OL Organic Letters
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

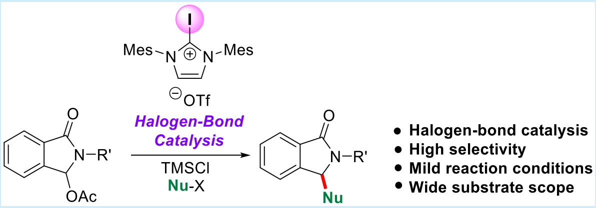
Halogen-Bond-Catalyzed Addition of Carbon-Based Nucleophiles to *N*-Acylimminium Ions

Yuk-Cheung Chan and Ying-Yeung Yeung*

Department of Chemistry, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China

Supporting Information

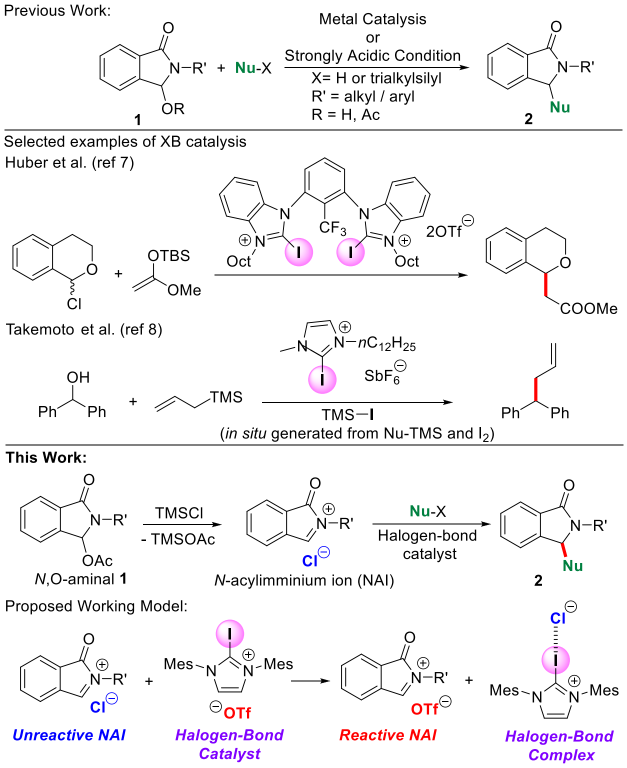
ABSTRACT: *N*-acylimminium ions are an important class of synthetic intermediates to produce diverse products upon treatment with different nucleophiles. Most of the reported catalytic protocol involved moisture-sensitive Lewis acids or transition metal. Herein, we reported an organocatalytic version by using halogen-bond catalyst as mild Lewis acid through anion-abstraction strategy. A preliminary result of enantioselective version by employing a chiral BINOL-phosphate anion has also been demonstrated.



N-acylimminium ions (NAI) are an important class of synthetic intermediates in organic synthesis.[1] This class of reactive intermediates can be transformed to a wide spectrum of useful products through reactions with various nucleophiles such as indoles, malonates, and silyl enol ether.[1a] For example, NAI-derived α-oxo-lactams **1** are frequently employed as intermediates for the synthesis of biologically relevant molecules. Typically, treatment of commercially available and inexpensive *N*,*O*-aminals **1** with Brønsted or Lewis acids can generate the highly active NAI in situ, through the elimination of the OR groups (Scheme 1). Different types of metal catalysts, including Au/Ag, Pd/Ag, Sn, Sc, and In, have been proven to be efficient in generating NAI.[2] Strongly acidic promoters, such as BF_3, trialkylsilyl triflate, $TiCl_4$ and trifluoromethanesulfonic acid (TfOH), were also investigated previously.[3] Recently, the use of σ-hole interaction to generate isoquinoline-derived acylimminium ions has also been documented.[4]

The halogen bond (XB) has emerged as a mild Lewis acid and has received increasing attention in the field of organocatalysis over the past few years.[5] XB has been successfully applied to C═X double bond (X = O, N, S, etc.) activation[6] and anion-binding catalysis.[7] For instance, Huber et al. reported the chloride ion binding of 1-chloroisochroman, followed by reaction with the ketene silyl acetal. Takemoto also reported the use of XB to activate silyl halide for the dehydroxylative coupling of benzyl alcohol derivatives.[8] We hypothesized that XB could serve as a mild and organocatalytic protocol for the environmentally benign generation of NAI with high functional group compatibility and hopefully enantioselective version with diverse class of nucleophiles. In this context, we disclosed our recent development of XB-catalyzed C−C bond formation between carbon-based nucleophiles and in-situ-generated NAI from *N*,*O*-aminals and trimethylsilyl chloride (TMSCl) under ambient conditions.

Scheme 1. Halogen-bond (XB)-Catalyzed Functionalizations of *N*,*O*-Aminals



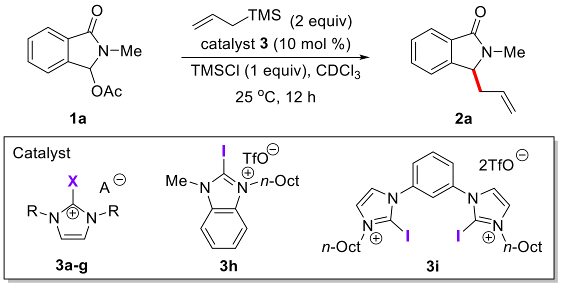
At the outset of our investigation, *N*,*O*-aminal **1a** and allyltrimethylsilane were employed as the reaction partners. TMSCl was used as an activator that could convert **1a** to the corresponding preactivated *N*-acylimminium chloride. We

Received: June 11, 2019

DOI: 10.1021/acs.orglett.9b02006
Org. Lett. XXXX, XXX, XXX−XXX

reasoned that the chloride anion could interact with the XB catalyst to undergo anion-metathesis and give the highly reactive *N*-acyliminium triflate (Scheme 1), which could be subsequently attacked by nucleophile (Nu−X) to furnish the allylation product **2a**. Only a trace amount of product was detected in the absence of catalyst (Table 1, entry 1). Reaction with 10 mol % of iodine $\mathrm{XB[BF_4]^-}$ catalyst **3a** was also found to be sluggish (Table 1, entry 2). To our delight, the $\mathrm{XB[OTf]^-}$ catalyst **3b** gave the desired product **2a** in 99% yield (Table 1, entry 3). Similar results were observed when using $\mathrm{XB[SbF_6]^-}$ **3c** and $\mathrm{XB[NTf_2]^-}$ **3d** as the catalysts (Table 1, entries 4 and 5). These results highlighted the intriguing anion dependence of the catalytic effect in XB catalysis.[7a,9] We speculate that the tetrafluoroborate in **3a** might act as a fluoride source that might poison the XB donor. The catalytic effect completely diminished when replacing the iodine atom in catalyst **3b** with hydrogen (i.e., **3e**), indicating the crucial role of the XB donor in this catalytic transformation (Table 1, entry 6). Lower reactivity was observed when replacing the mesityl (1,3,5-trimethylphenyl) substituents in **3b** with *n*-octyl/methyl or 2,6-diisopropylphenyl groups (Table 1, entries 7 and 8) or using the bidentate XB donor **3i** (Table 1, entry 10), suggesting that steric and/or electronic property of the substituent might affect the XB strength in the catalysts.[10]

Table 1. Conditions Optimization[a]

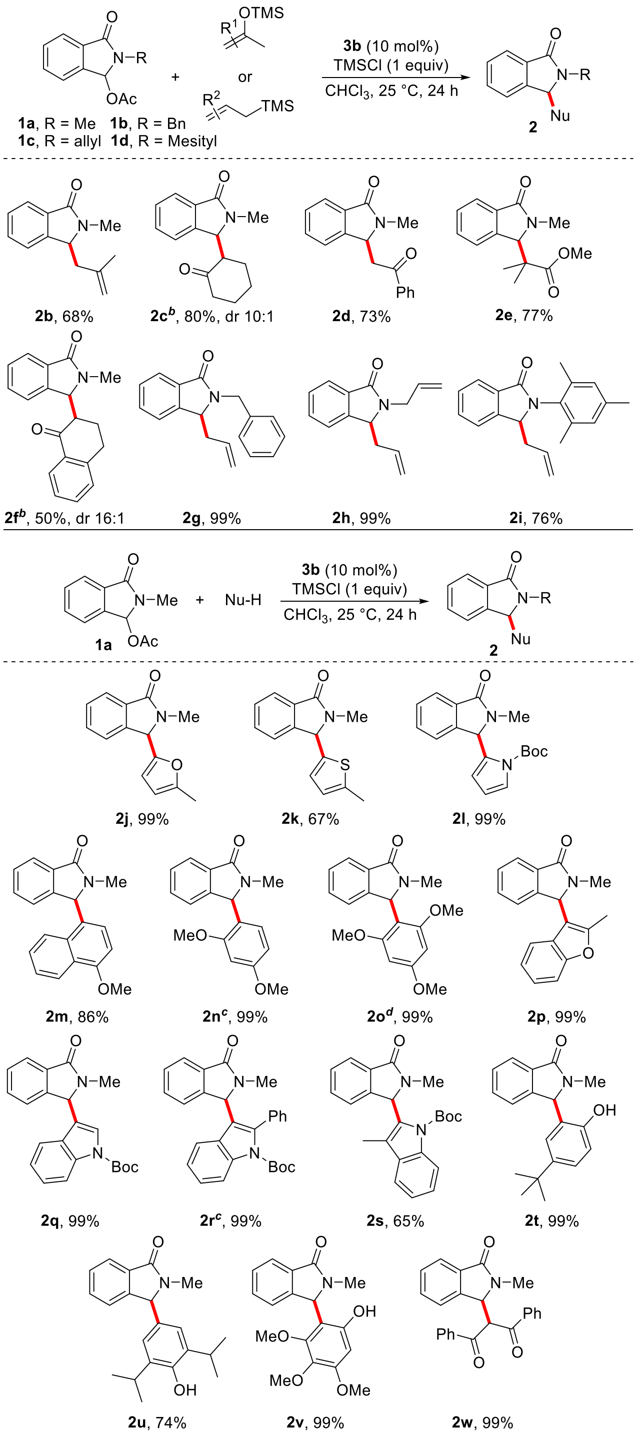


entry	catalyst	yield[b] (%)
1	none	trace
2	**3a** (R = Mesityl, X = I, A = $\mathrm{BF_4}$)	trace
3	**3b** (R = Mesityl, X = I, A = OTf)	99
4	**3c** (R = Mesityl, X = I, A = $\mathrm{SbF_6}$)	98
5	**3d** (R = Mesityl, X = I, A = $\mathrm{NTf_2}$)	98
6	**3e** (R = Mesityl, X = H, A = OTf)	trace
7	**3f** (R = 2,6-Dipp, X = I, A = OTf)	43
8	**3g** (R = Me/n-$\mathrm{C_8H_{17}}$, X = I, A = OTf)	81
9	**3h**	89
10	**3i**	79

[a] Reactions were performed with **1a** (0.05 mmol), catalyst **3** (10 mol %), TMSCl (0.05 mmol) and allyltrimethylsilane (0.10 mmol) in $\mathrm{CDCl_3}$ (0.5 mL) for 12 h at 25 °C. [b] The yield was determined by ^{1}H NMR analysis, using mesitylene as an internal standard. Mesityl = 1,3,5-trimethylphenyl; 2,6-Dipp = 2,6-diisopropylphenyl.

With the optimized catalyst in hand, various types of silyl nucleophiles were subjected to the evaluation (Scheme 2). Generally, the desired products **2a**−**2f** were obtained in good yield and diastereoselectivity. Other *N*,*O*-aminals such as **1b**−**1d** were also found to be compatible with the catalytic protocol, giving the corresponding product **2g**−**2i** in good-to-excellent yields. Other than silyl nucleophiles, different electron-rich aromatics, including acid sensitive arenes (thiophene, furan, pyrrole) alkoxybenzenes and indoles were also studied. The regioselectivity and chemical yields of **2j**−**2s** were generally excellent. When phenols were employed as the nucleophilic partners, the *C*-attack products **2t**−**2v** were furnished exclusively.[11] 1,3-dicarbonyl compound was also able to deliver the desired *C*-attack product **2w**.

Scheme 2. Substrate Scope[a]

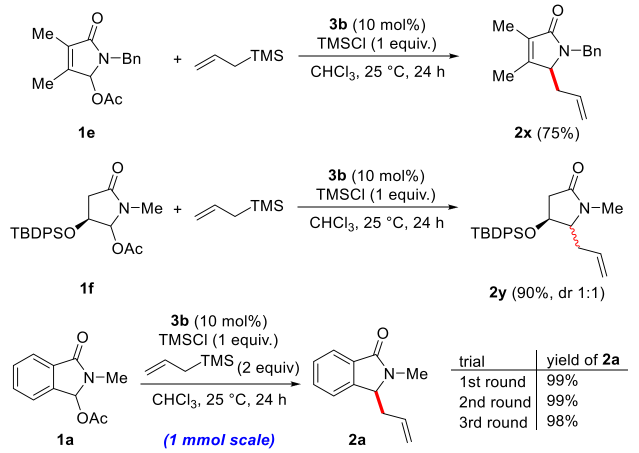


[a] Reactions were performed with substrate **1** (0.1 mmol), catalyst **3b** (10 mol %), TMSCl (0.1 mmol)) and nucleophile (0.2 mmol) in ethanol-free $\mathrm{CHCl_3}$ (1 mL) for 24 h at 25 °C. The yields were isolated yields. [b] The diastereomeric ratio (dr) was determined by ^{1}H NMR analysis on the crude reaction mixture. [c] One h. [d] No TMSCl was added.

DOI: 10.1021/acs.orglett.9b02006
Org. Lett. XXXX, XXX, XXX−XXX

The reaction was found to be compatible with substrates **1e** and **1f** that are absent of the aryl moiety (Scheme 3). In addition, the reaction was readily scalable in which **2a** was still obtained in quantitative yield when the reaction was conducted at 1 mmol scale. In addition, the XB catalyst could be recycled quantitatively and reused in the new rounds of reactions without diminishment of catalytic performance, which was not readily achievable using moisture-sensitive Lewis acids (see the Supporting Information for details).[12]

Scheme 3. Other Substrates and Scale-Up Reaction



Several experiments were performed to gain insight into the mechanism. First, ^{13}C NMR experiment on the XB catalyst was conducted (Figure 1). Upon mixing equimolar of **3b** and tetra-*n*-butylammonium chloride (TBACl), the ipso carbon signal of C−I was found to exhibit an ~11 ppm downfield shift.[13] However, a negligible chemical shift was observed for the mixture of **3b** and TMSCl. Thus, unlike Takemoto's case, whereas the XB might interact with TMSI to generate a better Lewis acidic silicon center for the activation of the benzylic hydroxyl substrates,[8] the above-mentioned results suggested that the association between **3b** and Cl$^-$ was much stronger than that of **3b** and TMSCl, revealing that **3b** was likely to be an anion binder during the catalytic cycle, instead of activating TMSCl. Indeed, substrate **1a** readily reacted with TMSCl in the absence of catalyst **3b**, as evidenced by the NMR study (see the Supporting Information for details).

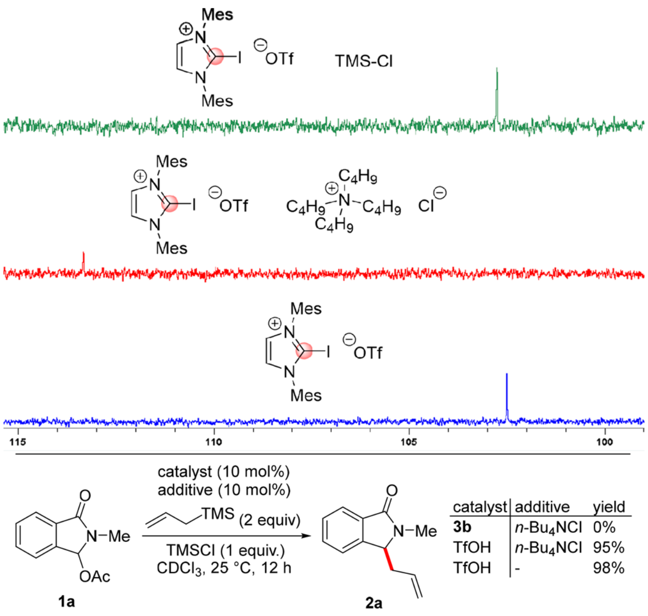
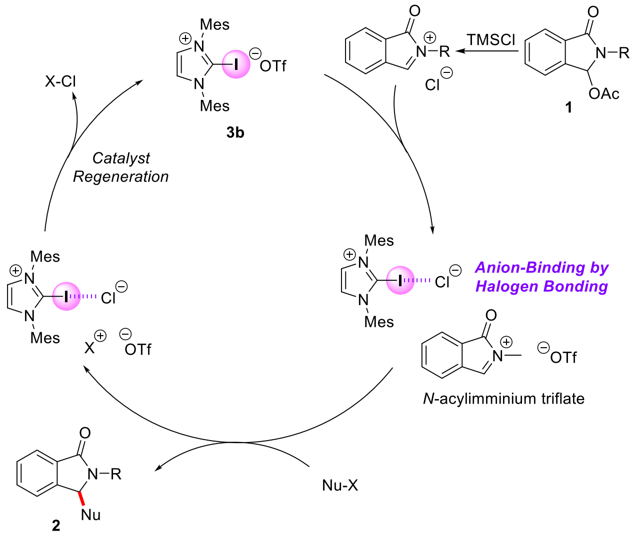


Figure 1. Control experiments.

We also studied the effect of additive on the reaction. It was found that the addition of TBACl (10 mol %, equimolar to **3b**) completely shut down the reaction; this was attributed to the interaction of chloride with XB, which would poison the catalyst (Figure 1). On the other hand, the same additive has no negative impact on the reaction catalyzed by TfOH.[14] This study further highlighted the role of catalyst as an anion binder during the catalysis.

A plausible catalytic cycle is depicted in Scheme 4. Substrate **1** first reacted with TMSCl to generate *N*-acylimminium chloride, which might then undergo anion binding (metathesis) with the XB catalyst **3b** through halogen-bond interaction to give *N*-acylimminium triflate as the active intermediate. After nucleophilic attack of the *N*-acylimminium triflate by Nu−X (X = H or TMS) to give the desired product **2**, the chloride anion of the halogen-bond complex was then captured by the X$^+$ to regenerate the catalyst **3b** (see the Supporting Information for details).

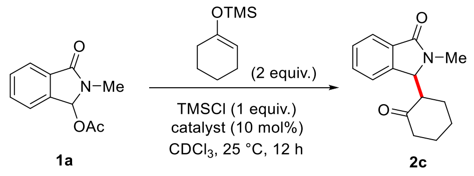
Scheme 4. A Plausible Reaction Mechanism



Further experimentations indicated that achieving the reaction with both high yield and diastereomeric ratio (dr) is not a trivial task. For instance, Lewis acids [Ti(O^{i}Pr)$_4$, Cu(CH$_3$CN)$_4$BF$_4$, AuOTf, Zn(OTf)$_2$], Brønsted acid (TfOH), and dihydrogen bond catalyst (Schreiner's thiourea) gave either low efficiency or low dr (Table 2, entries 1−6). In sharp contrast, XB catalysts **3b**−**3d** with various counteranions furnished **2c** in good yield and dr (Table 2, entries 7−9). These results highlighted the unique and tunable performance of XB in the reaction.

Motivated by the diastereoselectivity offered by counteranion depicted in Table 2, we briefly explored the asymmetric variant of the reaction. Preliminarily, when catalyst **3j** with (*S*)-BINOL derived phosphate anion was employed, 35% yield and 44% enantiomeric excess (ee) of **2o** was obtained. In contrast, 31% ee of **2o** was observed in the case of corresponding phosphoric acid catalysis. (See Scheme 5.) These results

Table 2. Catalyst Comparison[a]

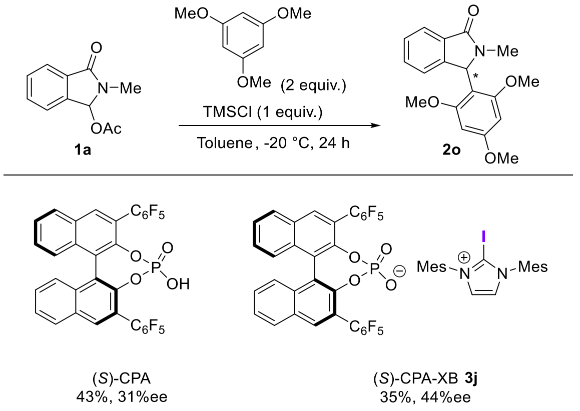


entry	catalyst	yield[b] (%)	diastereomeric ratio, dr[b]
1	$Ti(O^iPr)_4$	0	ND
2	$Cu(CH_3CN)_4BF_4$	99	1:1.6
3	AuOTf	99	1:1.5
4	$Zn(OTf)_2$	70	1.4:1
5	TfOH	99	1:1.2
6	Schreiner's thiourea	0	ND
7	**3b**	80	10:1
8	**3c**	85	4:1
9	**3d**	88	6:1

[a] Reactions were performed with **1a** (0.1 mmol), catalyst (10 mol %), TMSCl (0.1 mmol) and 1-(trimethylsiloxy)cyclohexene (0.20 mmol) in $CDCl_3$ (0.5 mL) for 12 h at 25 °C. [b] Determined via ^1H NMR analysis, using mesitylene as an internal standard.

demonstrated the difference between Brønsted acid and XB in asymmetric catalysis.[15]

Scheme 5. Preliminary Study on Asymmetric Reaction



In summary, we have developed a halogen-bond-catalyzed reaction of *N*,*O*-aminals with a wide range of *C*-nucleophiles in good yield and selectivity through in situ activating strategy with TMSCl and anion-binding catalysis. The mechanistic studies revealed that the XB catalyst served as an anion binder. Preliminary study of enantioselective version through the application of chiral BINOL-phosphate anion was demonstrated. Further study on coupling XB with a chiral counteranion in asymmetric catalysis is currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02006.

Experimental procedures and characterization data for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: yyyeung@cuhk.edu.hk.

ORCID

Ying-Yeung Yeung: 0000-0001-9881-5758

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the financial support from Research Grant Council of the Hong Kong Special Administration Region (Project No. CUHK14305317) and The Chinese University of Hong Kong Direct Grant (Project No. 4053279).

REFERENCES

(1) For selected reviews for *N*-acylimminium ions chemistry, see: (a) Wu, P.; Nielsen, T. E. *Chem. Rev.* **2017**, *117*, 7811–7856. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (c) Martínez-Estibalez, U.; Gómez-SanJuan, A.; García-Calvo, O.; Aranzamendi, E.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2011**, *2011*, 3610–3633. (d) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, *2009*, 339–368. (e) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, *2009*, 513–541. (f) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.

(2) For selected examples, see, for Au/Ag: (a) Boiaryna, L.; El Mkaddem, M. K.; Taillier, C.; Dalla, V.; Othman, M. *Chem. - Eur. J.* **2012**, *18*, 14192–14200. For Pd/Ag: (b) Dutta, M.; Mandal, S. M.; Pegu, R.; Pratihar, S. *J. Org. Chem.* **2017**, *82*, 2193–2198. For Sn: (c) Ben Othman, R.; Affani, R.; Tranchant, M.-J.; Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 776–780. For Sc: (d) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809–823. For In: (e) Russowsky, D.; Petersen, R. Z.; Godoi, M. N.; Pilli, R. A. *Tetrahedron Lett.* **2000**, *41*, 9939–9942.

(3) For selected examples, see, for BF_3: (a) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Vassilikogiannakis, G. *Org. Lett.* **2013**, *15*, 3714–3717. For R_3SiOTf: (b) Tranchant, M.-J.; Moine, C.; Othman, R. B.; Bousquet, T.; Othman, M.; Dalla, V. *Tetrahedron Lett.* **2006**, *47*, 4477–4480. For $TiCl_4$: (c) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121–125. (d) Das, M.; Saikia, A. K. *J. Org. Chem.* **2018**, *83*, 6178–6185.

(4) Benz, S.; Poblador-Bahamonde, A. I.; Low-Ders, N.; Matile, S. *Angew. Chem., Int. Ed.* **2018**, *57*, 5408–5412.

(5) For overviews of the halogen bond and application in organocatalysis, see: (a) Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. *Chem. Rev.* **2016**, *116*, 2478–2601. (b) Beale, T. M.; Chudzinski, M. G.; Sarwar, M. G.; Taylor, M. S. *Chem. Soc. Rev.* **2013**, *42*, 1667–1680. (c) Erdélyi, M. *Chem. Soc. Rev.* **2012**, *41*, 3547–3557. (d) Bulfield, D.; Huber, S. M. *Chem.—Eur. J.* **2016**, *22*, 14434–14450. (e) Schindler, S.; Huber, S. M. Halogen Bonds in Organic Synthesis and Organocatalysis. *Top. Curr. Chem.* **2014**, *359*, 167–203.

(6) For selected examples, see: (a) Kuwano, S.; Suzuki, T.; Hosaka, Y.; Arai, T. *Chem. Commun.* **2018**, *54*, 3847–3850. (b) Bruckmann, A.; Pena, M. A.; Bolm, C. *Synlett* **2008**, *2008*, 900–902. (c) Takeda, Y.; Hisakuni, D.; Lin, C. H.; Minakata, S. *Org. Lett.* **2015**, *17*, 318–321. (d) He, W.; Ge, Y.-C.; Tan, C.-H. *Org. Lett.* **2014**, *16*, 3244–3247. (e) Kobayashi, Y.; Nakatsuji, Y.; Li, S.; Tsuzuki, S.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2018**, *57*, 3646–3650. (f) Saito, M.; Kobayashi, Y.; Tsuzuki, S.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2017**, *56*, 7653–7657. (g) Chan, Y.-C.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2018**, *57*, 3483–3487. (h) Matsuzaki, K.; Uno, H.; Tokunaga, E.; Shibata, N. *ACS Catal.* **2018**, *8*, 6601–6605. (i) Xu, C.; Loh, C. C. J. *J. Am. Chem. Soc.* **2019**, *141*, 5381–5391. (j) Matsuzawa, A.; Takeuchi, S.; Sugita, K. *Chem.—Asian J.* **2016**, *11*, 2863–2866. (k) Ge, Y.-C.; Yang, H.; Heusler, A.; Chua, Z.; Wong, M. W.; Tan, C. H. *Chem.—Asian J.* **2019** DOI: 10.1002/asia.201900607.

(7) (a) Jungbauer, S. H.; Huber, S. M. *J. Am. Chem. Soc.* **2015**, *137*, 12110−12120. (b) Kniep, F.; Jungbauer, S. H.; Zhang, Q.; Walter, S. M.; Schindler, S.; Schnapperelle, I.; Herdtweck, E.; Huber, S. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7028−7032.

(8) For an example of the halogen-bonding interaction with trialkylsilyl halide, see: Saito, M.; Tsuji, N.; Kobayashi, Y.; Takemoto, Y. *Org. Lett.* **2015**, *17*, 3000−3003.

(9) Heinen, F.; Engelage, E.; Dreger, A.; Weiss, R.; Huber, S. M. *Angew. Chem., Int. Ed.* **2018**, *57*, 3830−3833.

(10) Haraguchi, R.; Hoshino, S.; Sakai, M.; Tanazawa, S.-G.; Morita, Y.; Komatsu, T.; Fukuzawa, S.-I. *Chem. Commun.* **2018**, *54*, 10320−10323.

(11) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815−816.

(12) For selected recent example for air- or moisture-stable Lewis acids, see: (a) Qiu, R.; Chen, Y.; Yin, S.-F.; Xu, X.; Au, C.-T. *RSC Adv.* **2012**, *2*, 10774−10793. (b) Loh, T.-P.; Chua, G.-L. *Chem. Commun.* **2006**, 2739−2749. (c) Bull, S. D.; Davidson, M. G.; Johnson, A. L.; Mahon, M. F.; Robinson, D. E. J. E. *Chem.—Asian J.* **2010**, *5*, 612−620. (d) Fasano, V.; LaFortune, J. H. W.; Bayne, J. M.; Ingleson, M. J.; Stephan, D. W. *Chem. Commun.* **2018**, *54*, 662−665. (e) Qiu, R.; Xu, X.; Peng, L.; Zhao, Y.; Li, N.; Yin, S. *Chem.—Eur. J.* **2012**, *18*, 6172−6182.

(13) (a) Walter, S. M.; Kniep, F.; Herdtweck, E.; Huber, S. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7187−7191. (b) Schulz, N.; Sokkar, P.; Engelage, E.; Schindler, S.; Erdelyi, M.; Sanchez-Garcia, E.; Huber, S. M. *Chem.—Eur. J.* **2018**, *24*, 3464−3473.

(14) Jungbauer, S. H.; Walter, S. M.; Schindler, S.; Rout, L.; Kniep, F.; Huber, S. M. *Chem. Commun.* **2014**, *50*, 6281−6284.

(15) Scheidt, K.; Squitieri, R.; Fitzpatrick, K.; Jaworski, A. *Chem.—Eur. J.* **2019**, DOI: 10.1002/chem.201902298.