Med. Chem.* **2019**, *183*, 111736.
9. Zhao, Z.; Yue, J.; Ji, X.; Nian, M.; Kang, K.; Qiao, H.; Zheng, X. *Bioorg. Chem.* **2021**, *108*, 104557.
10. Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179–187.
11. Bergman, J.; Desarbre, E.; Koch, E. *Tetrahedron* **1999**, *55*, 2363–2370.
12. Mandal, A.; Sahoo, H.; Dana, S.; Baidya, M. *Org. Lett.* **2017**, *19*, 4138–4141.
13. Li, B.; Mao, Q.; Zhou, J.; Liu, F.; Ye, N. *Org. Biomol. Chem.* **2019**, *17*, 2242–2246
14. Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 4611–4614.
15. Mustafa, A.; Asker, W.; Khattab, S.; Zayed, S. M. A. D. *J. Org. Chem.* **1961**, *26*, 787–789.
16. Zhang, Z.; Han, S.; Tang, M.; Ackermann, L.; Li, J. *Org. Lett.* **2017**, *19*, 3315–3318.
17. Yang, Z.-H.; Chen, Z.-H.; An, Y.-L.; Zhao, S.-Y. *RSC Advances* **2016**, *6*, 23438–23447.
18. Bettadapur, K. R.; Lanke, V.; Prabhu, K. R. *Org. Lett.* **2015**, *17*, 4658–4661.
19. Kumar, N. Y. P.; Rogge, T.; Yetra, S. R.; Bechtoldt, A.; Clot, E.; Ackermann, L. *Chem. Eur. J.* **2017**, *23*, 17449–17453.
20. Iyer, P. S.; O'Malley, M. M.; Lucas, M. C. *Tetrahedron Lett.* **2007**, *48*, 4413–4418.
21. Han, S. H.; Kim, S.; De, U.; Mishra, N. K.; Park, J.; Sharma, S.; Kwak, J. H.; Han, S.; Kim, H. S.; Kim, I. S. *J. Org. Chem.* **2016**, *81*, 12416–12425.
22. Nakao, Y.; Chen, J.; Imanaka, H.; Hiyama, T.; Ichikawa, Y.; Duan, W.-L.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 9137–9143.
23. He, Q.; Yamaguchi, T.; Chatani, N. *Org. Lett.* **2017**, *19*, 4544–4547.
24. Koltunov, K. Y.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *Eur. J. Org. Chem.* **2006**, 4861–4866
25. Talukdar, R. *RSC Adv.* **2020**, *10*, 31363–31376.
26. Dias, R. P.; Schammel, M. H.; Reber, K. P.; Sivey, J. D. *Anal. Methods* **2019**, *11*, 5521–5532.
27. Upton, B. M.; Kasko, A. M. *Chem. Rev.* **2016**, *116*, 2275−2306.
28. Malakar, T.; Zimmerman, P. M. *J. Org. Chem.* **2021**, *86*, 3008–3016.
29. Trummal, A.; Lipping, L.; Kaljurand, I.; Koppel, I. A.; Leito, I. *J. Phys. Chem. A* **2016**, *120*, 3663–3669.
30. Commercially available 0.1 M perchloric acid (1,4-dioxane solution) was used as a catalyst.
31. Shirouzu, H.; Morita, H.; Tsukamoto, M. *Tetrahedron* **2014**, *70*, 3635–3639.
32. Basu, N.; Oyama, K.-i.; Tsukamoto, M. *Tetrahedron Lett.* **2017**, *58*, 1921–1924.
33. Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 2342–2354.
34. Gutowski, K. E.; Dixon, D. A. *J. Phys. Chem. A* **2006**, *110*, 12044–12054.
35. Kütt, A.; Rodima, T.; Saame, J.; Raamat, E.; Mäemets, V.; Kaljurand, I.; Koppel, I. A.; Garlyauskayte, R. Y.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Bernhardt, E.; Willner, H.; Leito, I. *J. Org. Chem.* **2011**, *76*, 391–395.
36. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley; London, 1976.
37. For detail, see supplementary material.
38. The reaction of 1,3-dimethoxybenzene (**1b**) with methyl acrylate (**4b**) did not proceed under conditions identical to those in Table 3.

Supplementary Material

Supplementary material, including the detailed experimental procedures and spectral data related to this article, can be found in online at the journal's homepage.