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Unexpected Hydrobromic Acid-Catalyzed C–C Bond-Forming Reactions and Facile Synthesis of Coumarins and Benzofurans Based on Ketene Dithioacetals

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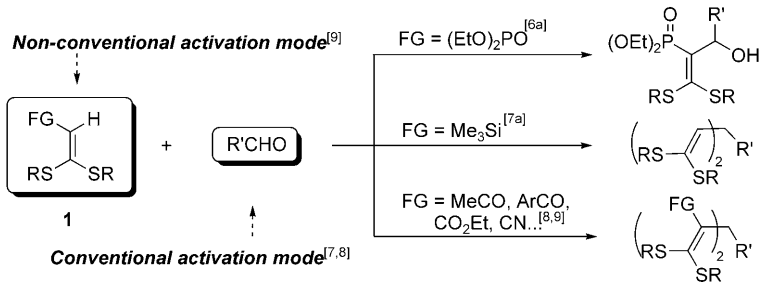
Abstract: Hydrobromic acid was found to be a unique catalyst in C–C bond-forming reactions with ketene dithioacetals. Distinctly different from other acids (including Lewis and Brønsted acids), the remarkable catalytic performance of hydrobromic acid in catalytic amounts was observed in the "acid"-catalyzed reactions of readily available functionalized ketene dithioacetals **1** with various electrophiles. Under the catalysis of 0.1 equivalents of hydrobromic acid, the reaction of **1** with carbonyl compounds **2a–l** gave polyfunctionalized penta-1,4-dienes **3** or conjugated dienes **4** in good to excellent yields. The reaction tolerated a broad range of substituents on both the ketene dithioacetals **1** and the carbonyl compounds **2**. Application of this efficient C–C bond-forming method generated coumarins **5** and benzofurans **7** under mild, metal-free conditions by hydrobromic acid-catalyzed reactions of **1** with salicylaldehydes **2m–o** and *p*-quinones **6a–d**, respectively. A new reactive species, a sulfur-stabilized carbonium ylide, formed depending on the nature of the counterion, and this was proposed as the key intermediate in the unique catalysis of hydrobromic acid.

Keywords: C–H activation · C–C coupling · hydrobromic acid · oxygen heterocycles · reaction mechanisms

Introduction

C–H functionalization leading to C–C bond formation has been a longstanding goal in organic synthesis and is an area of rapid growth that will continue to push the limits of chemical reactivity because C–H bonds can be viewed as being a ubiquitous functional group.[1–3] As versatile organic intermediates,[4,5] the α-C–H functionalization of ketene dithioacetals **1** (Scheme 1, FG = Functional Group) has become an attractive transformation due to the formation of more densely functionalized molecules with synthetic potential.[6–9] It was reported that the C–C bond formation reaction of **1** and acid-activated aldehydes can give the corresponding adducts efficiently (Scheme 1, conventional activation mode).[7,8] As part of our studies on ketene dithioacetal chemistry,[5a–e,8,9] we found that this kind of reaction was highly catalyst dependent.[8,9] In contrast to reactions promoted by $BF_3{\cdot}Et_2O$ (50 mol%),[7a] $EtAlCl_2$ (100 mol%),[7a] or $TiCl_4$ (120 mol%),[8a–c] which would be consistent with the activation of aldehydes by Lewis or Brønsted acids with high catalyst loadings, the reactions of **1** with aldehydes under the



Scheme 1. C–C bond formation reaction of functionalized ketene dithioacetals **1** with aldehydes.

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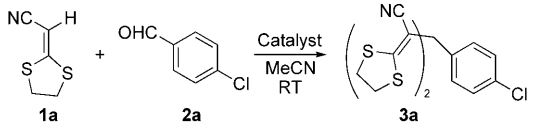
catalysis of $CuBr_2$ were shown to involve α-C–H activation of ketene dithioacetals **1** (Scheme 1, nonconventional activation mode).[9] Notably, in the latter cases, a wider range of substrates, including both ketene dithioacetals and electrophiles, are scalable with low catalyst loadings (10 mol%).[9] The significant acceleration of the $CuBr_2/BF_3{\cdot}Et_2O$ cocatalyzed reaction of **1** with aldehydes (Table 1, entry 7 vs. entries 1 and 6)[9b] seemed to give further support to the activation of **1** by $CuBr_2$.

Table 1. Comparison of catalysts.[a]



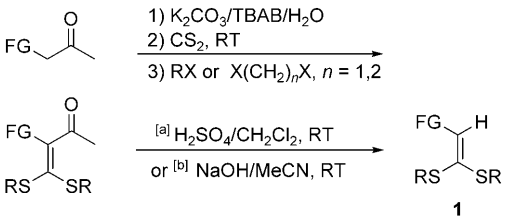
Entry	Catalyst [equiv]	t [h]	Yield [%][b]
1	$CuBr_2$ (0.1)	12	98[9a]
2	$TiCl_4$ (1.2)	2	93[8c]
3	$TiCl_4$ (0.5)	10	46
4	CuBr (1.0)	24	–[c][9a]
5	$CuCl_2$ (0.1)	48	45[9a]
6	$BF_3{\cdot}Et_2O$ (0.1)	35	70[9b]
7	$CuBr_2$ (0.1)/$BF_3{\cdot}Et_2O$ (0.1)	2	98[9b]
8	HBr (0.1, 46% aqueous)	3	98
9	HBr (0.1, 36% aqueous)	3	98
10	HCl (0.1, 36% aqueous)	24	trace
11	HI (0.1, 45% aqueous)	24	8
12	HI (0.1, 36% aqueous)	24	trace
13	H_2SO_4 (0.1, concentrated)	24	trace
14	PTS (0.1)	24	7
15	TFA (0.1)	24	–[c]
16	HOAc (0.1, glacial)	24	–[c]

[a] Reaction conditions: **1a** (1 mmol), **2a** (0.5 mmol), MeCN (5 mL), room temperature. [b] Isolated yield based on **2a**. [c] No reaction.

However, in the course of our continuing research, we became aware that the HBr, generated in situ in the $CuBr_2$-catalyzed C–C bond-forming reaction, played a crucial role in the activation of ketene dithioacetals. Furthermore, in contrast to other acids (including various Lewis and Brønsted acids), the remarkable catalytic performance of HBr in catalytic amounts was observed in this kind of "acid"-catalyzed reaction. Accordingly, the formation of a new reactive species, a sulfur-stabilized carbonium ylide, depending on the nature of the counterion, is proposed as the key intermediate in the unique catalysis of HBr. Herein, we report a novel catalytic method that involves several new chemical aspects, including: 1) the unusual catalytic power of HBr in the C–C bond forming reaction, which is recognized and evaluated for the first time; 2) a new reaction mechanism involving anion-catalyzed C–C bond formation; and 3) the successful application of this approach to the efficient synthesis of useful coumarins and benzofurans. This approach has the potential to develop the fields of both C–C bond-forming reactions and anion catalysis.

Results and Discussion

Preparation of functionalized ketene dithioacetals 1: According to the procedures reported previously,[8d] ketene dithioacetals **1a–l** were prepared through a two-step process involving the preparation of α-acetyl ketene dithioacetals, starting from the corresponding active methylene compounds, carbon disulfide, and alkyl halides in the presence of K_2CO_3 catalyzed by tetrabutylammonium bromide (TBAB) in water, followed by acid/base-promoted deacylation. The results are summarized in Scheme 2.



1	FG	R	Total yield
1a	CN	$(CH_2)_2$	62%[a]
1b	CN	Et	70%[b]
1c	CO_2Et	$(CH_2)_2$	86%[a]
1d	MeCO	$(CH_2)_2$	91%[a]
1e	PhCO	$(CH_2)_2$	81%[a]
1f	CO_2Et	Et	78%[a]
1g	MeCO	Et	82%[a]
1h	PhCO	Et	79%[a]
1i	CN	Me	83%[b]
1j	CO_2Et	Me	76%[a]
1k	MeCO	Me	82%[a]
1l	PhCO	Me	81%[a]

Scheme 2. Preparation of functionalized ketene dithioacetals **1**.

The remarkable catalytic performance of HBr in the "acid"-catalyzed C–C bond-forming reaction of ketene dithioacetal 1a and 4-chlorobenzaldehyde (2a): It was found that the reaction of α-cyano ketene cyclic dithioacetal **1a** (1 mmol) with 4-chlorobenzaldehyde **2a** (0.5 mmol) catalyzed by $CuBr_2$ (10 mol%) at room temperature in acetonitrile (5 mL) for 12 h, gave the 2:1 adduct, penta-1,4-diene **3a**, in 98% yield (Table 1, entry 1).[9a] With shorter reaction times (2 h), under similar conditions, **3a** was produced in 93% yield with $TiCl_4$ (120 mol%) as the promoter (Table 1, entry 2).[8c] The yield of **3a** was lower (46%) when substoichiometric amounts of $TiCl_4$ (50 mol%) was used even after longer reaction times (10 h; Table 1, entry 3). By comparison, no reaction was observed with CuBr (100 mol%) as the promoter (Table 1, entry 4).[9a] When catalyzed by $CuCl_2$ (10 mol%) or $BF_3{\cdot}Et_2O$ (10 mol%) at room temperature for 48 or 35 h, **3a** was afforded only in 45 and 70% yield, respectively (Table 1, entries 5 and 6).[9a,b] Notably, with $CuBr_2$ (10 mol%) and $BF_3{\cdot}Et_2O$ (10 mol%) as cooperative catalyst, the reaction was significantly accelerated (Table 1, entry 7 vs. entries 1 and 6). Taken together, the above results

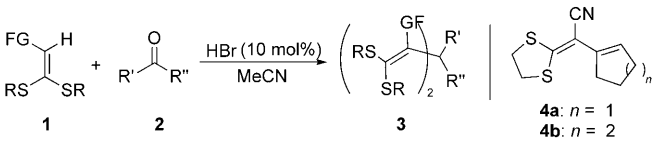
(Table 1, entries 1–7) suggest that $CuBr_2$ is a more effective catalyst than $TiCl_4$, $BF_3{\cdot}Et_2O$, $CuCl_2$, or CuBr, and that $CuBr_2$ plays a double role in both the activation of the carbonyl electrophiles and of the α-C–H bond of the ketene dithioacetals.[8c,9]

Although the experimental results (Table 1, entries 1–7) suggest that $CuBr_2$ is a more effective catalyst[6] than the other Lewis acids tested[7,8] in the C–C bond formation reaction based on ketene dithioacetals, the reaction mechanism has not yet been elucidated because no detailed information has previously been made available. To gain insight into the mechanism, we examined the catalytic activity of HBr, which was generated during the reaction of **1** and aldehydes during the catalysis by $CuBr_2$.[9a] Surprisingly, the adduct **3a** could be obtained in excellent yield by using HBr (46% or 36% aqueous, 10 mol%) as the catalyst. In this case, the reaction time was shortened to 3 h to give excellent yields under otherwise identical conditions (Table 1, entries 8 and 9 vs. entry 1). To better understand the origins of the observed catalysis, we evaluated the influence of other protic acids. As a comparison, interestingly, HCl (36% aqueous, 10 mol%) and HI (45% or 36% aqueous, 10 mol%) both proved to be less effective than HBr; in both cases, very small or trace amounts of **3a** were formed even after extended reaction times (Table 1, entries 10–12).

Combining the above results (Table 1, entries 1–12) with those obtained by Minami and co-workers,[7] highlights the remarkable catalytic performance of HBr and indicates that: 1) HBr is a more effective catalyst than $CuBr_2$ (Table 1, entry 8 vs. entry 1), 2) the HBr generated during the $CuBr_2$-catalyzed reaction of **1** and aldehydes[9a] should play the crucial role in the activation of **1**, and 3) the bromide anion is more than a spectator in this "acid" catalyzed reaction (Table 1, entries 8 and 9 vs. entries 10–12). Considering the substantial contribution made by the bromide anion to the α-Csp^2–H bond activation of ketene dithioacetals, the catalytic performance of other protic acids was further investigated. We found that HBr is unique because, in addition to HCl and HI (Table 1, entries 10–12), concentrated sulfuric acid (10 mol%) and 4-methylbenzenesulfonic acid (PTS, 10 mol%) were also less effective catalysts (Table 1, entries 13 and 14); trifluoroacetic acid (TFA, 10 mol%) and glacial acetic acid (10 mol%) were ineffective catalysts for the reaction of **1a** with **2a** (Table 1, entries 15 and 16).

HBr-catalyzed C–C bond formation of ketene dithioacetals 1 with carbonyl compounds 2: Under the reaction conditions detailed in Table 1, entry 8, a series of experiments were performed, the results of which are summarized in Table 2. It is clear that the reactions of a range of aldehydes, including benzaldehyde (Table 2, entry 2), aromatic aldehydes having both electron-withdrawing (Table 2, entries 1 and 3) and electron-donating (Table 2, entry 4) substituents, heteroaromatic aldehydes (Table 2, entries 5 and 6), an α,β-unsaturated aldehyde (Table 2, entry 7), and aliphatic aldehydes

Table 2. HBr-catalyzed C–C bond formation of **1** with **2**.[a]

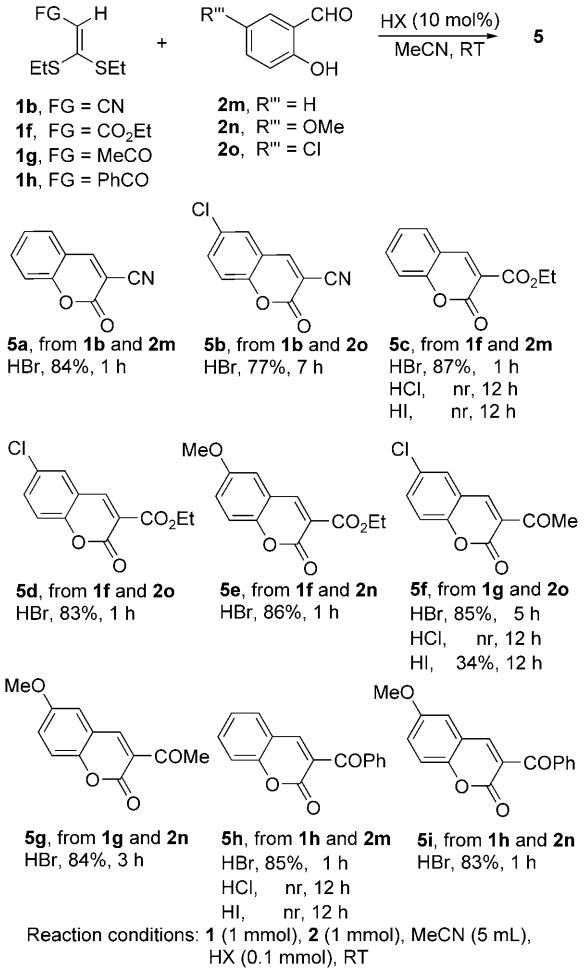


Entry	1	FG	R or R/R	2	R′	R″	3	t [h]	Yield [%][b]
1	**1a**	CN	$(CH_2)_2$	**2a**	4-ClC_6H_4	H	**3a**	4	98
2	**1a**	CN	$(CH_2)_2$	**2b**	Ph	H	**3b**	4	93
3	**1a**	CN	$(CH_2)_2$	**2c**	4-$NO_2C_6H_4$	H	**3c**	3	98
4	**1a**	CN	$(CH_2)_2$	**2d**	4-$MeOC_6H_4$	H	**3d**	1	91
5	**1a**	CN	$(CH_2)_2$	**2e**	2-furyl	H	**3e**	4	89
6	**1a**	CN	$(CH_2)_2$	**2f**	2-thienyl	H	**3f**	4	85
7	**1a**	CN	$(CH_2)_2$	**2g**	*E*-PhCH=CH	H	**3g**	2	90
8	**1a**	CN	$(CH_2)_2$	**2h**	Me	H	**3h**	6	80
9	**1a**	CN	$(CH_2)_2$	**2i**	H	H	**3i**	7	85
10	**1b**	CN	Et	**2a**	4-ClC_6H_4	H	**3j**	20	50
11	**1c**	CO_2Et	$(CH_2)_2$	**2a**	4-ClC_6H_4	H	**3k**	1	94
12	**1d**	MeCO	$(CH_2)_2$	**2a**	4-ClC_6H_4	H	**3l**	15	68
13	**1e**	PhCO	$(CH_2)_2$	**2a**	4-ClC_6H_4	H	**3m**	15	60
14[c]	**1a**	CN	$(CH_2)_2$	**2j**	Me	Me	**3n**	24	51
15[d]	**1a**	CN	$(CH_2)_2$	**2k**	$(CH_2)_4$		**4a**	18	52
16[d]	**1a**	CN	$(CH_2)_2$	**2l**	$(CH_2)_5$		**4b**	20	64

[a] Reaction conditions: **1** (1 mmol), **2** (0.5 mmol), HBr (46% aqueous, 0.05 mmol), MeCN (5 mL), room temperature. [b] Isolated yield based on **2**. [c] Reaction performed at 60°C. [d] Reaction conditions: **1a** (1 mmol), **2k** or **2l** (1 mmol), HBr (46% aqueous, 0.1 mmol), MeCN (5 mL), room temperature.

(Table 2, entries 8 and 9), with **1a** all proceed smoothly to give the corresponding adducts **3a–i** in excellent yields. In addition, we also found that the reaction could tolerate acyclic alkylthio (Table 2, entry 10) groups as well as various α-EWG groups (EWG = electron-withdrawing group; Table 2, entries 11–13) on **1** and led to the corresponding adducts **3j–m** in good to excellent yields. An explorative study using other electrophiles showed that the reaction of **1a** with acetone **2j** for 24 h at elevated temperature gave the adduct **3n** in 51% yield (Table 2, entry 14). The reactions of **1a** with cyclopentanone **2k** and cyclohexanone **2l** led to the formation of conjugated dienes **4a** and **4b** in good yields, respectively, through consecutive C–C coupling and dehydration (Table 2, entries 15 and 16).

Synthesis of coumarins 5 through the reaction of ketene diethylthioacetals 1 and salicylaldehydes 2 catalyzed by HBr: As described above, we have developed an efficient C–C bond-forming reaction under the catalysis of HBr. As a comparison with our previous work,[9a] we applied the approach to the synthesis of coumarins, which are frequently occurring structural subunits in numerous natural products with interesting biological activities.[10] As shown in Scheme 3, when salicylaldehydes **2m–o** (1 mmol) were selected as electrophiles to react with ketene diethylthioacetals **1b** (1 mmol), **1f** (1 mmol), **1g** (1 mmol), or **1h** (1 mmol) under the catalysis of HBr (46% aqueous, 10 mol%) in acetonitrile (5 mL), 3-substituted coumarin derivatives **5a–i** were obtained in high yields. Notably, none of the desired product **5c** was detected when the reaction of **1f** and **2m**



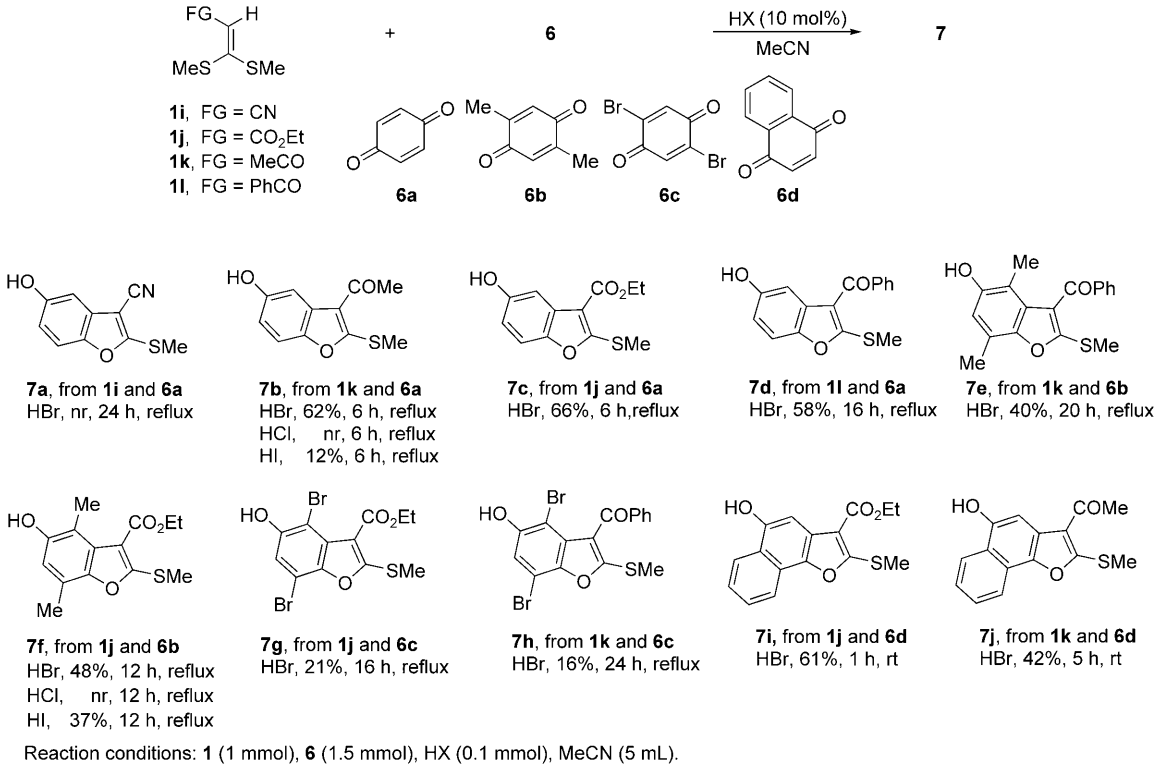
Scheme 3. Synthesis of coumarins **5** through the reaction of ketene diethylthioacetals **1** and salicylaldehydes **2** catalyzed by HX.

was performed with HCl (36% aqueous, 10 mol%) or HI (45% aqueous, 10 mol%) as catalysts (Scheme 3). Similarly, a remarkable catalytic performance of HBr was observed with **1h** and **2m** as substrates (Scheme 3, catalytic synthesis of **5h**). When the reaction of **1g** and **2o** was selected to investigate the catalytic performance of HX (X = Br, Cl, and I) in this process (Scheme 3, catalytic synthesis of **5f**), it was found that **5f** was isolated in 85% yield under the catalysis of HBr, whereas no reaction was detected with HCl as catalyst and a lower yield of **5f** was obtained with HI as catalyst.

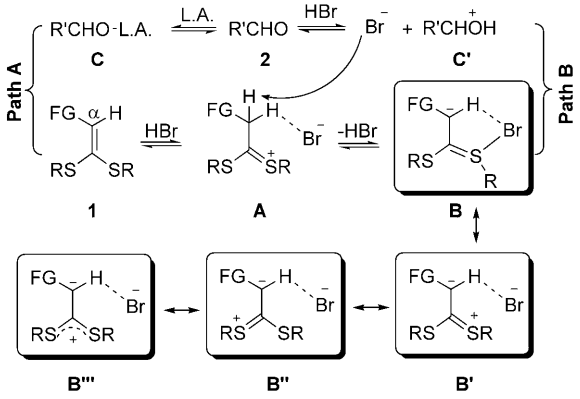
Synthesis of benzofurans 7 through the reaction of ketene diethylthioacetals 1 and *p*-quinones 6 catalyzed by HBr: Recently, we reported that benzofurans **7** can be easily prepared by the reaction of $CuBr_2$-activated ketene dimethylthioacetals **1** with $BF_3{\cdot}Et_2O$-activated *p*-quinones **6**.[9b] In contrast, under the same conditions, no reaction was detected in the absence of $BF_3{\cdot}Et_2O$.[9b] In this study, we found that all the reactions of **1** with **6**, except for the reaction between **1i** and **6a**, could also afford benzofurans **7** under the catalysis of only HBr (10 mol%). For example, the reaction of *p*-benzoquinone **6a** (1.5 mmol) with ketene dimethylthioacetal **1k** (1 mmol) catalyzed by HBr (46% aqueous, 10 mol%) in acetonitrile (5 mL), led to the formation of benzofuran **7b** in 62% yield after heating the reaction mixture to reflux for 6 h. In contrast, HCl (36% aqueous, 10 mol%) and HI (45% aqueous, 10 mol%) were found to be either ineffective or less effective as catalysts for this procedure under identical reaction conditions (Scheme 4). The synthetic method was then successfully employed to prepare the corresponding benzofurans **7c–j** in 16–66% yields. Moreover, the higher efficiency of HBr as a catalyst in this kind of C–C coupling and sequential cyclization was also clearly observed when **1j** and **6b** were used as substrates (Scheme 4, catalytic synthesis of **7f**).

Proposed reaction mechanism: The above results (Tables 1 and 2, and Schemes 3 and 4) suggest that: 1) HBr is a more efficient catalyst than either Lewis acids (e.g., $TiCl_4$, $BF_3{\cdot}Et_2O$, or $CuBr_2$) or protic acids (e.g., HCl, HI, H_2SO_4, PTS, or TFA); 2) the origins of the unexpected catalytic activity of $CuBr_2$ for the C–C bond formation reaction of functionalized ketene dithioacetals **1** with aldehydes **2** do indeed stem from the HBr generated during the reactions;[9] and, most importantly 3) the bromide anion plays a crucial role in the reaction by enhancing the nucleophilicity of the functionalized ketene dithioacetals **1** (Table 1, entries 8 and 9 vs. entries 10–16). These observations provide new insights into the mechanism of the C–C bond formation reaction with functionalized ketene dithioacetals **1** (Scheme 5).

It is easy to understand that in reactions catalyzed (or promoted) by Lewis acids, such as $EtAlCl_2$, $BF_3{\cdot}Et_2O$, and $TiCl_4$, C–C bond formation could result from nucleophilic attack of a ketene dithioacetal **1** on a Lewis acid activated aldehyde **C** (Scheme 5, Path **A**).[7,8] Because $CuBr_2$ is a weaker Lewis acid than $EtAlCl_2$, $BF_3{\cdot}Et_2O$, or $TiCl_4$,[11] according to the conventional activation mode, the rate of $CuBr_2$-catalyzed reaction of **1** with **2** should be slower, and similar to that catalyzed by $CuCl_2$ (Table 1, entry 5). However, in the case of $CuBr_2$-catalyzed reaction of **1** and **2**,[9a] the unexpected rate increase cannot be explained unless the HBr, generated during the reaction, is taken into consideration. In fact, the present results suggest that HBr is a true catalyst in the $CuBr_2$-catalyzed C–C bond forming reaction of **1**,[9] and that this HBr-catalyzed reaction involves a very different mechanism to the conventional version.[7,8] Thus, a new mechanism is proposed that takes into account the effects of the bromide anion. As depicted in Scheme 5, Path **B**, the reaction of **1** with aldehyde **2** is presumably initiated by the protonation of the polarized C=C bond of **1** to form intermediate **A**,[5f,12,13] in which the α-proton adjacent to two electron-withdrawing groups (FG and $RS^+ = CSR$) is highly acidic. Thus, base-assisted (Br^-) deprotonation of **A** should take place smoothly and further transform **A** into the carbon anion intermediate **B** through selective formation of the S–Br bond.[14] Alternative mesomeric structures of **B**, such as **B′**, **B″**, and **B‴**, also suggest that a sulfur-stabilized carbonium ylide[15–17] (**B‴**), which is a far better carbon



Scheme 4. Synthesis of benzofurans **7** through the reaction of ketene diethylthioacetals **1** and *p*-quinones **6** catalyzed by HX.



Scheme 5. Proposed reaction mechanism.

nucleophile than polarized ketene dithioacetal **1**, is involved and that it is, in fact, this species that induces this initial C–C formation reaction. The proposed mechanism thus involves activation of both the ketene dithioacetal **1** and the electrophile by a bromide anion and a proton, respectively, and indicates that HBr plays a cocatalytic role (Scheme 5, Path **B**). In addition, this description provides a better explanation for the results given in Table 1 (in particular, compare entry 1 vs. entries 2–6; entries 8 and 9 vs. entries 10–16; entry 1 vs. entry 7; and reference [9]).

Conclusion

We have shown that HBr is a unique catalyst for C–C bond formation reactions involving functionalized ketene dithioacetals **1**. Our conclusions are supported by the rate increase relative to those catalyzed (or promoted) by $CuBr_2$ and selected Lewis or Brønsted acids, and by the wide range of substrates that can be used for functionalized ketene dithioacetals and carbon electrophiles. Accordingly, a variety of products, such as polyfunctionalized penta-1,4-dienes **3**, conjugated dienes **4**, coumarins **5**, and benzofurans **7**, were synthesized successfully under mild, metal-free conditions. A new mechanism is proposed for the unique catalysis of HBr, which involves the generation of a strong nucleophilic species, a sulfur-stabilized carbonium ylide. Further studies are in progress.

Experimental Section

General: All reagents were purchased from commercial sources and used directly, unless otherwise indicated. Flash column chromatography was carried out by using 300–400 mesh silica gel under increased pressure. All reactions were monitored by TLC, which was performed on precoated aluminum sheets of silica gel 60 (F_{254}). ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature with Varian 500 MHz and 125 MHz instruments, respectively, using TMS as internal standard. All shifts are given in ppm. IR spectra (KBr) were recorded with a Magna-560 FTIR spectrophotometer in the range of 400–4000 cm^{-1}. Mass spec-

tra were measured with an Agilient 1100 LCMSD spectrometer. Elemental analyses were obtained with a VarioEL analyzer.

Typical procedure for the preparation of 1; Synthesis of 1d:[8d] CS_2 (0.73 mL, 12 mmol) was added under stirring to a solution of pentane-2,4-dione (1 mL, 10 mmol), K_2CO_3 (3.45 g, 25 mmol), and TBAB (321 mg, 1 mmol) in water (15 mL) at room temperature. After stirring at room temperature for 1 h, 1,2-dibromoethane (0.87 mL, 10 mmol) was added dropwise within 15 min. The resulting mixture was stirred for 8 h at room temperature then the precipitated solid was collected by filtration, washed with water (3×25 mL), and dried under vacuum to afford 3-(1,3-dithiolan-2-ylidene)pentane-2,4-dione (1.96 g, 97%) as a white solid. Concentrated H_2SO_4 (1.1 mL, 20 mmol) was added to a solution of the latter (1.01 g, 5 mmol) in CH_2Cl_2 (50 mL) at 0°C, and the mixture was allowed to warm to room temperature and stirred for 10 h. The mixture was poured onto saturated NaCl ice-water (50 mL) under stirring then the mixture was neutralized with aqueous Na_2CO_3 and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was washed with water (3×15 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel; petroleum ether/diethyl ether = 2:1, v/v) to give **1d** (750 mg, 94%) as a white solid.

Synthesis of polyfunctionalized penta-1,4-dienes 3; Typical procedure with 1a and 2a: HBr in acetonitrile (4 mL, 0.0125 M, 0.05 mmol) was added to a solution of **1a** (143 mg, 1 mmol) and **2a** (70 mg, 0.5 mmol) in acetonitrile (1 mL) at room temperature. The reaction mixture was stirred for 3 h (reaction monitored by TLC) and then poured onto ice-water (20 mL). The precipitate was collected by filtration, washed with water (3×50 mL), and dried in vacuo to afford the product **3a** (199 mg, 98%) as a white solid.

Compound 3a:[8c] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.53–3.60 (m, 8H), 4.51 (s, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.35 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.4 (2C), 40.1 (2C), 52.5, 96.3 (2C), 117.3 (2C), 129.2, 129.4 (2C), 134.2 (2C), 135.7, 165.1 ppm (2C).

Compound 3b:[8c] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.55–3.56 (m, 8H), 4.54 (s, 1H), 7.32–7.37 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.3 (2C), 39.9 (2C), 53.1, 96.6 (2C), 117.4 (2C), 127.9, 128.2 (2C), 128.9 (2C), 137.1, 164.7 ppm (2C).

Compound 3c:[8c] Yellowish solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.56–3.63 (m, 8H), 4.64 (s, 1H), 7.54 (d, J = 8.5 Hz, 2H), 8.23 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.8 (2C), 40.4 (2C), 52.8, 95.2 (2C), 117.2 (2C), 124.4, 129.3 (2C), 144.6 (2C), 147.9, 166.7 ppm (2C).

Compound 3d:[8c] Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.54–3.58 (m, 8H), 3.80 (s, 3H), 4.48 (s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 7.28 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.3 (2C), 40.0 (2C), 52.5, 55.2, 97.3 (2C), 114.3 (2C), 117.5 (2C), 129.2 (2C), 159.4 (2C), 164.1 ppm (2C).

Compound 3e:[8c] Red solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.54–3.60 (m, 8H), 4.66 (s, 1H), 6.37–6.40 (m, 2H), 7.43–7.44 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.7 (2C), 40.3 (2C), 47.7, 94.7 (2C), 108.9, 111.0, 117.3 (2C), 143.4, 149.5, 165.5 ppm (2C).

Compound 3f:[8c] Brown solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.56–3.59 (m, 8H), 4.80 (s, 1H), 7.01–7.03 (m, 1H), 7.11–7.12 (m, 1H), 7.28–7.29 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.3 (2C), 40.0 (2C), 48.4, 96.5 (2C), 116.9, 125.5, 126.3 (2C), 127.3, 139.4, 164.9 ppm (2C).

Compound 3g:[9a] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.55 (s, 8H), 4.40 (d, J = 6.0 Hz, 1H), 6.10–6.16 (m, 2H), 7.26–7.37 ppm (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.3 (2C), 39.3, 39.5, 52.4, 97.2, 98.7, 116.4, 117.8, 126.8, 127.6, 127.8 (2C), 128.8 (2C), 128.9, 139.3, 161.2, 161.7 ppm.

Compound 3h:[9a] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46–1.48 (m, 3H), 3.32–3.34 (m, 1H), 3.53–3.58 ppm (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3, 38.2 (2C), 39.8 (2C), 42.2, 98.0 (2C), 117.1 (2C), 162.8 ppm (2C).

Compound 3i: White solid; mp 162–164°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.27 (s, 2H), 3.56–3.59 ppm (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.4, 38.6 (2C), 39.8 (2C), 91.6 (2C), 109.7 (2C), 118.2 ppm (2C); ES-MS: m/z calcd. 298; found 299 $[M+1]^+$; elemental analysis calcd (%) for $C_{11}H_{10}N_2S_4$ (298.3): C 44.26, H 3.38, N 9.39; found: C 44.40, H 3.31, N 9.36.

Compound 3j:[9a] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25–1.28 (m, 6H), 1.31–1.35 (m, 6H), 2.94–3.03 (m, 8H), 5.61 (s, 1H), 7.24 (d, J = 8.5 Hz, 2H), 7.35 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.9 (2C), 15.6 (2C), 29.2 (2C), 30.4 (2C), 49.5, 116.4 (2C), 117.3 (2C), 129.2 (2C), 129.5 (2C), 133.9, 136.5, 156.9 ppm (2C).

Compound 3k:[9a] Pink solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, J = 7.0 Hz, 6H), 3.33(s, 8H), 3.97–4.00 (m, 4H), 5.42 (s, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.18 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (2C), 37.5 (2C), 38.5 (2C), 53.7 (2C), 60.5, 117.1, 127.9 (2C), 130.0 (2C), 131.8, 140.5 (2C), 161.1 (2C), 166.7 ppm (2C).

Compound 3l:[8a] Yellowish solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.93 (s, 6H), 3.24–3.29 (m, 8H), 5.69 (s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.28 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1 (2C), 37.5 (2C), 37.9 (2C), 53.5, 124.4, 129.3 (2C), 130.7 (2C), 133.4 (2C), 139.9, 163.9 (2C), 195.8 ppm (2C).

Compound 3m:[9a] Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.15–3.19 (m, 6H), 3.27–3.28 (m, 2H), 5.56 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.31–7.32 (m, 4H), 7.39–7.41 (m, 4H), 7.55 ppm (d, J = 7.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.8 (2C), 38.4 (2C), 56.3, 125.2 (2C), 128.1 (2C), 128.3 (4C), 128.7 (4C), 130.5 (2C), 131.6 (2C), 138.2 (2C), 138.6 (2C), 154.9 (2C), 195.1 ppm (2C).

Compound 3n:[8c] Yellow solid; ^{1}H NMR (500 MHz, DMSO): δ = 3.36 (s, 6H), 3.49–3.64 ppm (m, 8H); ^{13}C NMR (125 MHz, DMSO): δ = 26.7 (2C), 31.2 (2C), 37.6 (2C), 42.3, 99.9 (2C), 118.7 (2C), 165.0 ppm (2C).

Synthesis of dienes 4a; Typical procedure with 1a and 2k: HBr in acetonitrile (4 mL, 0.025 M, 0.1 mmol) was added to a solution of **1a** (143 mg, 1 mmol) and **2k** (0.088 mL, 1 mmol) in acetonitrile (1 mL) at room temperature. The reaction was allowed to proceed at room temperature until completion (18 h). The mixture was quenched with ice-water (20 mL), then extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/diethyl ether = 9:1, v/v) to give conjugated dienes **4a** (108 mg, 52%) as a colorless oil.

Compound 4a: Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.91–1.97 (m, 2H), 2.47–2.50 (m, 2H), 2.68–2.71 (m, 2H), 3.48–3.50 (m, 2H), 3.57–3.59 (m, 2H), 5.97 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.6, 33.5, 35.3, 37.6, 40.7, 96.7, 118.7, 131.1, 137.6, 159.1 ppm; ES-MS: m/z calcd. 209; found 210 $[M+1]^+$; elemental analysis calcd (%) for $C_{10}H_{11}NS_2$ (209.2): C 57.38, H 5.30, N 6.69; found: C 57.20, H 5.39, N 6.75.

Compound 4b: Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.59–1.63 (m, 2H), 1.67–1.69 (m, 2H), 2.14–2.15 (m, 2H), 2.22 (s, 2H), 3.48–3.49 (m, 4H), 5.90 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 22.5, 25.4, 27.5, 37.7, 39.2, 100.6, 118.2, 129.8, 133.3, 159.3 ppm; ES-MS: m/z calcd. 223; found 224 $[M+1]^+$; elemental analysis calcd (%) for $C_{11}H_{13}NS_2$ (223.2): C 59.15, H 5.87, N 6.27; found: C 59.01, H 5.96, N 6.35.

Synthesis of 3-substituted 2*H*-chromen-2-ones 5; Typical procedure with 1h and 2m: HBr in acetonitrile (4 mL, 0.025 M, 0.1 mmol) was added to a stirred solution of **2m** (0.12 mL, 1.1 mmol) and **1h** (252 mg, 1 mmol) in MeCN (1 mL) at room temperature. The reaction was allowed to proceed at room temperature until completion (1 h). The mixture was quenched with aqueous $NaHCO_3$ (10 mL, 5%), then extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford the pure product **5h** (212 mg, 85%) as a white solid.

Compound 5a:[9a] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.44 (m, 2H), 7.62–7.64 (m, 1H), 7.72–7.76 (m, 1H), 8.30 ppm (s, 1H); ^{13}C NMR (125 MHz,$CDCl_3$): δ = 103.5, 113.7, 117.3, 117.6, 125.9, 129.5, 135.7, 152.0, 154.8, 156.6 ppm.

Compound 5b:[9a] Yellow solid; ^{1}H NMR (500 MHz, DMSO): δ = 7.54 (d, J = 9.0 Hz, 1H), 7.81–7.83 (m, 1H), 7.89 (d, J = 2.5 Hz, 1H), 8.84 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ = 103.6, 114.3, 118.8, 118.9, 128.7, 129.1, 134.8, 152.1, 152.7, 156.5 ppm.

Compound 5c:[9a] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.42 (t, J=7.0 Hz, 3H), 4.40–4.44 (m, 2H), 7.32–7.37 (m, 2H), 7.61–7.67 (m, 2H), 8.54 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.2, 61.9, 116.7, 117.8, 118.2, 124.8, 129.5, 134.3, 148.6, 155.1, 156.7, 163.0 ppm.

Compound 5d:[9a] Yellow solid; ^{1}H NMR (500 MHz, DMSO): δ=1.41 (t, J=7.0 Hz, 3H), 4.40–4.45 (m, 2H), 7.32 (d, J=8.5 Hz, 1H), 7.58–7.60 (m, 2H), 8.44 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ=14.1, 62.1, 118.2, 118.8, 119.4, 128.4, 130.0, 134.0, 147.0, 153.4, 155.9, 162.6 ppm.

Compound 5e:[9a] Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.42 (t, J=7.0 Hz, 3H), 3.87 (s, 3H), 4.40–4.44 (m, 2H), 7.00 (d, J=3.0 Hz , 1H), 7.22–7.24 (m, 1H), 7.29 (d, J=9.0 Hz, 1H), 8.48 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.2, 55.9, 61.9, 109.8, 110.7, 117.9, 118.2, 122.6, 148.3, 149.8, 156.3, 156.9, 163.2 ppm.

Compound 5f:[9a] Yellow solid; ^{1}H NMR (500 MHz, DMSO): δ=2.57 (s, 3H), 7.49 (d, J=9.0 Hz, 1H), 7.75–7.77 (m, 1H), 8.06 (d, J=2.0 Hz, 1H), 8.59 ppm (s, 1H). ^{13}C NMR (125 MHz, DMSO): δ=30.0, 118.2, 119.6, 125.4, 128.6, 129.5, 133.8, 145.7, 153.2, 158.0, 195.0 ppm.

Compound 5g:[9a] Yellow solid; ^{1}H NMR (500 MHz, DMSO): δ=2.57 (s, 3H), 3.80 (s, 3H), 7.32 (t, J=2.5 Hz, 1H), 7.39 (d, J=9.0 Hz, 1H), 7.48 (d, J=2.5 Hz, 1H), 8.58 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ= 30.1, 55.8, 112.2, 117.2, 118.6, 122.4, 124.5, 146.9, 149.1, 155.8, 158.6, 195.2 ppm.

Compound 5h:[9a] White solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.38 (m, 1H), 7.42 (d, J=8.5 Hz, 1H), 7.48–7.51 (m, 2H), 7.61–7.68 (m, 3H), 7.89 (d, J=8.0 Hz, 2H), 8.09 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.9, 118.1, 124.9, 126.9, 128.6, 129.2 (2C), 129.6 (2C), 133.6, 133.8, 136.2, 145.5, 154.7, 158.4, 191.6 ppm.

Compound 5i:[9a] White solid; ^{1}H NMR (500 MHz, DMSO): δ=3.82 (s, 3H), 7.32–7.34 (m, 1H), 7.42–7.45 (m, 2H), 7.55 (t, J=7.5 Hz, 2H), 7.69 (t, J=7.5 Hz, 1H), 7.92 (t, J=7.0 Hz, 2H), 8.36 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ=55.8, 111.6, 117.5, 118.7, 121.3, 126.6, 128.8 (2C), 129.5 (2C), 133.9, 136.1, 145.2, 148.6, 155.8, 158.2, 191.8 ppm.

Synthesis of benzofurans 7; Typical procedure with 1k and 6a: HBr in acetonitrile (4 mL, 0.025 M, 0.1 mmol) was added to a stirred solution of **1k** (162 mg, 1.0 mmol) and **6a** (162 mg, 1.5 mmol) in MeCN (1 mL) at room temperature. The reaction mixture was heated at reflux for 6 h, until the starting material **1k** was consumed (reaction monitored by TLC). The resulting mixture was poured into saturated aqueous NaCl (20 mL), neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was washed with water (3× 20 mL), dried ($MgSO_4$) and concentrated in vacuo to yield the crude product, which was purified by silica gel chromatography (petroleum ether/diethyl ether=5:1, v/v) to give **7b** (138 mg, 62%) as a white solid.

Compound 7b:[9b] White solid; ^{1}H NMR (500 MHz, DMSO): δ=2.52 (s, 3H), 2.66 (s, 3H), 6.71 (dd, J=2.5, 9.0 Hz, 1H), 7.20 (d, J=2.5 Hz, 1H), 7.40 (d, J=9.0 Hz, 1H), 9.50 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ=13.1, 30.3, 105.5, 111.2, 111.9, 116.4, 126.7, 148.8, 154.7, 162.8, 192.0 ppm.

Compound 7c:[9b] White solid; ^{1}H NMR (500 MHz, DMSO): δ=1.34 (t, J=7.5 Hz, 3H), 2.66 (s, 3H), 4.29 (q, J=7.0 Hz, 2H), 6.69 (dd, J=2.5, 9.0 Hz, 1H), 7.18 (d, J=2.5 Hz, 1H), 7.39 (d, J=9.0, 1H), 9.43 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ=13.2, 14.8, 60.6, 105.7, 107.3, 111.6, 112.4, 127.4, 149.2, 155.1, 163.3, 163.5 ppm.

Compound 7d:[9b] Yellow solid; ^{1}H NMR (500 MHz, DMSO): δ=2.63 (s, 3H), 6.56 (d, J=2.0 Hz, 1H), 6.70 (dd, J=2.0, 9.0 Hz, 1H), 7.43 (d, J= 9.0 Hz, 1H), 7.56 (t, J=7.5 Hz, 2H), 7.65–7.70 (m, 3H), 9.37 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ=13.5, 105.1, 111.3, 112.4, 116.1, 127.0, 128.2 (2C), 128.7 (2C), 132.3, 139.1, 148.9, 154.3, 163.3, 189.7 ppm.

Compound 7e:[9b] White solid; ^{1}H NMR (500 MHz, DMSO): δ=1.74 (s, 3H), 2.40 (s, 3H), 2.52 (s, 3H), 6.70 (s, 1H), 7.54 (t, J=7.5 Hz, 2H), 7.68 (t, J=7.5 Hz, 1H), 7.78 (d, J=7.0 Hz, 2H), 9.12 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ=13.2, 15.0, 16.1, 112.1, 114.7, 118.5, 121.6, 127.0, 129.5 (2C), 129.7 (2C), 134.2, 138.6, 148.4, 152.0, 154.0, 191.8 ppm.

Compound 7f:[9b] White solid; ^{1}H NMR (500 MHz, DMSO): δ=1.32 (t, J=7.0 Hz, 3H), 2.34 (s, 6H), 2.63 (s, 3H), 4.28 (d, J=7.0 Hz, 2H), 6.62 (s, 1H), 9.08 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ=13.4, 13.8, 14.7 (2C), 60.9, 110.2, 113.0, 113.6, 117.9, 125.6, 148.3, 152.4, 161.1, 163.7 ppm.

Compound 7g:[9b] White solid; ^{1}H NMR (500 MHz, DMSO): δ=1.33 (t, J=7.0 Hz, 3H), 2.65 (s, 3H), 4.32 (q, J=7.0 Hz, 2H), 7.14 (s, 1H), 10.54 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ=14.6, 14.7, 61.6, 98.6, 102.0, 112.6, 115.4, 127.5, 146.2, 152.8, 160.5, 162.5 ppm.

Compound 7h:[9b] White solid; ^{1}H NMR (500 MHz, DMSO): δ=2.55 (s, 3H), 7.20 (s, 1H), 7.53 (t, J=7.5 Hz, 2H), 7.69 (t, J=7.0 Hz, 1H), 7.82 (d, J=7.0 Hz, 2H), 10.58 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ= 15.9, 97.9, 101.7, 115.8, 121.5, 128.5, 129.0 (2C), 129.4 (2C), 134.1, 137.8, 145.9, 151.9, 154.4, 189.6 ppm.

Compound 7i:[9b] White solid; ^{1}H NMR (500 MHz, DMSO): δ=1.38 (t, J=7.0 Hz, 3H), 2.78 (s, 3H), 4.33 (q, J=7.0 Hz, 2H), 7.34 (s, 1H), 7.48 (t, J=8.0 Hz, 1H), 7.63 (t, J=7.5 Hz, 1H), 8.11 (d, J=8.0 Hz, 1H), 8.20 (d, J=8.5 Hz, 1H), 10.26 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ= 13.4, 14.9, 60.7, 100.1, 108.7, 119.5, 120.7, 122.6, 123.0, 123.8, 124.8, 127.9, 144.4, 151.2, 160.8, 163.6 ppm.

Compound 7j:[9b] White solid; ^{1}H NMR (500 MHz, DMSO): δ=2.59 (s, 3H), 2.80 (s, 3H), 7.39 (s, 1H), 7.48–7.51 (m, 1H), 7.62–7.65 (m, 1H), 8.13 (d, J=8.0 Hz, 1H), 8.20 (d, J=8.5 Hz, 1H), 10.25 ppm (s, 1H); ^{13}C NMR (125 MHz, DMSO): δ=13.6, 30.3, 99.8, 118.0, 119.1, 120.1, 122.0, 122.1, 123.2, 124.4, 127.4, 144.0, 150.8, 160.0, 192.3 ppm.

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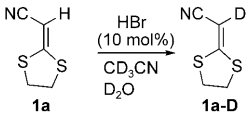
[13] The hydrobromic acid-catalyzed hydrogen–deuterium exchange reaction of **1a** with heavy water was performed: D_2O (0.025 mL) was added to a solution of **1a** and HBr (0.025 mL, 1.4 equiv) in CD_3CN (0.5 mL) at ambient temperature. The deuterated **1a** was detected by ^1H NMR spectroscopic analysis. Comparing the ^1H NMR spectra of **1a** and **1a**-D at different times, it is observed that there were clear changes in the ratio of the peak area at $\delta = 3.58$ and 5.43 ppm (see the ^1H NMR spectra in the Supporting Information for this experiment). The stepwise decrease in the peak area at $\delta = 5.43$ ppm indicates that the α-hydrogen of **1a** is gradually deuterated under the acidic conditions. This experiment thus provides evidence for the transformation of **1** into intermediate **A** as described in Scheme 5.



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