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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201703641
Angew. Chem. 10.1002/ange.201703641

Link to VoR: <http://dx.doi.org/10.1002/anie.201703641>
<http://dx.doi.org/10.1002/ange.201703641>

Electrophilic activation of iodonium ylides via halogen bond donor catalysis for cross-enolate coupling

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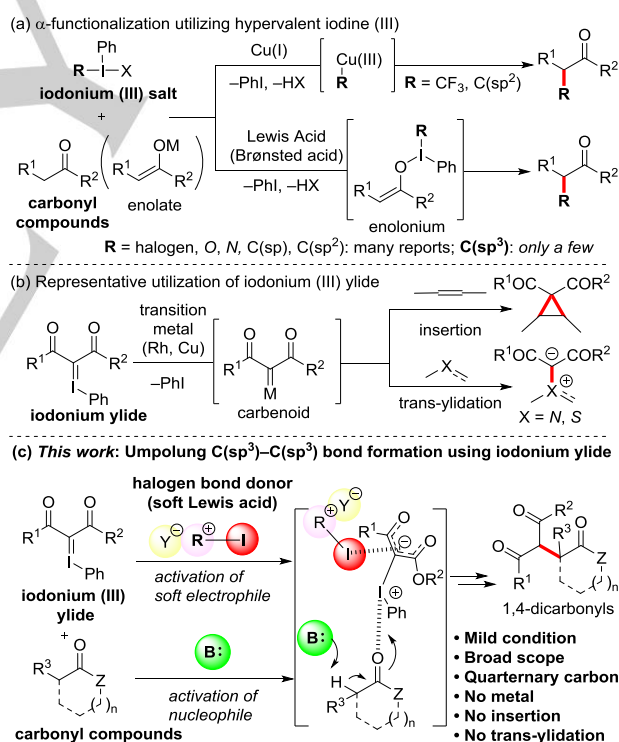
Abstract: The umpolung alkylation of silyl enol ethers with an iodonium(III) ylide has been achieved under mild conditions to afford various 1,4-dicarbonyl compounds in high yields by the implementation of a halogen-bonding catalyst. Unlike typical transition metal activation of such ylide precursors which typically proceed via carbenoid intermediates, experimental and computational studies indicate that halogen bonding (XB) between the XB donor catalyst and the iodonium ylide plays a crucial role in promoting the reaction. Identification of a compatible Brønsted-base catalyst enabled extension of this methodology to enols generated in situ to give the corresponding adducts in good yields.

Hypervalent iodine compounds have become essential in organic synthesis because a variety of oxidation and oxidative bond-forming reactions can be achieved with these reagents.^[1] In particular, recent advances in the use of iodonium(III) salts have enabled the α -functionalization of various carbonyl compounds under mild conditions. In these reactions, a copper(I) catalyst^[2] or a stoichiometric amount of acid^[3] is used to activate the iodonium salts (Scheme 1a). Compared with α -arylation and alkynylation, $C(sp^3)-C(sp^3)$ bond-forming reactions^[4] are less well developed, despite the utility of the resulting products.^[1–3] We envisioned that cross coupling of an iodonium(III) ylide^[1,5] with carbonyl compounds would enable $C(sp^3)-C(sp^3)$ bond formation and provide 1,4-dicarbonyl compounds (Scheme 1c), which found in a variety of important natural product scaffold, or used in their preparations.^[6] Many approaches have been investigated for the synthesis of these important synthetic intermediates;^[7–10] however, the activation of iodonium ylides seems to be the most challenging aspect of such a potential reaction. This is the result of their facile decomposition, insertion, and trans-ylidation under hard Lewis acidic conditions,^[5,11] even though such reactions generally occur via metal carbenoids in the presence of rhodium or copper catalysts (Scheme 1b).^[1,5]

We thus focused on halogen bonding (XB), which is a non-covalent interaction between halogenated compounds and Lewis bases.^[12] Although XB donors have recently begun to be used in synthetic organic chemistry as easy-to-handle organo-Lewis acids,^[13] their activation mode is mainly limited to the sp^2 -hybridized nitrogen atoms of quinolines and imines,^[14] carbonyl oxygen atoms,^[15] and alkyl halides.^[16,17] We envisaged that the soft Lewis acidity of XB donors^[18–20] would allow them to preferentially interact with soft electrophiles (Scheme 1c). Herein, we report the first efficient electrophilic activation of iodonium(III)

ylides, for which an XB donor was found to be effective. In addition, we have developed the first XB donor/Brønsted base cooperative catalytic system, which enables in situ formation of the nucleophilic component without deactivation of the XB-donor catalyst.

First, we studied the interaction between XB donors and iodonium ylide **2a**^[21] by reaction of **2a** with silyl enol ether **1a** as pre-activated nucleophile (Table 1). As expected, both 2-iodoimidazolium and 2-iodobenzimidazolium salt-type XB donors^[13–18] **4** and **5** efficiently promoted the umpolung C–C bond formation to furnish desired product **3a** in excellent yields (Table 1, entries 1–2). In sharp contrast, imidazolium salt **6**, which does not contain an iodine atom did not promote the reaction at all (Table 1, entry 3). These results indicate that hydrogen bonding (HB) and a cationic heteroaromatic ring were not effective for the activation of the iodonium ylide, and strongly suggest that an XB interaction plays a crucial role in the promotion of the reaction.



Scheme 1. Summary of this work

It is worth noting that other potential catalysts, including Schreiner's thiourea **7**,^[22] phosphoric acid **8**,^[23] Lewis acid metals,^[3] and transition metals,^[1,5] did not accelerate the reaction efficiently (Table 1, entries 4–10), either because of catalyst decomposition (Table 1, entries 5–6) or degradation of the iodonium ylide^[11] (Table 1, entries 6–10). When $Rh_2(OAc)_4$, which is known to form metal–carbenoid species^[1,5] with iodonium ylides, was employed, neither **2a** nor the corresponding cyclopropane intermediate were observed (Table

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1, entry 10). From these results, formation of **3a** through cyclopropanation of **1a** followed by ring opening is highly unlikely as the operative mechanistic pathway. Solvent effects were found to be important; dichloromethane and toluene gave lower yields than THF (Table 1, entries 11–12). This could be explained by the coordination of THF to the iodine(III) center, which suppresses the decomposition of the iodonium ylides.^[24]

Table 1: Optimization of umpolung C–C bond formation with **1a** and iodonium ylide **2a**

| Entry | Catalyst | Solvent | Yield (%) ^[a] |
|-------|------------------------------------|---------------------------------|--------------------------|
| 1 | 4 | THF | 99 ^[b] |
| 2 | 5 | THF | 91 ^[b] |
| 3 | 6 | THF | 0 |
| 4 | 7 | THF | 19 |
| 5 | 8 | THF | 0 |
| 6 | BF ₃ ·OEt ₂ | THF | 0 |
| 7 | Sc(OTf) ₃ | THF | 16 |
| 8 | TMSOTf | THF | 0 |
| 9 | I ₂ | THF | 0 |
| 10 | Rh ₂ (OAc) ₄ | THF | 0 |
| 11 | 5 | Toluene | 60 |
| 12 | 5 | CH ₂ Cl ₂ | 54 |

4 (X = I) **5** (X = H) **6** (X = H) **7** **8**

[a] Unless otherwise noted, ¹H NMR yields are based on dimethylsulfone as an internal standard. [b] Isolated yields.

To gain insight into the reaction mechanism, we performed a ¹³C NMR experiment (Figure 1a). Upon mixing XB donor **4** and the iodonium ylide in THF-*d*₈, the ¹³C NMR peak of the C2 position of **4** broadened and shifted downfield in accordance with previous reports.^[14,18] Notably, the peaks of the ylide carbon atom of the iodonium ylide shifted significantly downfield (ca. 9 ppm), which clearly indicates the increased electrophilicity of **2a**. To obtain further information about the interaction, we performed computational studies in which **2a** and a simplified *N,N*-dimethyliodonimidazolium cation were used as model structures (Figure 1b). Starting from various initial structures, two possible XB interaction modes were found; interaction between the σ-hole of the XB donor and the carbonyl oxygen atom of **2a** (mode A), and XB between the donor and the ylide carbon atom (mode B).^[25] In both cases, calculation of the interaction energy potentials indicated long-range attractive interactions in the gas phase (red) and even under the effect of solvation (blue), suggesting that electrostatic and dispersion forces greatly contribute to the interaction. These results are in good agreement with those for previously reported XB interactions.^[26] From the calculated interaction energies, the intermediate interacting through the O atom (mode A) is more favorable than that interacting through the C atom (mode B). Our present understanding of the mechanism involves silyl enol ether **1** attack at the iodine atom of XB-activated ylide **2** to form an enolonium species,^[27] with subsequent rearrangement^[4,28] furnishes 1,4-dicarbonyls **3**. However, further mechanistic studies are in progress to distinguish between this and other potential mechanistic scenario.^[25]

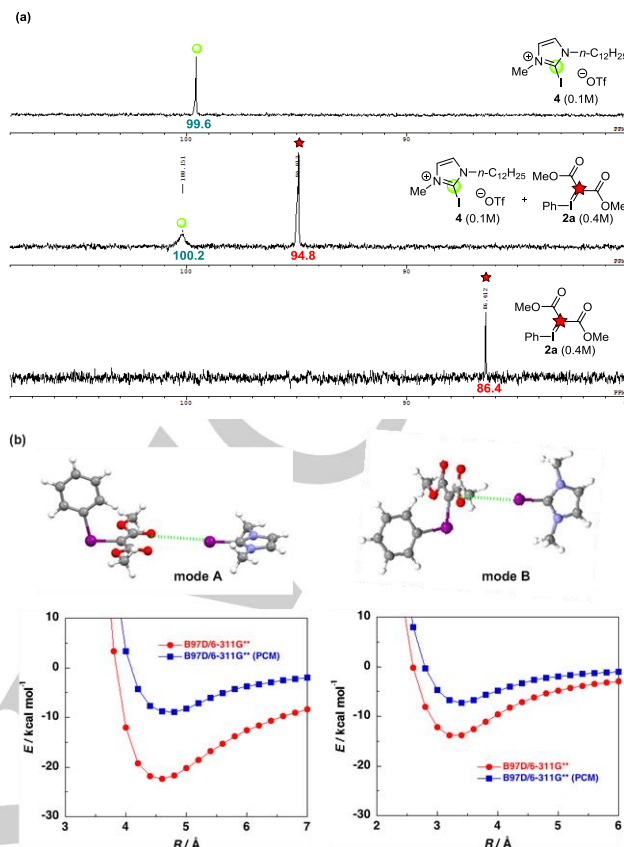


Figure 1. (a) ¹³C NMR spectra of ylide **2a** and XB donor **4** in THF-*d*₈. (b) Two possible interaction modes for **2a** and XB donor (mode A and B), and plots of B97D/6-311G** level interaction energies calculated for these modes with and without the evaluation of the effects of solvation by THF using PCM calculations.

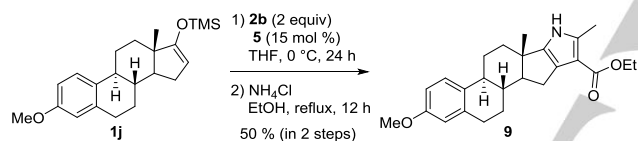
Table 2: Substrate scope for umpolung C–C bond formation^[a]

| 1b–1l | 2a (R = Me, EWG = CO ₂ Me) 2b (R = Et, EWG = COMe) 2c (R = Me, EWG = CN) | 3b–3l |
|--|---|-------|
| | | |
| | | |
| 3b , 90% ^[b] 3c , 71% ^[c] 3d , 94% ^[b] <i>d.r.</i> = 4 : 1 3e , 71% ^[b] 3f , 91% ^[c] 3g , 80% ^[c] 3h , 45% ^[c] 3i , 40% ^[b] (single diastereomer) 3j , 96% ^[b] (single diastereomer) 3k , 65% ^[d] 3l , 65% ^[e] | | |

[a] Isolated yields. [b] With **2a** and **4**. [c] With **2a** and **5**. [d] With **2b** and **5**. [e] With **2c** and **5**.

With the optimized conditions in hand, we next investigated the substrate scope for the umpolung C–C bond formation (Table 2). Gratifyingly, both five- and six-membered cyclic silyl enol ethers **1b–1e**, derived from cyclopentanone, indanones, cyclohexanone, and tetralones, gave desired products **3b–3e** in 71%–94% yields. The chemical yields seem to be highly dependent on the nucleophilicity of the silyl enol ethers, and aromatic ring-conjugated silyl enol ethers **1c** and **1e** gave the corresponding adducts in lower yields. In contrast, the 4-phenylcyclohexanone-derived substrate was very effective for the synthesis of 1,4-dicarbonyl compound **3d** (94%). Notably, electron-rich heteroaromatic indole rings were tolerated in the reaction and provided product **3g** in good yield. Such heteroaromatic rings have been reported to react with iodonium ylides under acidic conditions.^[11] 1,4-ketoester **3h**, which bears an all-carbon quaternary center, was synthesized in somewhat lower yield.

To further demonstrate the utility of this method, we next investigated the late-stage functionalization^[29] of biologically active compounds, which is attracting increasing attention in medicinal chemistry. For example, readily available ketones, such as camphor and estrone derivatives, were successfully functionalized to afford **3i** and **3j** in 40% and 96% yields, respectively. Iodonium ylides **2b** and **2c**, which bear ketone and cyano groups, respectively, were also applied in this coupling reaction to give corresponding γ -ketoesters **3k** and **3l** in good yields, thus demonstrating the synthetic utility of this methodology. Silyl enol ether **1j** was reacted with **2b** under the optimized conditions and then treated with NH_4Cl in ethanol to afford pentacyclic fused-pyrrole **9** in 50% yield over two steps (Scheme 2).



Scheme 2: Synthetic application of umpolung alkylation

A limitation of the silyl enol ether protocol is the necessity to pre-activate the nucleophilic coupling partner. However, the implementation of a basic co-catalyst to generate these species *in situ* carries the associated risk of catalyst deactivation by halogen bonding between **4** and the basic co-catalyst (as well as competitive decomposition of the iodonium ylide). In order to circumvent this, we examined the strength of the XB interaction of **4** with various bases by ^1H NMR. The changes in the chemical shifts of the H4 and H5 signals of **4** (green) were determined after mixing **4** with an equimolar amount of each base in $\text{THF}-d_8$ (Figure 2). As expected, relatively large upfield shifts (0.05–0.08 ppm) were observed when **4** was mixed with DABCO or tetramethylguanidine, which are known strong XB acceptors.^[30] Interestingly, Et_3N and proton sponge (PS) did not initiate such upfield shifts (0.003–0.013 ppm), despite their pK_b values.^[31] More importantly, we confirmed that the upfield shift was considerably greater (0.213 ppm) when XB donor **4** was treated with **2a**.^[31] From these results, we chose PS as the cooperative base catalyst for the umpolung C–C bond formation.

3-Substituted oxindoles were chosen as the substrates (Table 3) because the resulting oxindoles with all-carbon quaternary centers at the C3 position are attractive intermediates for oxindole natural products.^[32] In a preliminary screening, coupling of 3-methyloxindole **10a** and iodonium ylide **2a** was performed in the presence of XB donor **4** and several bases, and as expected, the combination with PS was found to give the best yield of **11a** (23%, see Table S2 in the Supporting Information).^[25] We then

screened a series of XB donors in combination with PS,^[25] and found that XB donor **12**, which contains a sterically hindered counter anion, improved the yield of **11a** to 71% (Table 3). In contrast to previously reported oxidative cross-enolate coupling reactions,^[6,7] this is the first example of a reaction that utilizes an enol generated *in situ* with a catalytic amount of base.

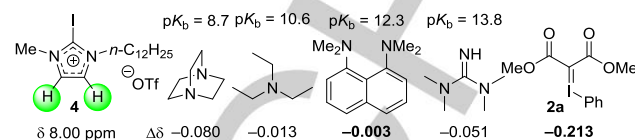
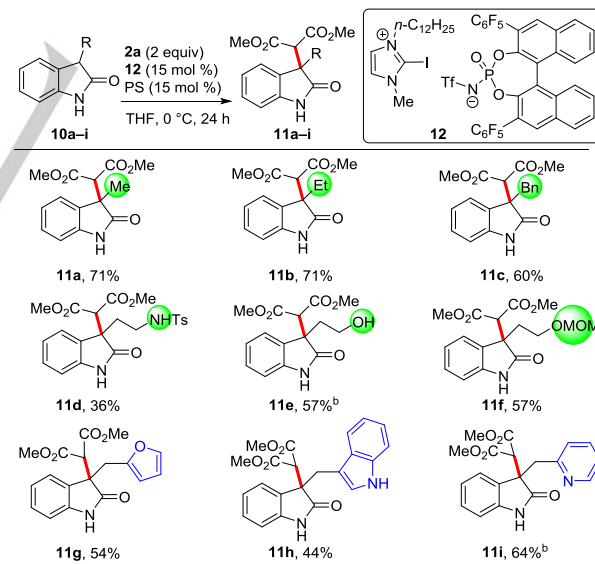


Figure 2. ^1H NMR peak shifts of **4** ($\text{THF}-d_8$) when mixed with equimolar amounts of a base or iodonium ylide **2a**

Using the optimized reaction conditions, we next investigated the substrate scope of the present acid/base catalysis (Table 3). As expected, substrates containing simple alkyl chains, namely ethyl or benzyl groups, at the C3 position of the oxindole gave desired products **11b** and **11c** in 71% and 60% yields, respectively. Fortunately, several functional groups, including –NH and –OH groups, as well as heteroaromatic rings, such as furan, indole, and pyridine, were tolerated in the oxidative coupling reaction to give corresponding 3,3-disubstituted oxindoles **11d–11i** in moderate to good yields. Notably, production of **11e** and **11i** was markedly faster than reactions with the other substrates, which suggests that coordination of a hydroxyl group or pyridine to the iodonium ylide accelerates the reaction. It should also be emphasized that neither O–H insertion nor ylide exchange were observed in these cases.

Table 3: XB donor/base co-catalyzed umpolung C–C bond formation^[a]



[a] Isolated yields. [b] The substrates were consumed within 3 hours.

In conclusion, we have found that an XB donor effectively promotes reactivity of an iodonium ylide via halogen bond activation, and various silyl enol ethers were successfully coupled to give the corresponding 1,4-dicarbonyl compounds in good yields. Mechanistic studies suggested that there was an XB interaction between the carbonyl oxygen atom on the iodonium ylide and the iodine atom of the XB donor. It was also revealed that the XB donor can be used in the presence of a

base as a co-catalyst, which synergistically promotes otherwise inaccessible reactions. We believe that the present soft XB-donor/Brønsted base pair will expand the potential for cooperative catalysis and broaden the utility of XB donor catalysis. Further investigation of the detailed reaction mechanism and the asymmetric version of this reaction is now underway in our laboratory.

Experimental Section

To a solution of oxindole **10a** (0.05 mmol, 7.3 mg), proton sponge (0.0075 mmol, 1.6 mg), and XB donor **12** (0.0075 mmol, 8.9 mg) in THF (0.5 mL), iodonium ylide (0.075 mmol, 25.6 mg) was added at 0 °C. After being stirred at the same temperature for 24 hours, the reaction mixture was directly purified by preparative TLC to give **11a** (9.8 mg, 71%).

The Gaussian 09 program^[33] was used for the calculations of intermolecular interaction energies. The interaction energies were calculated at the B97D/6-311G** level.^[34] The DGDZVP basis set^[35] was used for iodine. BSSE^[36] was corrected by the counterpoise method.^[37] Effects of solvation was evaluated using Polarizable Continuum Model (PCM).^[38] BSSE was not corrected in the PCM calculations. Details of computational methods are shown in Supporting Information.

Acknowledgements

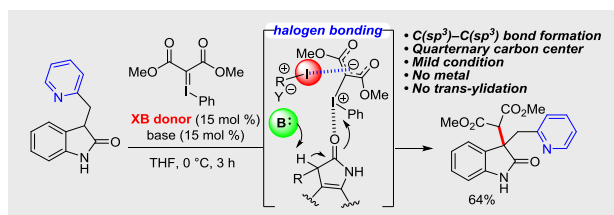
We gratefully acknowledge a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysis" (Y. T.) and a Grant-in-Aid for Challenging Exploratory Research (Y. K.) from MEXT, Japan. M. S. is grateful for a JSPS Fellowship for Young Scientists. We thank Prof. M. P. Sibi (North Dakota State University), Prof. F. D. Toste, and Mark Levin (University of California, Berkeley) for fruitful discussions.

Keywords: organocatalyst • umpolung • hypervalent iodine • XB donor

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COMMUNICATION



The umpolung alkylation of silyl enol ethers with an iodonium(III) ylide has been achieved under mild conditions to afford various 1,4-dicarbonyl compounds in high yields by the implementation of a halogen-bonding catalyst. Identification of a compatible Bronsted-base catalyst enabled extension of this methodology to enols generated in situ to give the corresponding adducts in good yields.

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Page No. – Page No.

Electrophilic activation of iodonium ylides via halogen bond donor catalysis for cross-enolate coupling