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Carbene-Catalyzed Enantioselective Addition of Sulfinate to Ketones

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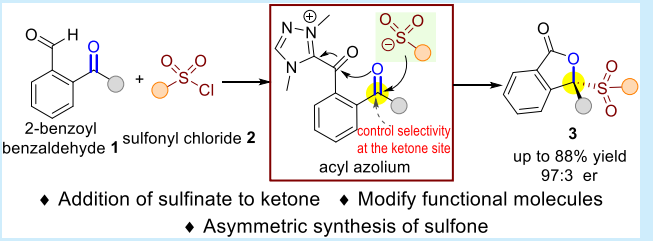
ABSTRACT: A carbene-catalyzed enantioselective addition of sulfinate to ketones between 2-benzoylbenzaldehyde and sulfonyl chloride is disclosed. Up to now, the carbon and heteroatom nucleophiles have effectively undergone catalytic enantioselective addition to carbonyl molecules to introduce functionalities and chirality. Sulfone, as an important class of sulfur-containing functional groups, represents highly valuable motifs in medicines and natural products. It remains undeveloped for the catalytic asymmetric addition of sulfinate to carbonyls. Herein we disclosed the first catalytic enantioselective addition of sulfinate to ketones for the synthesis of sulfones via N-heterocyclic carbene (NHC) catalysis. The sulfonyl chloride behaves both as an oxidant and as a nucleophilic substrate in this carbene-catalyzed process. Experimental studies suggested that the Breslow intermediate can be SET oxidized by sulfonyl chloride to generate the sulfonyl radical. This novel synthetic approach for the asymmetric addition of sulfinate to carbonyls can also be used to modify the commercially available functional molecules.



The asymmetric addition of carbon and heteroatom nucleophiles to carbonyls (such as ketones and aldehydes) is a common approach for introducing functionalities and building molecular chirality in organic synthesis.[1] Both metal-based complexes[2] and organic catalysts[3] can be used to mediate these reactions and induce high levels of stereoselectivities. Examples of such catalytic asymmetric reactions include amine-catalyzed aldol-type reactions,[4] phosphoric acid-mediated acetal formations,[5] and N-heterocyclic carbene (NHC)-catalyzed benzoin-type reactions.[6] The use of heteroatom nucleophiles in these reactions is of considerable interest, as it offers unique structures (such as acetals) and functions. At present, heteroatom nucleophiles capable of effectively undergoing catalytic (formal) enantioselective addition to carbonyl molecules include alcohols,[7] carboxylic acids,[8] amines and related nitrogen nucleophiles such as amides,[9] and phosphines and the related diphenylphosphine oxide[10] (Figure 1a). Sulfur is an essential element with profound presence in life.[11] Sulfone, as an important class of sulfur-containing functional groups, is widely present in medicines and natural products.[12] However, unlike thiols, for which catalytic enantioselective reactions are relatively well-developed,[13] catalytic asymmetric reactions using sulfinate (to prepare the corresponding sulfones) are much less developed. Reported examples primarily focus on addition to carbon−carbon double/triple bonds mediated by metal[14] and organic catalysts,[15] including earlier studies from our laboratory.[16] To the best of our knowledge, the catalytic asymmetric addition of sulfinate to carbonyls (carbon−oxygen double bonds), such as ketones, remains undeveloped. Here we developed the first catalytic enantioselective addition of sulfinate to ketones for access to sulfones (Figure 1b). Our reaction starts with 2-benzoylbenzaldehyde and toluenesulfonyl chloride (TsCl) in the presence of an NHC catalyst,[17] affording the sulfone product with excellent yields and enantiomeric excess values. The overall reaction involves an NHC-mediated redox process that converts the aldehyde moiety of the ketone substrate to the acyl azolium intermediate **IV** and the toluenesulfonyl chloride to a sulfinate anion. A (formal) enantioselective addition of the sulfinate anion to intermediate **IV**, followed by a lactone formation process, sets up the newly formed chiral center (Figure 1c). Ketones, along with the related carbonyl groups and their analogues, are among the most common and most-used functional groups in organic chemistry. Thus, we therefore expect our present study to open up opportunities for building previously ignored chiral molecules for possible new applications. Our ongoing work includes expanding the reaction scope toward more general substrates and constructing/modifying molecules with applications in medicines.

2-Benzoylbenzaldehyde **1a** was chosen as a model substrate to react with toluenesulfonyl chloride **2a** to search for the optimal reaction conditions (Table 1). A typical reaction

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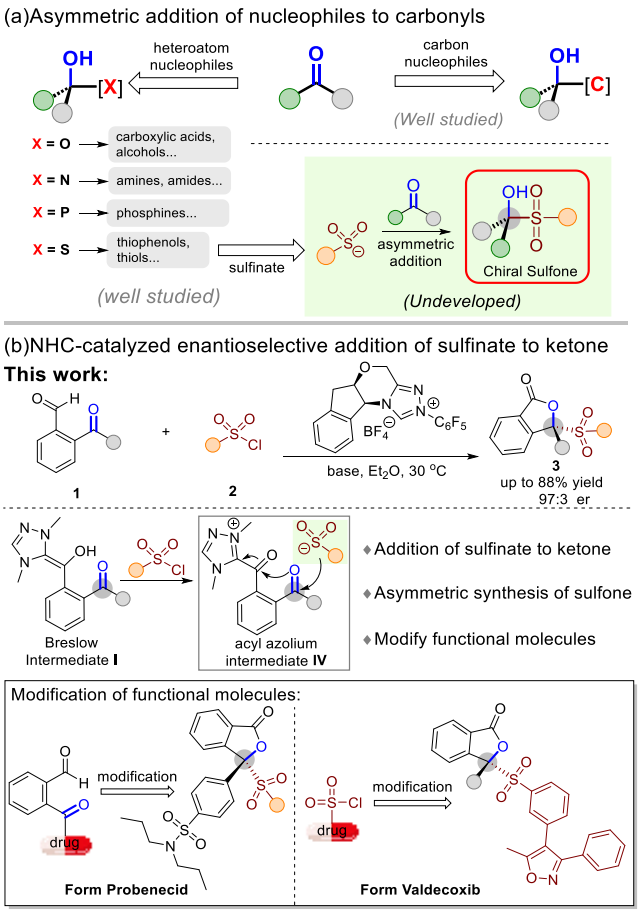
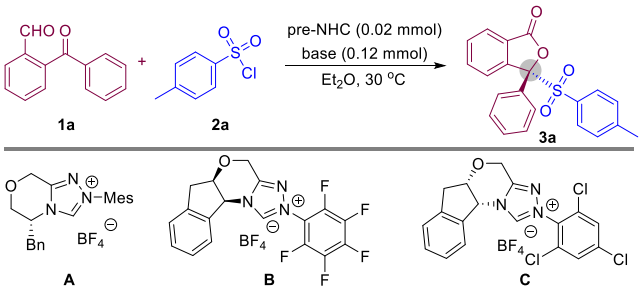


Figure 1. Catalytic enantioselective addition to carbonyls.

Table 1. Optimization of Reaction Conditions[a]



Entry	Pre-NHC	Base	Solvent	Yield(%)[b]	Er[c]
1[d]	**A**	Cs_2CO_3	Toluene	3	-
2[d]	**B**	Cs_2CO_3	Toluene	53	85:15
3[e]	**B**	Cs_2CO_3	Toluene	52	80:20
4[e]	**B**	Cs_2CO_3	THF	65	78:22
5	**B**	Cs_2CO_3	THF	68	79:21
6	**C**	Cs_2CO_3	THF	43	62:38
7	**B**	Na_2CO_3	THF	63	68:32
8	**B**	DBU	THF	<10	91:9
9	**B**	DBU	MTBE	23	96:4
10	**B**	DBU	Et_2O	22	90:10
11	**B**	Cs_2CO_3	Et_2O	72	92:8
12[f]	**B**	Cs_2CO_3	Et_2O	70	95:5

[a]Unless otherwise specified, the reactions were carried using **1a** (0.10 mmol), **2a** (0.12 mmol), base (0.12 mmol), pre-NHC (0.02 mmol), and solvent (2 mL) at 30 °C for 12 h. [b]Isolated yield of **3a**. [c]The ee values were determined via HPLC on a chiral stationary phase. [d]The reactions were carried out according to our previous work,[16b] and the yield was estimated via ^{1}H NMR analysis using dibromomethane as an internal standard, [e]Without water as additive. [f]0.015 mmol pre-NHC was used with TsOH (0.02 mmol) as additive.

condition involved 0.10 mmol **1a**, 0.12 mmol **2a**, 0.02 mmol NHC precatalyst, 0.12 mmol base, and 2 mL of solvent, allowing the reaction to proceed at 30 °C for 12 h. Inspired by our previous work,[16b] we initially employed the same conditions using aminoindanol-derived triazolium **A**;[18] the desired product **3a** could be obtained in a mere 3% yield by ^{1}H NMR analysis (entry 1). When electron-withdrawing substituted triazolium salt **B**[19] was used to catalyze the reaction, **3a** could be observed with 53% yield and 85:15 er value (entry 2). Without water, the reaction could give a 52% yield and 80:20 er value (entry 3). These results suggested that the addition of water cannot promote the overall yield. We further optimized the reaction conditions based on entry 3. Solvents also had a clear impact on the reaction outcomes; the reaction carried out in THF could give the desired product **3a** in a much improved 65% yield and encouraging 78:22 er value (entry 4). After evaluating the NHC precatalysts **B** and **C**[20] with typical reaction conditions (entries 5 and 6), using the triazolium precatalyst **B** led to the formation of product **3a** with 68% yield and an encouraging 79:21 er value (entry 5). Several organic and inorganic bases were examined here, and it was found that the er value was slightly enhanced by using DBU, and **3a** was obtained in 91:9 er value but much erosion of the yield (entries 7 and 8). We next explored a diverse set of solvents and found that Et_2O performed the best to give **3a** with a reduced 22% yield and 90:10 er value (entries 9 and 10).

The product yield was further improved to 72% when Cs_2CO_3 was employed, with no loss of enantioselectivity of the product (entry 11). To our delight, with the addition of TsOH as additive and use of 0.015 mmol of pre-NHC **C**, the desired product **3a** could be afforded in excellent enantioselectivity (95:5 er) and excellent 70% yield; we propose that the carbonyl group of **1a** can be activated by TsOH, thus improving the corresponding selectivity (entry 12).

With acceptable reaction conditions in hand, the reaction scope of both 2-benzoylbenzaldehyde **1** and toluenesulfonyl chloride **2a** was explored. Different substitution patterns of 2-benzoylbenzaldehyde **1** were investigated (Table 2). Substituents with both electron-withdrawing groups (**3b−e,h−j**) and electron-donating groups (**3f,g,k,l**) could be incorporated at the *para*- and *meta*-positions of the *β*-phenyl group of 2-benzoylbenzaldehyde **1**, with the corresponding desired products being afforded in good yields and enantioselectivities. In synthetic applications, our approach could be prepared on larger scales with little impact on product yield (e.g., **3a**, 2 mmol, 437 mg, 60% yield, 97:3 er). The absolute configuration of **3b** was confirmed through X-ray diffraction analysis, and the absolute configurations of all products in this paper have been assigned by this same analogy. When a naphthalene unit was introduced to the *β*-phenyl group of 2-benzoylbenzaldehyde **1**, the desired product could be obtained in satisfactory yield and enantioselectivity (**3m**). It is worth noting that the *β*-phenyl group could be replaced by heteroaromatic groups (**3n,o**) and alkyl groups (**3p,q**), and the yields and enantioselectivities of desired products can be improved, which might have resulted from the decreased steric hindrance on the position. Additionally, the installation of either electron-withdrawing Cl/F or electron-donating CH_3 at the 4- or 5-position on the

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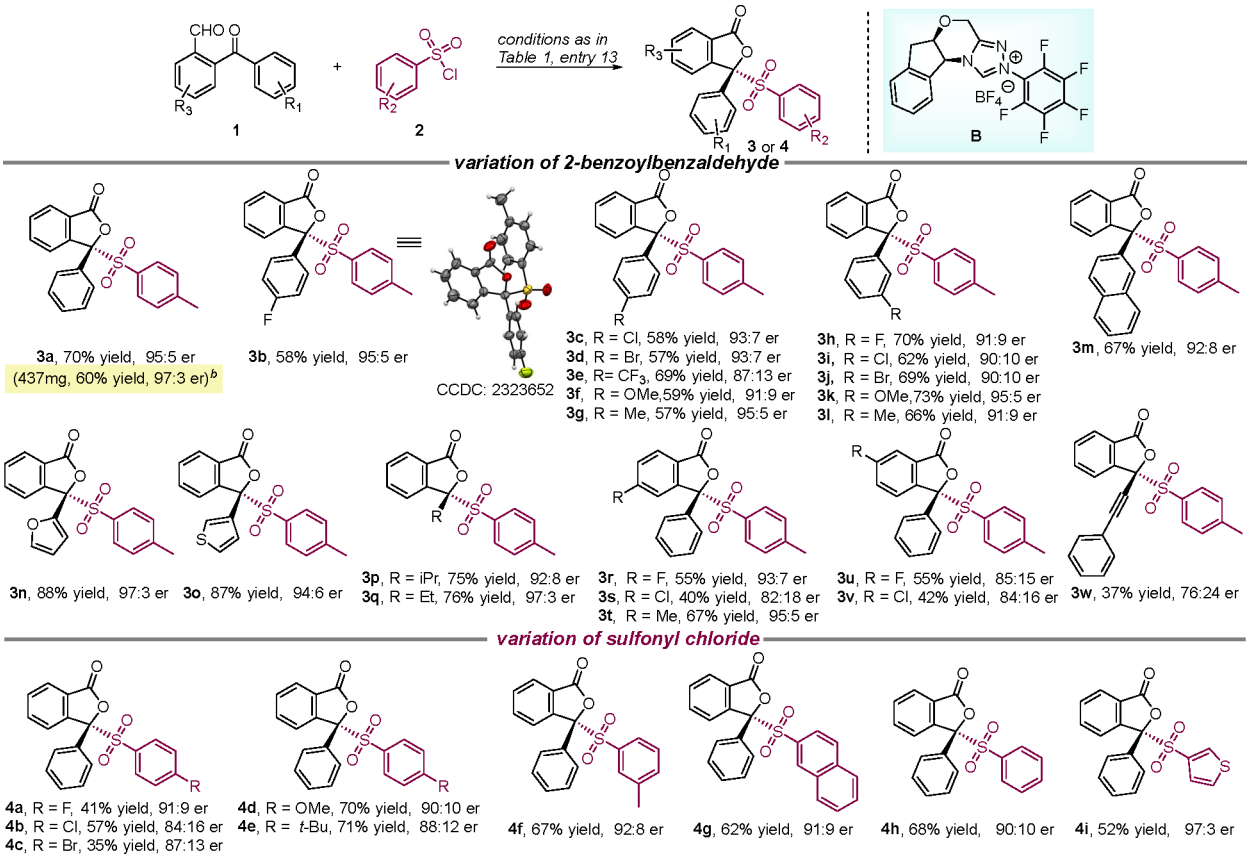
Table 2. Scope of 2-Benzoylbenzaldehyde 1a and Toluenesulfonyl Chloride 2a[a]



[a]Reaction conditions as stated in Table 1, entry 13. Yields are isolated yields after purification by column chromatography. er values were determined via HPLC on chiral stationary phase. [b]The reaction was carried out on a 2.0 mmol scale based on **1a**.

aromatic ring of 2-benzoylbenzaldehyde could also be achieved in good yields and enantioselectivities (**3r−v**). The *β*-phenyl group of the 2-benzoylbenzaldehyde can be changed to the phenylacetylene group, and the product **3w** could be obtained in 37% yield and 76:24 er. However, when the linker between the aldehyde and ketone was replaced by an aliphatic chain (such as ethyl or anisole), the corresponding products could not be obtained.

The catalytic conditions tolerated various types of sulfonyl chlorides **2** (Table 2). Placing different substituents with electron-withdrawing groups (**4a−c**) and electron-donating groups (**4d,e**) on the *para*-position of sulfonyl chlorides resulted in moderate to excellent yields and enantioselectivities. When a sulfonyl chloride bearing a methyl group at the *meta*-position of the phenyl ring was used under the optimal conditions, the product **4f** was accessed with comparable outcomes. Additionally, this protocol was also compatible for the naphthalene group and benzene group of sulfonyl chloride, facilitating the formation of desired products with good yields and er values (**4g,h**). A heterocyclic group such as thiophene was also used in this reaction, giving an acceptable yield (52%) and excellent enantioselectivity (97:3 er) (**4i**). Furthermore, the phenyl group of sulfonyl chlorides could also be replaced by alkyl groups (such as propyl, isopropyl, or cyclopropane). When the yields of the corresponding products were estimated via ^{1}H NMR analysis, we proposed that the alkyl sulfonyl chlorides had weaker oxidizable ability which led to the decreased yields (for more details, please see the Supporting Information).

Furthermore, the asymmetric ketone sulfonated protocol can be used to modify commercially available functional molecules (Figure 2). The carboxylic acid groups can be widely found in pharmaceuticals, such as probenecid, ibuprofen, and ataluren, which can be transferred into the corresponding substrates, and these substrates can be easily converted into corresponding sulfones **5a−7a** with good enantioselectivities via the new synthetic strategy. Additionally, molecules containing sulfonamide motifs, such as valdecoxib and celecoxib, could also be

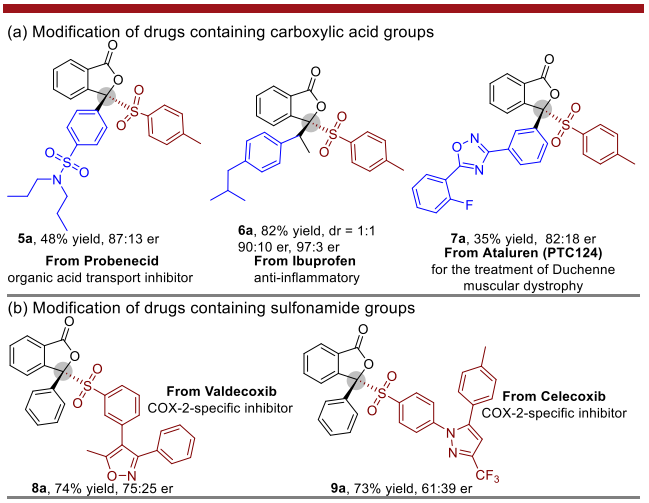


Figure 2. Postfunctionalization of biologically active molecules.

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converted into the corresponding sulfonyl chloride derivatives, which were employed to react with 2-benzoylbenzaldehyde **1a** to obtain the chiral products **8a** and **9a** with excellent yields and promising er values. These encouraging results suggested that this new methodology was a powerful synthetic strategy for drug modification. Further studies on the bioactivities of these postmodification molecules for pharmaceutical and agricultural applications are in progress in our laboratories.

To further understand the mechanism, radical clock experiments were performed, and (cyclopropylidenemethyl)-2-methoxybenzene **10** was employed as the radical clock probe; it was reported by the Tang group that the sulfonyl radical can react with **10** to form the radical addition product **10a**.[21] In the radical clock experiment, 1.0 equiv. of **10** was added to the reaction mixture under the standard conditions. The desired product **10a** can be isolated, and the structure was confirmed according to the report by the Tang group (Figure 3a). Meanwhile, the same experiment was carried out; but

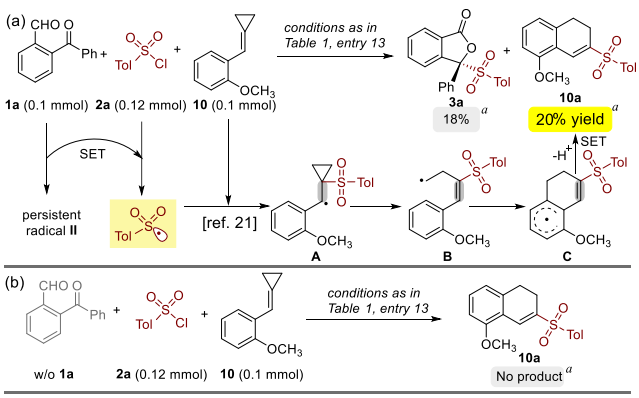

Figure 3. Radical clock experiment. [a]Yield was estimated via ^{1}H NMR analysis.

without **1a**, the radical addition product **10a** cannot be detected by ^{1}H NMR analysis (Figure 3b). Several competitive experiments were also carried out (for more details, please see the Supporting Information). These results suggested that the Breslow intermediate **I** can be SET oxidized by sulfonyl chloride to generate the sulfonyl radical (pathway A), but the electron-pair-transfer process cannot be ruled out (pathway B).

Based on these observations, we propose a plausible mechanism, as depicted in Figure 4. The mechanism of the overall reaction may contain two possibilities. One pathway

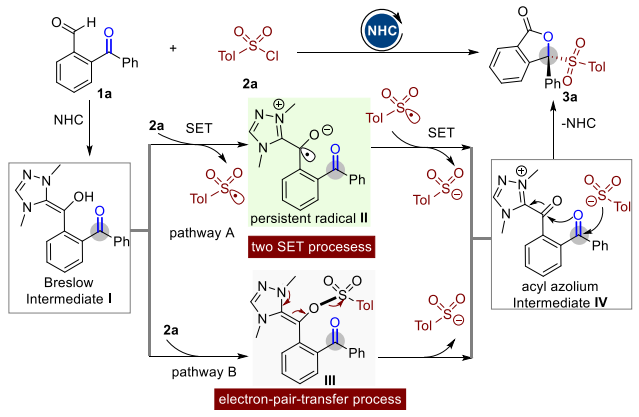

Figure 4. Proposed catalytic cycle.

involves two SET processes, while the other involves an electron-pair-transfer process. In the reaction, the NHC catalyst reacted with to **1a** to form the corresponding Breslow intermediate **I**. Then sulfonyl chloride **2a** may work as an SET oxidant, and the Breslow intermediate **I** was oxidized by sulfonyl chloride to generate the sulfonyl radical and persistent radical intermediate **II** via a SET process. Then the radical intermediate **II** was further oxidized to give the corresponding acyl azolium intermediate **IV** and a sulfinate anion. Moreover, the sulfonyl chloride **2a** may directly react with Breslow intermediate **I** to form corresponding sulfonate intermediate **III**, which was proposed in our previous work.[16b] Subsequently, the corresponding acyl azolium intermediate **IV** and the sulfinate anion were generated. Simultaneously, the NHC catalyst provides both reaction activation and stereoselectivity controls. The sulfinate anion reacted with the highly reactive carbonyl moiety of **IV** to produce sulfone **3a** with high optical purity.

In summary, we have developed an NHC-catalyzed enantioselective strategy for the enantioselective addition of sulfinate to ketones of 2-benzoylbenzaldehyde by sulfonyl chloride. The enantioselective sulfonation to ketone motif has so far remained largely underexplored. Herein we report the first catalytic enantioselective addition of sulfinate to ketones for synthesis of sulfones via N-heterocyclic carbene catalysis. The sulfonyl chloride behaves both as an oxidant and as a nucleophilic substrate in this NHC-catalyzed process. A radical clock experiment was performed to support that the Breslow intermediate can be SET oxidized by sulfonyl chloride to generate the sulfonyl radical. Our protocol of the asymmetric addition of sulfinate to carbonyls can also be used to modify commercially available functional molecules. Inspired by these findings, ongoing studies in our laboratories include expanding the reaction scope toward more general substrates and construction/modification of molecules with applications in medicine and agriculture.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c01473.

Full experimental and characterization data for all compounds (PDF)

Accession Codes

CCDC 2323652 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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