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Authors: Huimiao Zhang and Patrick Toy

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Halogen-Bond-Catalyzed Friedel–Crafts Reactions of Furans Using a 2,2’-Bipyridine-Based Catalyst

Huimiao Zhang,[a] and Patrick H. Toy[a,]*

[a] Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. of China
Tel: +852-28592167
Fax: +852-28571586
E-mail: phtoy@hku.hk

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Abstract. A halogen-bond donor based on a 2,2’-bipyridine framework has been synthesized, and used to catalyze Friedel–Crafts reactions of furans. Electrophiles used successfully in these reactions included various enones, an aldehyde, and a carboxylic acid anhydride. The yields of the reactions were generally good using a moderate catalyst loading (0.025 or 0.1 equiv) at a relatively low temperature (room temp. or 50 °C) in acetonitrile. The catalyst used was designed with a biaryl scaffold so that if it indeed proved to be an efficient halogen-bond donor organocatalyst, an enantioenriched version of it could potentially serve as a stereoselective catalyst.

Keywords: halogen bond; organocatalysis; Friedel–Crafts reaction; furans; enones

Non-covalent halogen bonds are interactions that can be considered to be functionally related to hydrogen bonds,[1] and the use of organic halides as halogen-bond donors to catalyze organic reactions has become an active area of research.[2] In this context organic halides have been used experimentally to activate quinolines,[3] imines,[4] acyl iminium ions,[5] carbon-halogen bonds,[6] silicon-halogen bonds,[7] metal-halogen bonds,[8] aldehydes and ketones,[9] Michael acceptors,[10] thioamides,[11] trichloroacetimidates,[12] hydantoins,[13] alkoxyallenes,[14] vinyl indoles,[15] ethers,[16] and iodonium ylides[17] in various transformations. There has even been a report of using organic halides as templating catalysts for macrocyclization reactions.[18] As for the organic halide catalysts used in these reactions, the majority of them were achiral. While some chiral catalysts have been reported, e.g. **1**-**7** (Figure 1), only a few of these were used in stereoselective reactions.[19-22] In the first reported example of asymmetric catalysis using an organic halide, **4** was used in Michael/Henry reaction cascades for the synthesis of thiochromanes that were moderately enantioselective (10 examples, 19-69% ee).[23] Later, **5**, in which the chirality is in the anion, was used to catalyze a Friedel–Crafts reaction between a Michael acceptor and indole that was poorly enantioselective (22% ee).[24] More recently **6** was used to catalyze a Mukiyama aldol reaction that was modestly enantioselective (33% ee).[25] Finally, and perhaps most successfully, alkaloid-based compounds such as **7** were reported as catalysts for a range highly enantioselective Mannich reactions (3 different types of reactions, 39 total examples, 65-98% ee).[26]

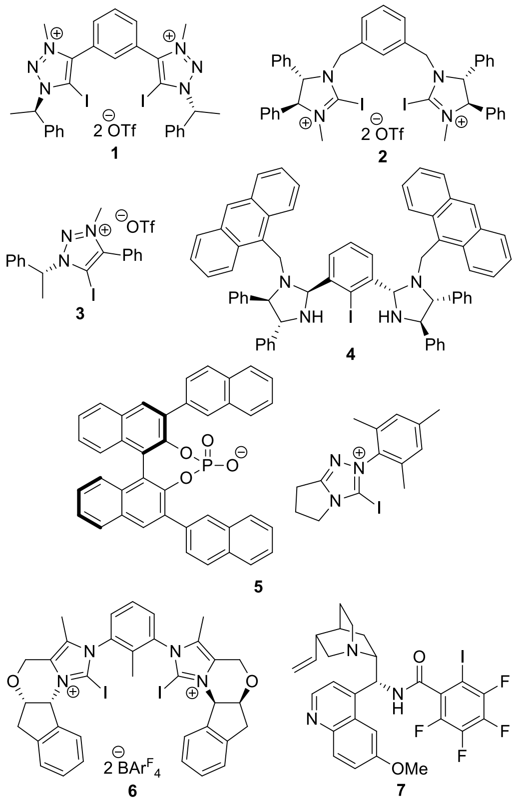

Figure 1 Chiral halogen-bond donor catalysts.

In the field of halogen-bond catalysis, we previously reported the use of an achiral bidentate bis(benzimidazolium iodide) salt to catalyze Friedel–Crafts reactions of aldehyde and ketone electrophiles and indole nucleophiles to form bis(indolyl)methanes,[27] and Povarov reactions between imines and electron-rich dienophiles,[28] that were similar to reactions reported by others using different halogen-bond-donating catalysts.[29,30] As we considered the possibility of performing the later reactions enantioselectively and surveyed the state of the art, we realized that organic halide halogen-bond donors with an axis of chirality, as in the anion of **5**, have not been examined as catalysts, even though chiral compounds such as those based on a 1,1'-binapthyl skeleton have been wildly successful as catalysts and ligands in asymmetric catalysis.[31] We were thus inspired by the report of **8** as a catalyst in bromocarbocyclization reactions (Figure 2).[13] Since it is well established that bidentate halogen-bond donors are more efficient catalysts than monodentate analogues,[6c,6f] and we previously found that iodonium tetrafluroborate and triflate salts were both viable catalysts,[27,28] we targeted **9a** and **9b** for evaluation as halogen-bond donor catalysts, since enantiomerically enriched versions of them could potentially be prepared if they proved to be good catalysts. Herein we report the synthesis of **9a** and its use as a catalyst for Friedel–Crafts reactions of furans.

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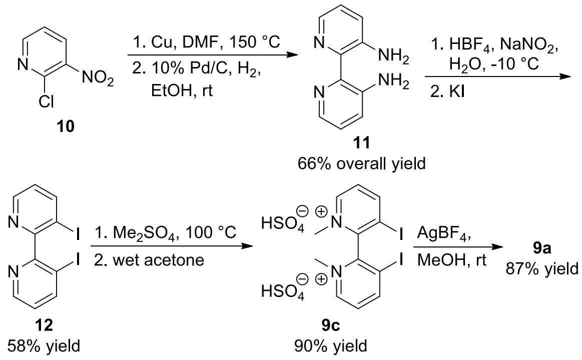
9a: X = BF_4
9b: X = OTf

Figure 2 Pyridinium iodide halogen-bond donors.

Synthesis of our targeted catalysts started with commercially available **10** (Scheme 1). This was transformed into **11** via an Ullman coupling/reduction reaction sequence.[32] Subsequent conversion of **11** into **12** was achieved using a procedure previously reported for the synthesis of an isomer of it.[33] Disappointingly, treatment of **12** with $(Me_3O)BF_4$ or MeOTf failed to cleanly afford **9a** or **9b**, respectively, no matter what conditions we used. Usually a mixture of mono- and di-methylated products was obtained, and re-subjecting the mixtures to alkylation conditions never resulted in pure **9a** or **9b**. However, we were able to successfully react **12** with Me_2SO_4 at high temperature to afford **9c**, which in turn could be converted into **9a** using $AgBF_4$. At this point we examined the stability of **9a** in solution since its decomposition could in theory lead to the formation of acid, I_2 or a radical species that could potentially catalyze the reactions we planned to perform. For this study we chose to use CD_3CN/D_2O (9:1) as the solvent at 70 °C since MeCN proved to be a good solvent for halogen-bond catalysis in our previous research, and water could inadvertently be present due to local environmental conditions. Gratifyingly ^1H-NMR analysis showed no evidence of any hydrolysis/decomposition of **9a**, even after 24 h (see Supporting Information).



Scheme 1 Synthesis of **9c** and **9a**.

The structures of **9a** and **9c** were confirmed by single-crystal X-ray structural analysis, and they both show evidence of halogen bonding in the solid state (Figure 3). Notably, the pyridinium rings of both structures are nearly perpendicular, with dihedral angles of 86.2° and 89.7°, respectively, for **9a** and **9c**. In the structure of **9a**, the C-I-F bond angle is 166°, as might be expected for a halogen bond. Additional evidence of halogen bonding in **9a** is the I to F distance of 2.98 Å, which is shorter than the sum of the van der Waals radii (3.45 Å).[34] The structure of **9c** exhibits similar features, with a C-I-O bond angle of 162°, and an I to O distance of 2.80 Å, compared to the sum of the van der Waals radii of 3.50 Å.[34]

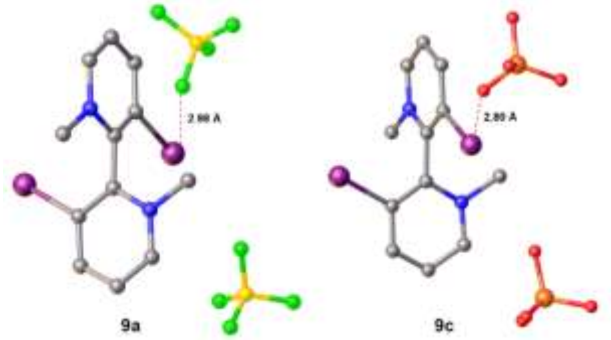


Figure 3 X-ray structures of **9a** and **9c** (hydrogen atoms omitted for clarity).

Since halogen-bond-catalyzed Friedel–Crafts reactions between various Michael acceptor electrophiles and indole,[25,27,35] *N*-methylpyrrole,[36] and a variety of thiophenes[37] have previously been reported, we chose to study reactions between nucleophilic furans and various electrophiles in this project.[38-40] Specifically, the reaction between 2-methylfuran (**13a**) and methyl vinyl ketone (**14a**) to

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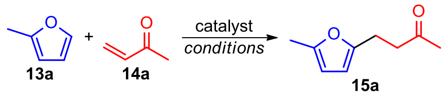
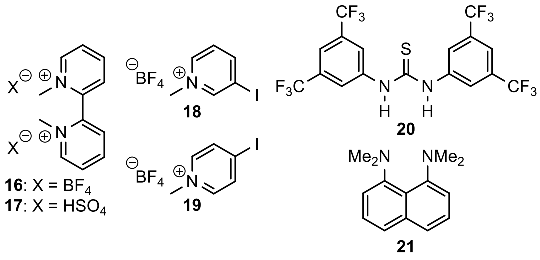
form **15a** was initially examined (Table 1). Gratifyingly, when 0.025 equiv of **9a** was used to catalyze the reaction at room temperature in MeCN, very high yield of **15a** was obtained after 4 h (entry 1). When MeOH was used as the solvent, the reaction was much more sluggish, and 24 h was required to obtain a similar yield (entry 2). When **9c** was used as the catalyst, slightly lower yield was obtained compared to when **9a** was used (entry 3), so **9a** was used for going forward. In order to assess the scalability of the reaction catalyzed by **9a**, it was performed on a 15-fold larger scale, with good results (entry 4). A control reaction using no catalyst resulted in no reaction after 24 h (entry 5), as did reactions using uncharged **12** (entry 6), and non-halogenated analogues **16** and **17** (see Supporting Information) at 50 °C (entries 7 and 8). Thus, it is clear that the catalyst for these reactions must be an electron-deficient organic halide. When twice the amount of Bu$_4$NCl compared to the amount of **9a** was added, no reaction occurred (entry 9), providing additional evidence of halogen bonding between **9a** and **14a** being operative in this reaction. Replacing **9a** with 0.10 equiv of monoiodo analogues **18** and **19** (see Supporting Information) resulted in only very low yield of **15a** after 24 h at 50 °C (entries 10 and 11). Thus, it seems that there is synergy between the two iodine atoms in **9a** that make it a very effective catalyst. In order to compare halogen-bonding catalysis to hydrogen bonding catalysis, thiourea **20** was examined in this reaction, but no reaction occurred (entry 12).

In order to rule out the possibility of adventitious/hidden acid being responsible for the observed catalysis, a reaction was performed using **9a** together with pyridine (0.013 equiv), and good yield of **15a** could still be obtained, albeit after a longer reaction time (entry 13). A similar result was obtained when proton sponge **21** (0.013 equiv) was added to the reaction instead of pyridine (entry 14). Furthermore, when HBF$_4$ was used as the catalyst instead of **9a**, only very low yield of **15a** was obtained under otherwise identical reaction conditions (entry 15). This was also the case when I$_2$ was used as the catalyst for this reaction (entry 16), so it seems unlikely that I$_2$ contamination of **9a**, or its generation during the reaction is responsible for the observed catalysis. In order to also rule out the possibility of a radical process being involved in the reaction, a reaction with an equal amount of BHT compared to **9a** was performed, and the reaction proceeded unchanged (entry 17). Overall the results of entries 13-17 support our observation that **9a** does not decomposed during the reactions to generate an acid, iodine or radical species that functions as a hidden catalyst, and provide support for the notion that **9a** does indeed act as a halogen-bond donor catalyst in these reactions.

Table 1 Friedel–Crafts reactions between **13a** and **14a**.[a]



Entry	Catalyst (equiv)	Solvent	Temp	Time (h)	Yield[b] (%)
1	**9a** (0.025)	MeCN	rt	4	84
2	**9a** (0.025)	MeOH	rt	24	83
3	**9c** (0.025)	MeCN	rt	4	75
4[c]	**9a** (0.025)	MeCN	rt	4	83
5	Nil	MeCN	rt	24	0
6	**12** (0.025)	MeCN	50 °C	24	0
7	**16** (0.025)	MeCN	50 °C	24	0
8	**17** (0.025)	MeCN	50 °C	24	0
9	**9a** (0.025), Bu$_4$NCl (0.05)	MeCN	rt	4	0
10	**18** (0.10)	MeCN	50 °C	24	25
11	**19** (0.10)	MeCN	50 °C	24	30
12	**20** (0.025)	MeCN	50 °C	24	0
13	**9a** (0.025), pyridine (0.013)	MeCN	rt	24	68
14	**9a** (0.025), **21** (0.13)	MeCN	rt	24	70
15	HBF$_4$ (0.025)	MeCN	rt	4	12
16	I$_2$ (0.025)	MeCN	rt	4	12
17	**9a** (0.025), BHT (0.025)	MeCN	rt	4	85



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[a] General reaction conditions: **13a** (1.0 mmol), **14a** (1.5 mmol), catalyst (0.025 mmol), in MeCN (3 mL).

[b] Isolated yield.

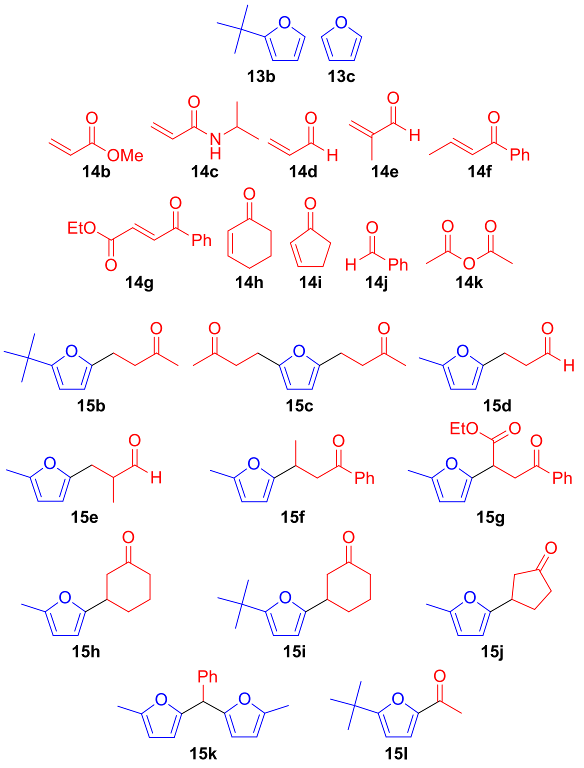
[c] Reaction performed using **13a** (15.0 mmol), **14a** (22.5 mmol), **9a** (0.375 mmol) in MeCN (45 mL).

Next, in order to test the general utility of **9a** in catalyzing Friedel–Crafts reactions between nucleophilic furans and various electrophiles, we performed a series of reactions involving combinations of **13a-c** and **14a-k** to produce **15b-l** (Table 2). Replacing **13a** with **13b** in the reaction with electrophile **14a** allowed for **15b** to be prepared efficiently (entry 1). When **13c** was used as the nucleophile with **14a** (3.0 equiv), a double Friedel–Crafts reaction was achieved to afford **15c** in high yield, albeit with higher catalyst loading (0.10 equiv) and temperature (50 °C) (entry 2). When **14a** was replaced by either ester **14b** or amide **14c** in the reaction with **13a**, no product was formed (entries 3 and 4). When aldehyde **14d** or **14e** was used as the electrophile in reactions with **13a**, product **15d** or **15e** was obtained, respectively, in high yield (entries 5

Table 2 Friedel–Crafts Reactions Catalyzed by **9a**[a]

furan **13** + electrophile **14** $\xrightarrow[\text{conditions}]{\mathbf{9a}\text{, MeCN}}$ product **15**

Entry	Furan	Electrophile	Product	**9a** (equiv)/ Temp (°C)/ time (h)	Yield[b] (%)
1	**13b**	**14a**	**15b**	0.025/rt/4	80
2	**13c**	**14a**	**15c**	0.10/50/4	80
3	**13a**	**14b**	nil	0.10/50/24	nil
4	**13a**	**14c**	nil	0.10/50/24	nil
5	**13a**	**14d**	**15d**	0.025/rt/4	80
6	**13a**	**14e**	**15e**	0.025/rt/4	82
7	**13a**	**14f**	**15f**	0.10/50/4	80
8	**13a**	**14g**	**15g**	0.025/rt/24	86
9	**13a**	**14h**	**15h**	0.10/50/24	80
10	**13b**	**14h**	**15i**	0.10/50/24	82
11	**13a**	**14i**	**15j**	0.10/50/48	30
12	**13a**	**14j**	**15k**	0.10/50/24	80
13	**13b**	**14k**	**15l**	0.10/50/24	40



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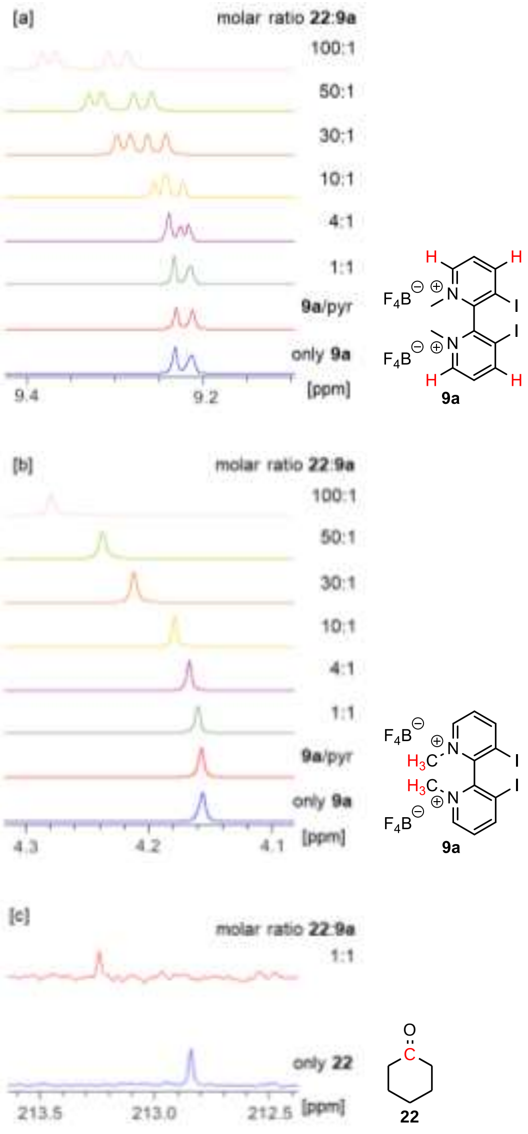
[a] General reaction conditions: **13** (1.0 mmol), **14** (1.5 mmol), **9a**, in MeCN (3 mL).
[b] Isolated yield.

and 6). Michael acceptors with β-substituents **14f** and **14g** were also viable electrophiles, as evidenced by the synthesis of **15f** and **15g**, respectively (entries 7 and 8). However, higher catalyst loading and temperature were required for the former reaction, and a longer reaction time was necessary for the later reaction. Cyclic enones **14h** and **14i** were used successfully with high catalyst loading and temperature in the synthesis of **15h-j** (entries 9-11).



[a] ^{1}H NMR signals of the ring protons of **9a**.
[b] ^{1}H NMR signal of methyl protons of **9a**.
[c] ^{13}C NMR signal of carbonyl carbon of **22**.

Figure 4 NMR studies.

Finally, we found that other electrophiles besides Michael acceptors could also be in these reactions. For example, benzaldehyde (**14j**) reacted with **13a** (3.0 equiv) to afford **15k** (entry 12), and acetic anhydride (**14k**) afforded **15l** in moderate yield when reacted with **13b** (entry 13).

Additional evidence for halogen bonding being operative in our reactions was obtained from a series of NMR studies. For these we chose to study the interaction between **9a** and cyclohexanone (**22**), since this ketone was used as a surrogate in for **14a** in a previous report (Figure 4).[10a] In the first experiments, we examined the change in chemical shift of 4 of the ring protons in **9a** as increasing amounts of **22** were added (Figure 4a). These measurements were performed in the presence of 2 equiv of pyridine to ensure that no hidden acid was present. As can be seen, this base had no noticeable effect on the chemical shift of the protons of interest, but addition of ever increasing amounts of **22** clearly shifted the protons downfield, which is evidence for a halogen-bonding interaction between **9a** and **22**.[10a] This notion is supported by the observation that the protons of the methyl groups of **9a** likewise exhibited a similar downfield shift in the presence increasing amounts of **22** (Figure 4b).[37] It should be noted that similar trends were observed when of mixtures of **13a** and **9a** were studied (Figure SI-1), that indicate that **9a** can also interact with the oxygen atom of the furan substrates. Finally, the carbonyl carbon atom of **22** also shifted downfield in the presence of an equimolar amount of **9a** (Figure 4c).

Based on our results, we believe that **9a** is able to catalyze Friedel–Crafts reactions of between furan nucleophiles **13** and carbonyl electrophiles **14** by formation of complex **A** (Figure 5). The greater catalytic efficiency of **9a** compared to that of **18** and **19** (Table 1, entry 1 vs. entries 10 and 11) seems to indicate that both iodine atoms of **9a** are involved in substrate activation, as in the case of other organic halide halogen-bond donor catalysts bearing multiple halogen atoms.[6c,6f] Reaction of the furan at the carbonyl carbon is thus facilitated so that the reaction can proceed to produce the observed products.

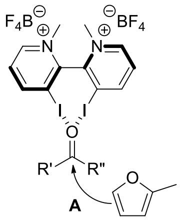


Figure 5 Halogen-bond activation of carbonyl compounds by **9a**.

In summary, we have designed and synthesized a new bidentate halogen-bond donor catalyst based on a 2,2'-bipyridine skeleton that possesses an axis of chirality, and used it to catalyze a range of Friedel–Crafts reactions between furan nucleophiles and a variety of electrophiles. Having established the utility of this catalyst, we are now exploring the possibility of preparing enantiomerically enriched versions of **9a** that can be examined as stereoselective organic catalysts, and we will present our results in due course.

Experimental Section

General Procedure for the Friedel–Crafts Reactions: To a solution of **9a** (0.025 or 0.10 equiv) in anhydrous CH_3CN (3 mL) was added furan **13** (1 mmol) and electrophile **14** (1.5 mmol). The mixture was stirred at rt or 50 °C under an argon atmosphere, and the progress of the reaction was monitored by TLC or ^1H NMR analysis. After it was finished, the mixture was concentrated, and the product **15** was purified by silica gel chromatography (EtOAc:hexane).

Crystal Structures: CCDC 2008497 (**9c**) and CCDC 2008498 (**9a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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Halogen-Bond-Catalyzed Friedel–Crafts Reactions of Furans Using a 2.2’-Bipyridine-Based Catalyst

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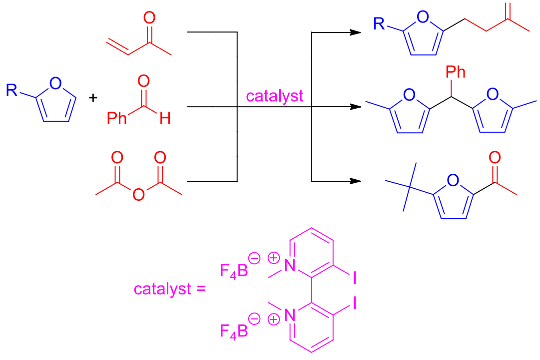
Huimiao Zhang, and Patrick H. Toy*



bidentate halogen bond donor