



## PAPER



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# Synthesis of $\text{CCl}_3$ -substituted amides, ketones, and indenenes by intermolecular reactions of $\beta\text{-CCl}_3$ -enones or $\beta\text{-CCl}_3$ - $\beta$ -hydroxy ketones with various nucleophiles in $\text{CF}_3\text{SO}_3\text{H}$

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Intermolecular reactions of 1-aryl-4,4,4-trichloro-3-hydroxybutan-1-ones ( $\beta\text{-CCl}_3$ - $\beta$ -hydroxy ketones) or 1-aryl-4,4,4-trichlorobut-2-en-1-ones ( $\beta\text{-CCl}_3$ -enones) with nucleophiles in Brønsted superacid  $\text{CF}_3\text{SO}_3\text{H}$  (triflic acid, TfOH) result in various  $\text{CCl}_3$ -substituted compounds in good yields. Reactions with nitriles give rise to  $\text{CCl}_3$ -amides. Reactions with cyclohexane or 1,2,4,5-tetramethylbenzene as hydride ion sources afford products of ionic hydrogenation, namely, saturated  $\text{CCl}_3$ -ketones. Reactions with arenes furnish arylated  $\text{CCl}_3$ -ketones, which may be further cyclized into  $\text{CCl}_3$ -indenenes. Plausible reaction mechanisms are discussed based on DFT calculations of electronic, orbital, and electrophilic properties of the intermediate cationic species.

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## Introduction

Trichloromethyl ( $\text{CCl}_3$ )-substituted compounds play an important role in chemistry, biology, and medicine. They are widely found in nature in the kingdom of marine sponges. The series of substances bearing the  $\text{CCl}_3$  group, such as sintokamides,<sup>1–3</sup> dysamides,<sup>4–6</sup> dysidin,<sup>7</sup> dysidenin,<sup>8,9</sup> and neodysidenin,<sup>10,11</sup> were isolated from the marine sponge *Dysidea* sp. living near the shores of the Southeast Asian seas, the Red Sea, and Australia. Apart from the  $\text{CCl}_3$  group, these structures contain an azaheterocycle along with an amide bond, and some of them are considered to be derivatives of dipeptides (Fig. 1).

Many natural and synthetic  $\text{CCl}_3$ -compounds exhibit various types of biological activity, for instance, anticancer properties,<sup>1–3,12–14</sup> cytotoxicity and inhibition of protein phosphatase,<sup>5</sup> inhibition of human lipoxygenases,<sup>11</sup> molluscicidal<sup>15</sup> and antiplasmodial<sup>16</sup> activities, and many others. Thus, much attention has been constantly paid to the synthesis of novel  $\text{CCl}_3$ -substituted compounds and the investigation of their properties.<sup>17–22</sup>

Recently, we have shown that both 1-aryl-4,4,4-trichloro-3-hydroxybutan-1-ones ( $\beta\text{-CCl}_3$ - $\beta$ -hydroxy ketones) **1** and 1-aryl-4,4,4-trichlorobut-2-en-1-ones ( $\beta\text{-CCl}_3$ -enones) **2** undergo intramolecular cyclization into 3-trichloromethylindan-1-ones

( $\text{CCl}_3$ -indanones) **I** in Brønsted superacid  $\text{CF}_3\text{SO}_3\text{H}$  (triflic acid, TfOH) (Scheme 1).<sup>23</sup> The cyclization proceeds through an intermediate formation of the reactive mesomeric cation  $\text{B} \leftrightarrow \text{B}'$ , which is the O-protonated form of the starting  $\beta\text{-CCl}_3$ -enone **2**.  $\beta\text{-CCl}_3$ - $\beta$ -Hydroxy ketones **1** in TfOH at first give rise to O,O-diprotonated species **A**, followed by dehydration into cation **B** and cyclization into  $\text{CCl}_3$ -indanones **I**.<sup>23</sup> In this cyclization, aryl substituents in cations **B** act as internal (intramolecular) nucleophiles. One may expect that species **B** could react with external (intermolecular) nucleophiles such as arenes, nitriles and sources of hydride ions (alkanes), leading to adducts **II** (Scheme 1).

Based on our previous works<sup>23–26</sup> on superelectrophilic activation of  $\text{CCl}_3$ -substituted alkenes, we undertook this particular study on the reactions of compounds **1** and **2** with various nucleophiles in an intermolecular way in the Brønsted superacid TfOH.

## Results and discussion

Starting compounds,  $\beta\text{-CCl}_3$ - $\beta$ -hydroxy ketones **1** and  $\beta\text{-CCl}_3$ -enones **2**, used in this study were previously synthesized and described by us<sup>23</sup> (Fig. 2).

In the beginning, we conducted the Ritter reaction between ketones **1** or enones **2** with nitriles in TfOH at room temperature for 2–30 days. The reaction with acetonitrile MeCN afforded the corresponding  $\text{CCl}_3$ -acetamides **3** in yields up to 95% (Schemes 2, 3). Other nitriles, EtCN and  $\text{Cl}_3\text{CCN}$ , may also

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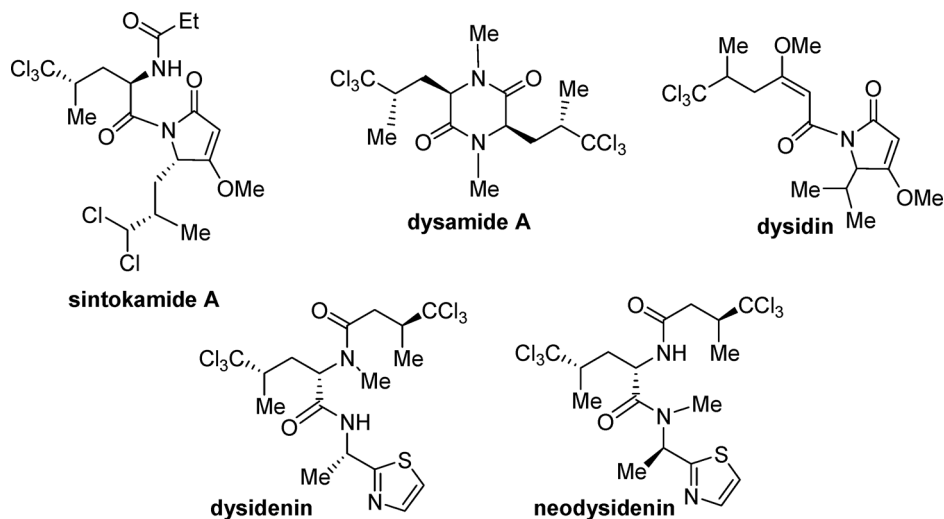
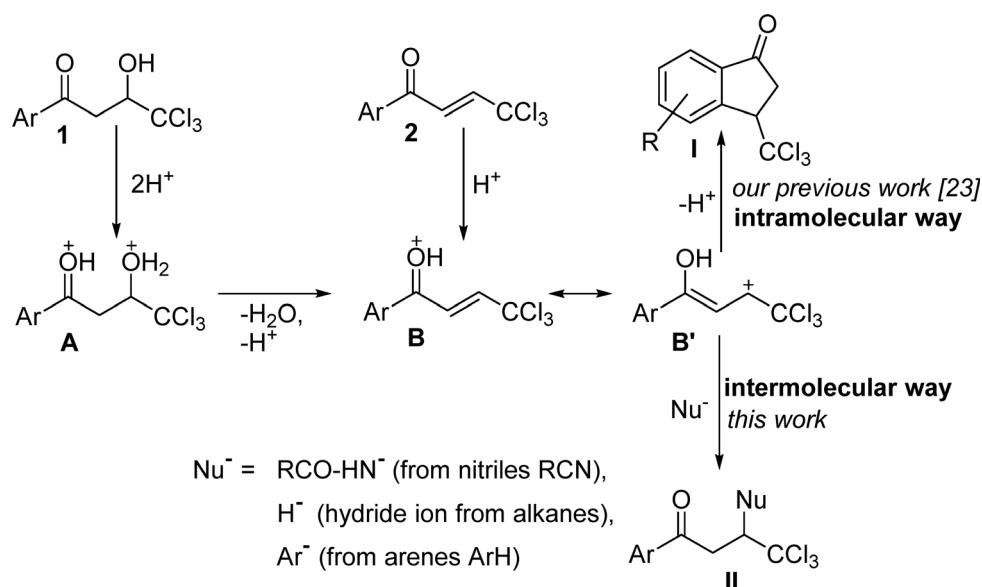


Fig. 1 Natural biologically active CCl<sub>3</sub>-substituted compounds.



Scheme 1 Data of our previous work<sup>23</sup> on intramolecular cyclization of compounds **1** and **2** into indanones **I** in TfOH and data of this study on intermolecular reactions of compounds **1** and **2** with various nucleophiles leading to compounds **II**.

be involved in this reaction, leading to amides **3ea** and **3eb** (Scheme 2). However, benzonitrile PhCN did not take part in the reaction with compounds **1** and **2**, but it underwent TfOH-promoted trimerization into the corresponding 2,4,6-triphenyl-1,3,5-triazine. Apart from that, malononitrile H<sub>2</sub>C(CN)<sub>2</sub> and methyl cyanoacetate NCCH<sub>2</sub>CO<sub>2</sub>Me gave rise to complex mixtures of oligomeric products in these reactions. It should be specially emphasized that acetamides **3** contain both trichloromethyl and amide groups, which are structurally close to natural biologically active compounds (Fig. 1). One may expect that compounds **3** may possess various kinds of biological properties.

Then, ionic hydrogenation of compounds **1** and **2** by cyclohexane, as a source of hydride ion, in TfOH (room temperature,

2 h – 7 days) was carried out with the formation of CCl<sub>3</sub>-ketones **4** (Schemes 4 and 5). Previously, we conducted the same ionic hydrogenation of unsaturated compounds by cyclohexane under the superelectrophilic activation conditions.<sup>27–29</sup>

Ionic hydrogenation of the methyl-substituted ketone **1b** took a long time (30 days) with incomplete conversion of the starting compound (Scheme 6). Apart from the expected target ketone **4b**, the product of cyclization **7b** was isolated in this reaction, revealing concurrent formation of compounds **4b** and **7b** by inter- or intra-molecular ways, respectively, from the corresponding cation **B** (Scheme 1).

Intermolecular reactions of ketones **1** or enones **2** with arenes (benzene, *m*-, *p*-xylenes and anisole) in TfOH at room

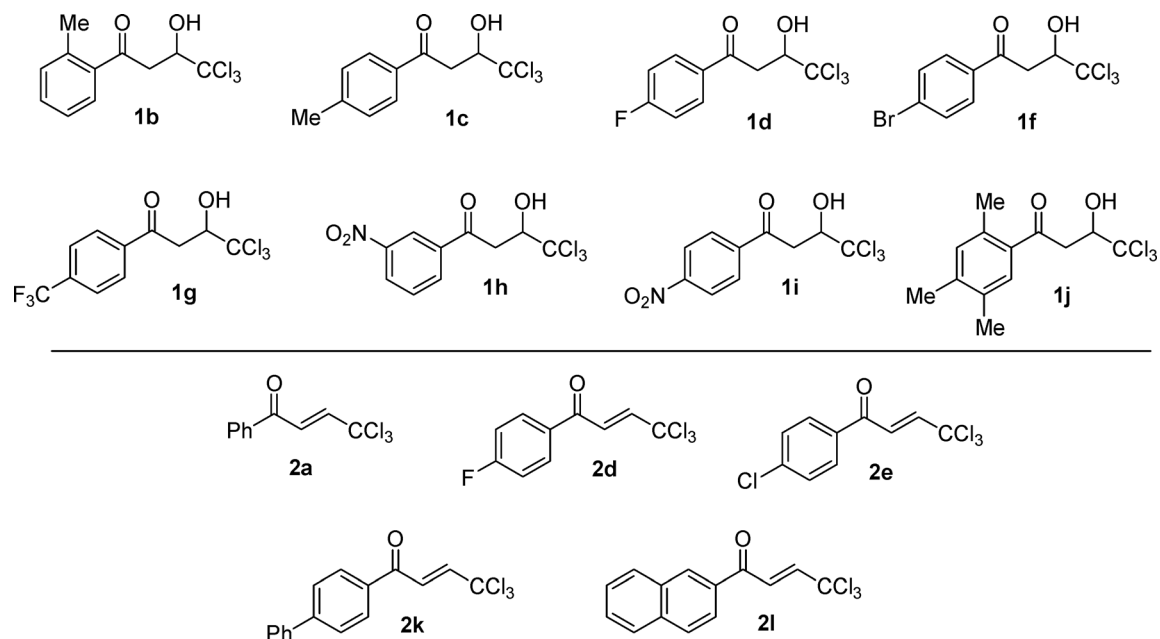
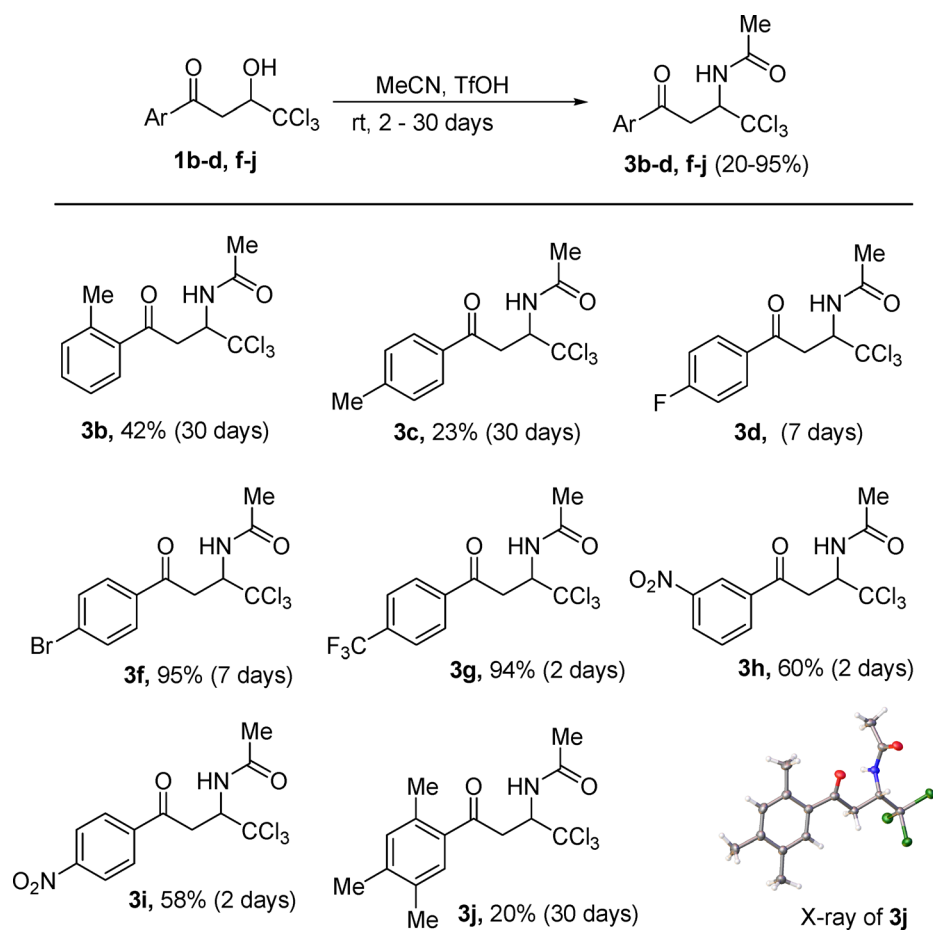
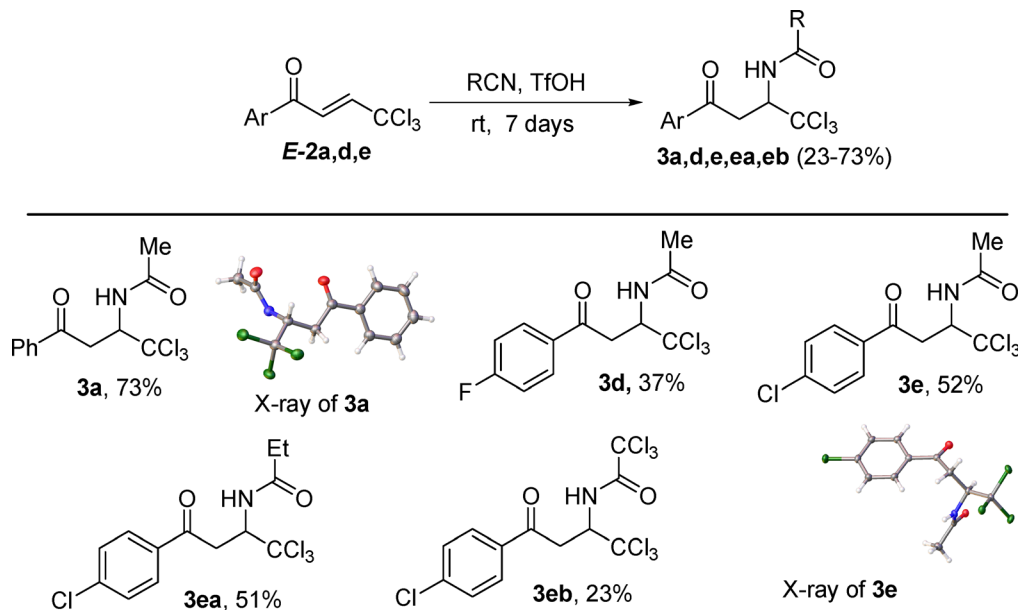


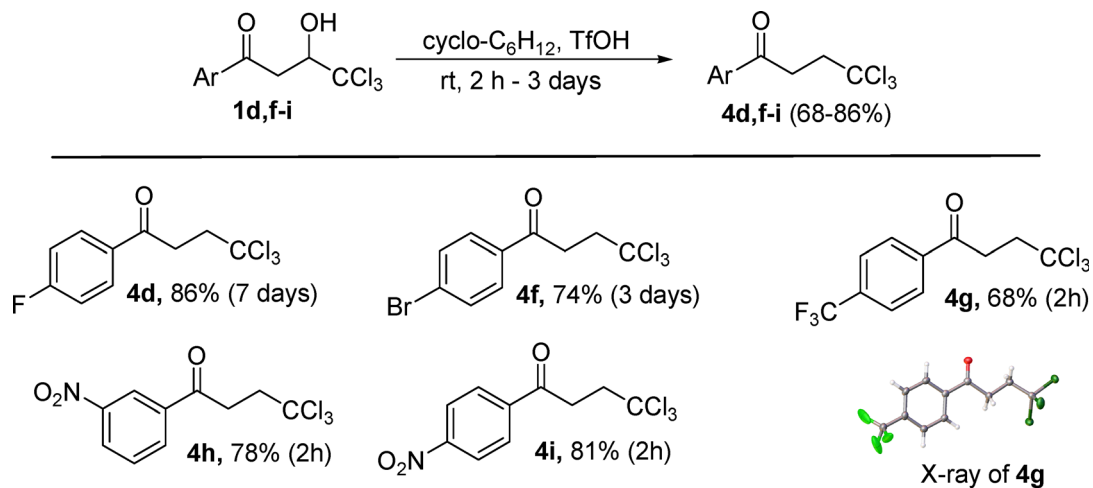
Fig. 2 Starting compounds,  $\beta$ - $\text{CCl}_3$ - $\beta$ -hydroxy ketones **1** and  $\beta$ - $\text{CCl}_3$ -enones **2**, used in this study (see their synthesis in our previous work<sup>23</sup>).



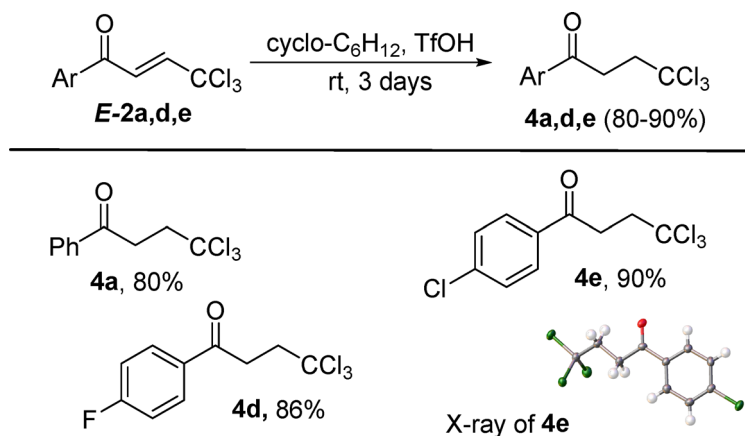
Scheme 2 Reactions of  $\beta$ - $\text{CCl}_3$ - $\beta$ -hydroxy ketones **1** with acetonitrile in TfOH leading to  $\text{CCl}_3$ -amides **3** (ellipsoid contours of probability levels are 50% for X-ray structures).



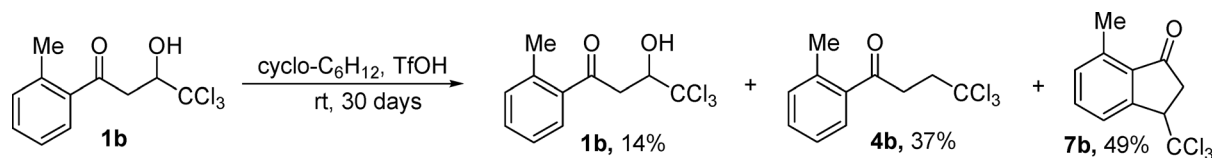
**Scheme 3** Reactions of  $\beta$ - $\text{CCl}_3$ -enones **2** with nitriles in TfOH leading to  $\text{CCl}_3$ -amides **3** (ellipsoid contours of probability levels are 50% for X-ray structures).



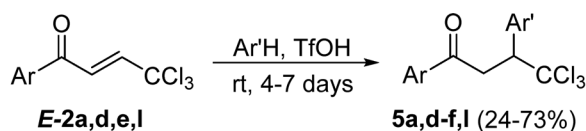
**Scheme 4** Ionic hydrogenation of  $\beta$ - $\text{CCl}_3$ - $\beta$ -hydroxy ketones **1** by cyclohexane in TfOH leading to  $\text{CCl}_3$ -ketones **4** (ellipsoid contours of probability levels are 50% for X-ray structures).



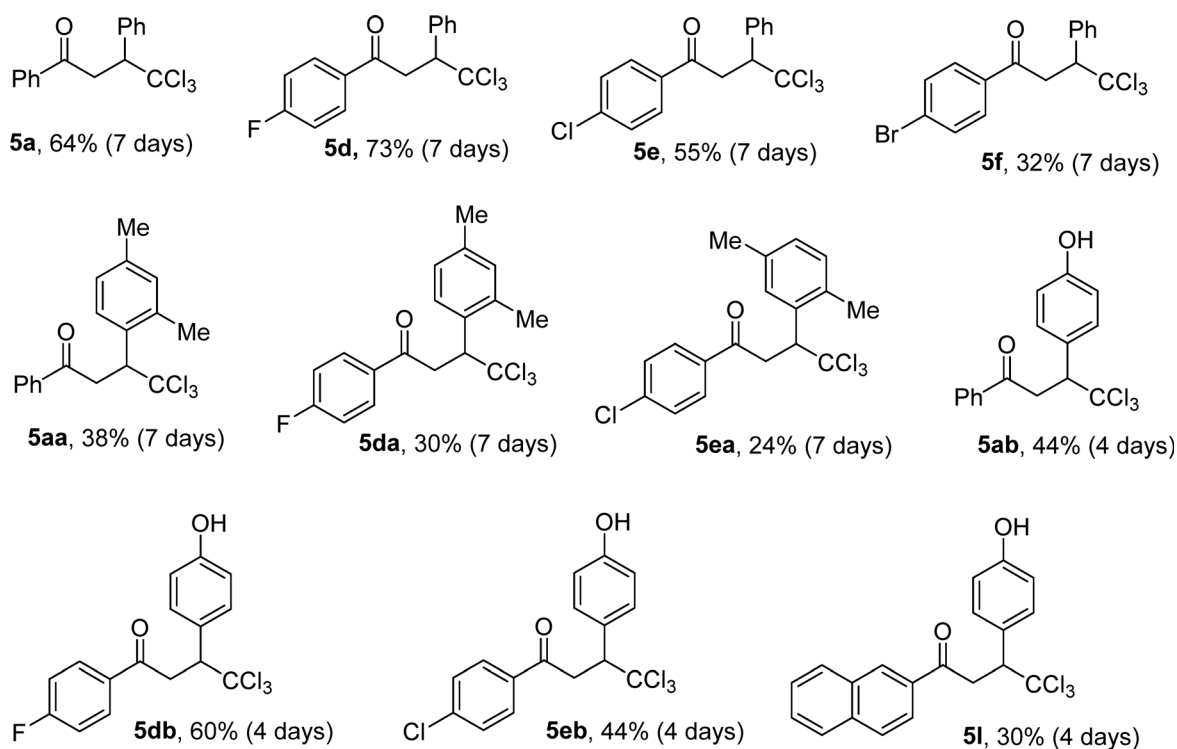
**Scheme 5** Ionic hydrogenation of  $\beta$ - $\text{CCl}_3$ -enones **2** by cyclohexane in TfOH leading to  $\text{CCl}_3$ -ketones **4** (ellipsoid contours of probability levels are 50% for X-ray structures).



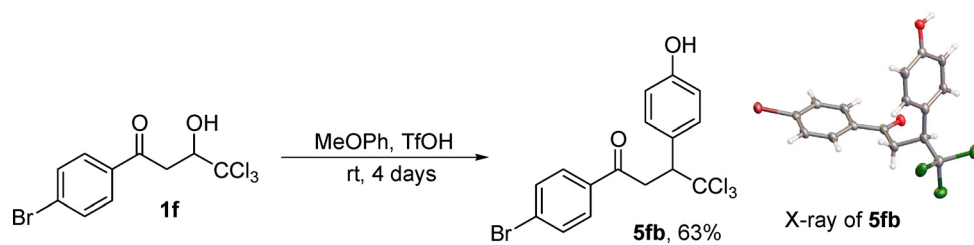
Scheme 6 Transformations of  $\beta$ -CCl<sub>3</sub>- $\beta$ -hydroxy ketone **1b** in TfOH in the presence of cyclohexane.



Ar'H = PhH, 1,3-Me<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 1,4-Me<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, MeOPh



Scheme 7 Hydroarylation of  $\beta$ -CCl<sub>3</sub>-enones **2** by arenes in TfOH leading to CCl<sub>3</sub>-ketones **5**.



Scheme 8 Reaction of  $\beta$ -CCl<sub>3</sub>- $\beta$ -hydroxy ketone **1f** with anisole in TfOH leading to CCl<sub>3</sub>-ketone **5fb** (ellipsoid contours of probability levels are 50% for X-ray structures).

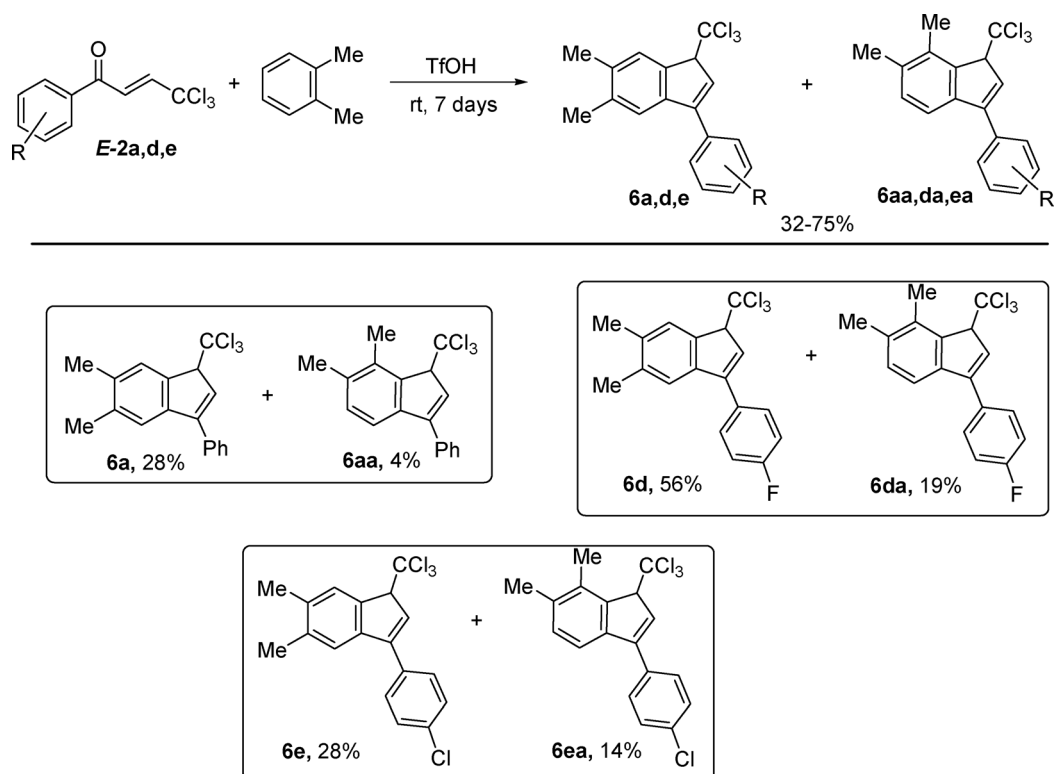
temperature for 7 days furnished  $\text{CCl}_3$ -ketones **5** (Schemes 7 and 8). Taking into account the initial transformation of  $\beta$ - $\text{CCl}_3$ - $\beta$ -hydroxy ketones **1** in TfOH into cation **B** (Scheme 1 and our previous study<sup>23</sup>), compounds **5** are products of hydroarylation of the carbon-carbon double bond of  $\beta$ - $\text{CCl}_3$ -enones **2**. It should be noted that reactions with anisole (MeOPh) gave hydroxyphenyl-substituted compounds **5ab**, **5bd**, **5eb**, **5l** and **5fb** due to the demethylation of the methoxy group in TfOH during the long reaction time of 7 days.

Reactions of  $\beta$ - $\text{CCl}_3$ -enones **2** with  $\pi$ -donating arenes [*o*-xylene and pseudocumene (1,2,4-trimethylbenzene)] went deeper and resulted in mixtures of regioisomeric  $\text{CCl}_3$ -indenes **6** (Schemes 9 and 10). We were not able to separate the regioisomers of compounds **6** by usual preparative column or thin-layer chromatography. However, indene **6d** was individually obtained by HPLC purification (see the experimental part).

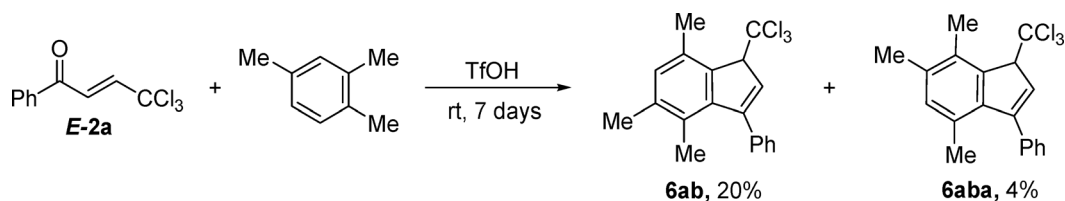
Surprisingly, the same reaction of compounds **1** and **2** with durene (1,2,4,5-tetramethylbenzene) afforded the products of

ionic hydrogenation **4**, rather than the expected products of hydroarylation **5** or indenes **6** (Scheme 11). In this case, a methyl group of durene is a source of a hydride ion, which after elimination from the durene molecule gives rise to a rather stable trimethylbenzyl cation.

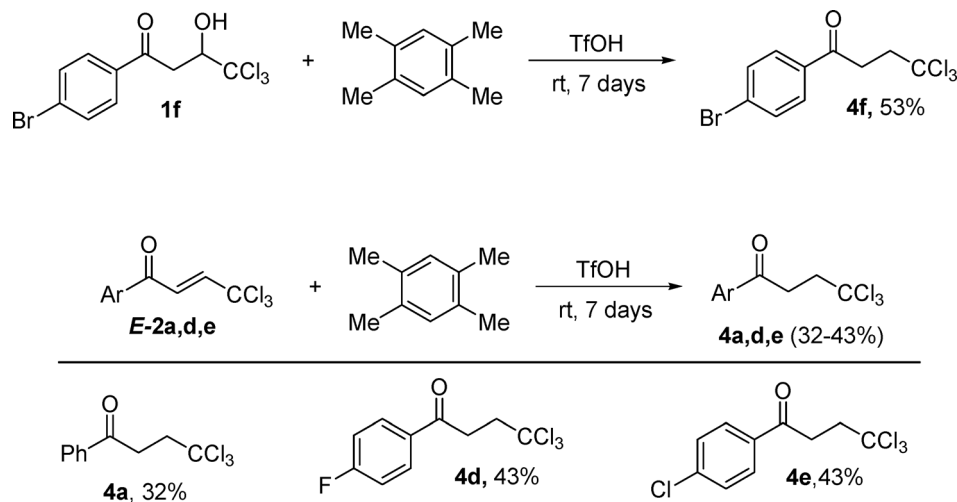
Based on the data obtained on the reactions of compounds **1** and **2** with various nucleophiles in TfOH, one may propose plausible reaction mechanisms leading to substances **3–6** (Scheme 12). Both compounds **1** and **2** in TfOH form the mesomeric cation  $\text{B} \leftrightarrow \text{B}'$ . The reaction of the latter with nitriles proceeds through the intermediate formation of cations **C**, **D**, and results in amide **3** after hydrolysis of superacidic reaction solution. Cation **B** in reaction with cyclohexane or durene as hydride ion sources furnishes ketone **4**. The interaction of species **B** with aromatic nucleophiles  $\text{Ar}'\text{H}$  gives at first cation **E**, which is hydrolyzed into ketone **5** under the reaction work-up. However, cation **E** may undergo intramolecular cyclization onto the rather electron-rich aryl substituent  $\text{Ar}'$ , in the cases of



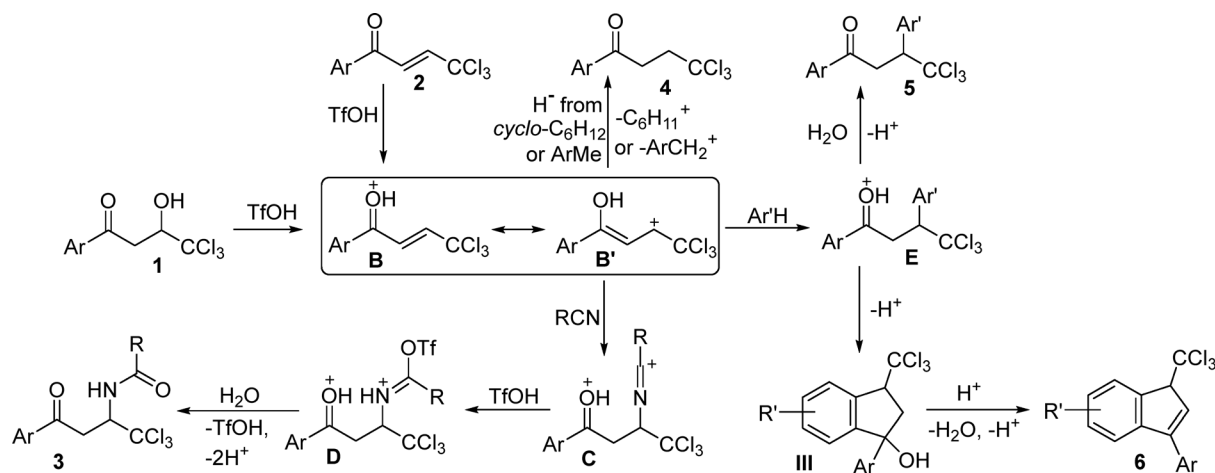
Scheme 9 Reactions of  $\beta$ - $\text{CCl}_3$ -enones **2** with *o*-xylene in TfOH leading to  $\text{CCl}_3$ -indenes **6**.



Scheme 10 Reactions of  $\beta$ - $\text{CCl}_3$ -enone **2a** with pseudocumene in TfOH leading to  $\text{CCl}_3$ -indenes **6**.



Scheme 11 Ionic hydrogenation of  $\beta$ - $\text{CCl}_3$ - $\beta$ -hydroxy ketone **1f** and  $\text{CCl}_3$ -enones **2** by durene in TfOH leading to  $\text{CCl}_3$ -ketones **4**.



Scheme 12 Plausible mechanisms of reactions of compounds **1** and **2** with various nucleophiles in TfOH leading to substances **3-6**.

reactions with *o*-xylene and pseudocumene (see Schemes 9 and 10), with the formation of hydroxyindan **III**. Dehydration of the latter affords finally indene **6**.

It should be noted, that attempts to accelerate the reaction of the starting compounds **1** and **2** with nitriles, cyclohexane and arenes by increasing the temperature led to a decrease in the yields of the target products, amides **3**, ketones **4** and **5**, indenones **6**. Apart from that, the formation of indanones **7**, as products of intermolecular cyclization (analogously to our previous work<sup>23</sup>) and a large amount of oligomeric material was detected.

Then, DFT calculations of key reaction intermediates, cations **B**, derived from the protonation of compounds **2** were carried out. The thermodynamics of their formation, as Gibbs energies  $\Delta G_{298}$  of the corresponding reactions, energies of HOMO/LUMO, electrophilicity indexes  $\omega$ ,<sup>30,31</sup> charge distribution, and the contribution of the atomic orbital into the LUMO in species **B** were estimated (Table 1).

The formation of these O-monoprotonated species **B** from enones **2** is favorable;  $\Delta G_{298}$  values of the protonation are

negative ( $-67$  to  $-28$  kJ mol<sup>-1</sup>). Calculations show that the largest part of the positive charge in cations **B** is localized on the carbonyl carbon C<sup>1</sup> (0.54–0.61e). This carbon gives a contribution into the LUMO of 9.0%–19.2%. Contrary to that, the carbon C<sup>3</sup> bears negative charge ( $-0.14$  to  $-0.08e$ ), and its contribution into the LUMO is 10.6%–20.9%, which is comparable with the contribution of the carbon C<sup>1</sup>. Thus, the electrophilic properties of the atom C<sup>3</sup> may be mainly explained by an orbital factor, rather than a charge one.

In this study, it was observed that reactions of compounds **1** and **2** having electron-withdrawing substituents ( $\text{NO}_2$ ,  $\text{CF}_3$ , F, Cl) with nucleophiles proceed much faster, than for substrates **1** and **2** containing electron-donating methyl or methoxy groups (compare reaction times in Schemes 2–11). The same was found for the cyclization of compounds **1** and **2** into  $\text{CCl}_3$ -indanones **I** (see Scheme 1) in our previous study.<sup>23</sup> This different behavior may be explained in terms of electrophilicity index  $\omega$  of species **B**, which ranges from 5.0 to 6.1 eV (Table 1). Cations **Bd**, **e**, **g-i**, **m** with acceptors  $\text{NO}_2$ ,  $\text{CF}_3$ , F, Cl possess

**Table 1** Selected calculated (DFT) electronic characteristics of the protonated forms **B** generated from  $\beta$ -CCl<sub>3</sub>-enones **2**, and values of Gibbs energies of protonation reactions **2**  $\rightarrow$  **B** ( $\Delta G$ , kJ mol<sup>-1</sup>)

Entry	Species	$E_{\text{HOMO}}$ , eV	$E_{\text{LUMO}}$ , eV	$\omega$ , <sup>a</sup> eV	$q(\text{C}^1)$ , <sup>b</sup> e	$q(\text{C}^3)$ , <sup>b</sup> e	$k(\text{C}^1)_{\text{LUMO}}$ , <sup>c</sup> %	$k(\text{C}^3)_{\text{LUMO}}$ , <sup>c</sup> %	$\Delta G$ , <sup>d</sup> kJ mol <sup>-1</sup>
1	 <b>2a</b>	-7.47	-2.93	3.0	0.54	-0.18	8.9	11.3	—
2	 <b>Ba</b>	-8.13	-4.42	5.3	0.59	-0.11	12.8	11.1	<b>2a</b> $\rightarrow$ <b>Ba</b> -45
3	 <b>2b</b>	-7.15	-2.83	2.9	0.55	-0.18	4.7	5.5	—
4	 <b>Bb</b>	-7.82	-4.35	5.3	0.59	-0.11	19.2	18.9	<b>2b</b> $\rightarrow$ <b>Bb</b> -47
5	 <b>2c</b>	-7.21	-2.86	2.9	0.55	-0.19	8.2	10.8	—
6	 <b>Bc</b>	-8.02	-4.31	5.1	0.57	-0.12	12.7	12.7	<b>2c</b> $\rightarrow$ <b>Bc</b> -55
7	 <b>2d</b>	-7.45	-2.93	3.0	0.54	-0.18	8.8	10.8	—
8	 <b>Bd</b>	-8.43	-4.42	5.1	0.58	-0.11	11.0	19.0	<b>2d</b> $\rightarrow$ <b>Bd</b> -45
9	 <b>2e</b>	-7.35	-2.99	3.1	0.54	-0.17	9.4	11.2	—
10	 <b>Be</b>	-8.05	-4.48	5.5	0.58	-0.11	12.5	10.6	<b>2e</b> $\rightarrow$ <b>Be</b> -42

Table 1 (continued)

Entry	Species	$E_{\text{HOMO}}$ , eV	$E_{\text{LUMO}}$ , eV	$\omega$ , <sup>a</sup> eV	$q(\text{C}^1)$ , <sup>b</sup> e	$q(\text{C}^3)$ , <sup>b</sup> e	$k(\text{C}^1)_{\text{LUMO}}$ , <sup>c</sup> %	$k(\text{C}^3)_{\text{LUMO}}$ , <sup>c</sup> %	$\Delta G$ , <sup>d</sup> kJ mol <sup>-1</sup>
11	 2g	-7.75	-3.09	3.2	0.54	-0.17	12.2	7.2	—
12	 Bg	-8.41	-4.67	5.7	0.60	-0.10	13.0	20.9	2g → Bg -28
13	 2h	-7.87	-3.28	3.4	0.54	-0.16	6.4	4.5	—
14	 Bh	-8.66	-4.70	5.6	0.61	-0.09	12.6	19.1	2h → Bh -29
15	 2i	-7.86	-3.56	3.8	0.54	-0.16	8.2	4.9	—
16	 Bi	-8.53	-4.87	6.1	0.61	-0.08	12.2	11.3	2i → Bi -28
17	 2l	-6.53	-2.92	3.1	0.55	-0.18	8.9	10.8	—
18	 Bl	-7.04	-4.36	6.0	0.58	-0.12	12.1	18.8	2l → Bl -52
19	 2m	-7.38	-3.02	3.1	0.54	-0.17	9.7	11.4	—

Table 1 (continued)

Entry	Species	$E_{\text{HOMO}}$ , eV	$E_{\text{LUMO}}$ , eV	$\omega$ , <sup>a</sup> eV	$q(\text{C}^1)$ , <sup>b</sup> e	$q(\text{C}^3)$ , <sup>b</sup> e	$k(\text{C}^1)_{\text{LUMO}}$ , <sup>c</sup> %	$k(\text{C}^3)_{\text{LUMO}}$ , <sup>c</sup> %	$\Delta G$ , <sup>d</sup> kJ mol <sup>-1</sup>
									<b>2m</b> → <b>Bm</b> -35
20	 <b>Bm</b>	-8.03	-4.57	5.7	0.60	-0.10	13.8	16.5	
21	 <b>2n</b>	-7.0	-2.78	2.8	0.54	-0.18	5.2	6.7	—
									<b>2n</b> → <b>Bn</b> -57
22	 <b>Bn</b>	-7.8	-4.20	5.0	0.57	-0.14	11.9	15.0	
23	 <b>2o</b>	-6.71	-2.79	2.9	0.54	-0.19	7.8	10.8	—
									<b>2o</b> → <b>Bo</b> -67
24	 <b>Bo</b>	-7.53	-4.14	5.0	0.54	-0.14	10.0	18.8	
25	 <b>2p</b>	-6.86	-2.84	2.9	0.56	-0.18	6.2	10.4	—
									<b>2p</b> → <b>Bp</b> -47
26	 <b>Bp</b>	-7.55	-4.14	5.0	0.55	-0.14	9.0	18.2	

<sup>a</sup> Global electrophilicity index  $\omega = (E_{\text{HOMO}} + E_{\text{LUMO}})^2/8(E_{\text{LUMO}} - E_{\text{HOMO}})$ . <sup>b</sup> Natural charges. <sup>c</sup> Contribution of atomic orbital into the molecular orbital. <sup>d</sup> Gibbs energy of protonation reactions.

higher indexes  $\omega$  5.1–6.1 eV compared to cations **Bb**, **c**, **n–p** with donors Me, MeO having  $\omega$  values of 5.0–5.1 eV. Thus, the latter species are less reactive, and their reactions take longer time.

## Conclusions

Methods of synthesis of novel  $\text{CCl}_3$ -substituted compounds have been developed on the basis of intermolecular reactions of  $\beta\text{-CCl}_3\text{-}\beta\text{-hydroxy}$  ketones or  $\beta\text{-CCl}_3\text{-enones}$  with various

nucleophiles (nitriles, arenes, hydride ion) in triflic acid TfOH. The following compounds have been obtained:  $\text{CCl}_3$ -amides, various  $\text{CCl}_3$ -ketones, and  $\text{CCl}_3$ -indenes. These reactions open up new ways for the preparation of practically valuable  $\text{CCl}_3$ -compounds showing various types of biological activity.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental details, characterization data, NMR spectra, X-ray data, and DFT calculations. See DOI: <https://doi.org/10.1039/d5nj03928b>.

CCDC 2491771–2491781 (**3a**, **3e**, **3j**, **4e**, **4g** and **5fb**) contain the supplementary crystallographic data for this paper.<sup>32a–k</sup>

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