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Article

Carbene-Catalyzed Enantioselective Sulfonylation of Enone Aryl Aldehydes: A New Mode of Breslow Intermediate Oxidation

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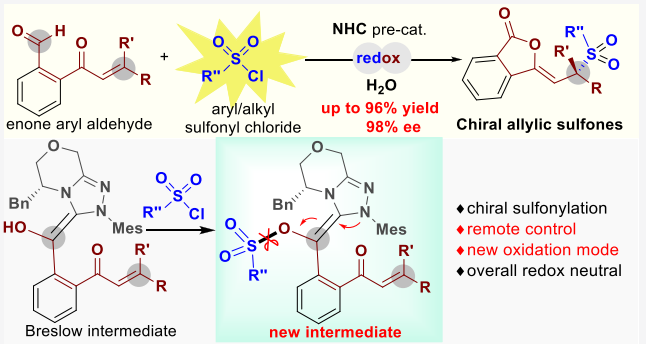
ABSTRACT: A carbene-catalyzed sulfonylation reaction between enone aryl aldehydes and sulfonyl chlorides is disclosed. The reaction effectively installs sulfone moieties in a highly enantioselective manner to afford sulfone-containing bicyclic lactones. The sulfonyl chloride behaves both as an oxidant and a nucleophilic substrate (via its reduced form) in this *N*-heterocyclic carbene (NHC)-catalyzed process. The NHC catalyst provides both activation and stereoselectivity control on a very remote site of enone aryl aldehyde substrates. Water plays an important role in modulating catalyst deactivation and reactivation routes that involve reactions between NHC and sulfonyl chloride. Experimental studies and DFT calculations suggest that an unprecedented intermediate and a new oxidation mode of the NHC-derived Breslow intermediate are involved in the new asymmetric sulfonylation reaction.



INTRODUCTION

Chiral sulfones are unique moieties in medicines and natural products with important applications (Figure 1a).[1] For example, aryl sulfone-containing MK-0752 is a potent γ-secretase inhibitor for the treatment of breast cancer.[2] Danirixin is a reversible and selective CXCR2 antagonist with inhibitory effects on CXCL8 for the treatment of breast cancer.[3] Natural product (−)-agelasidine A bearing an allylic sulfone molecule was isolated from sea sponge Agelas sp. and exhibited antispasmodic activity.[4] The sulfone units are also found in bicyclic lactam drugs such as tazobactam[5] and sulbactam.[6] Given the proven significance, enantioselective installation of sulfone groups to various molecules receives considerable attention.[7] Both transition-metal catalyst-[8] and organic catalyst[9]-mediated synthetic strategies have been developed. Representative methods include asymmetric substitution,[10] asymmetric hydrothiolation−oxidation,[11] asymmetric hydrogenation,[12] and enantioselective hydrosulfonylation.[13]

Here, we disclose a new approach for catalytic asymmetric installation of alkyl and aryl sulfone moieties for access to optically enriched allylic sulfones bearing bicyclic enol lactones (Figure 1b). Under the catalysis of *N*-heterocyclic carbenes,[14] an enone aryl aldehyde[15] and a sulfonyl chloride react with each other through a redox and several nucleophilic addition processes to furnish the product with excellent yields and enantiomeric purities. In our strategy, the reactivity and stereoselectivity of the enone β-carbon are controlled via the *N*-heterocyclic carbene (NHC) catalyst that is added to an aldehyde moiety five atoms away from the aldehyde. The sulfonyl chloride plays two main roles: one as an oxidant and the other one as the sulfonylation substrate. This oxidation of Breslow intermediate **I** by sulfonyl chloride is an electron-pair-transfer process and features a previously unknown mechanistic pathway in NHC organic catalysis. Specifically, the hydroxyl unit of Breslow intermediate **I** reacts with sulfonyl chloride to form an unprecedented intermediate **II**. An intramolecular redox process of **II** generates an acyl azolium intermediate **III** with the concurrent release of a sulfinate anion. Enantioselective addition of the sulfinate anion to the β-carbon of the enone moiety of **III** followed by an enol lactone formation affords the final sulfonylation product with the regeneration of the NHC catalyst. A broad range of aryl and alkyl sulfonyl chlorides can behave as effective sulfonylation substrates to give the corresponding products in gram scales with excellent yields and enantioselectivities. Our new mode of NHC-mediated oxidation and intermediate offers rich opportunities for further reaction development and applications.

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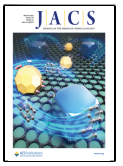

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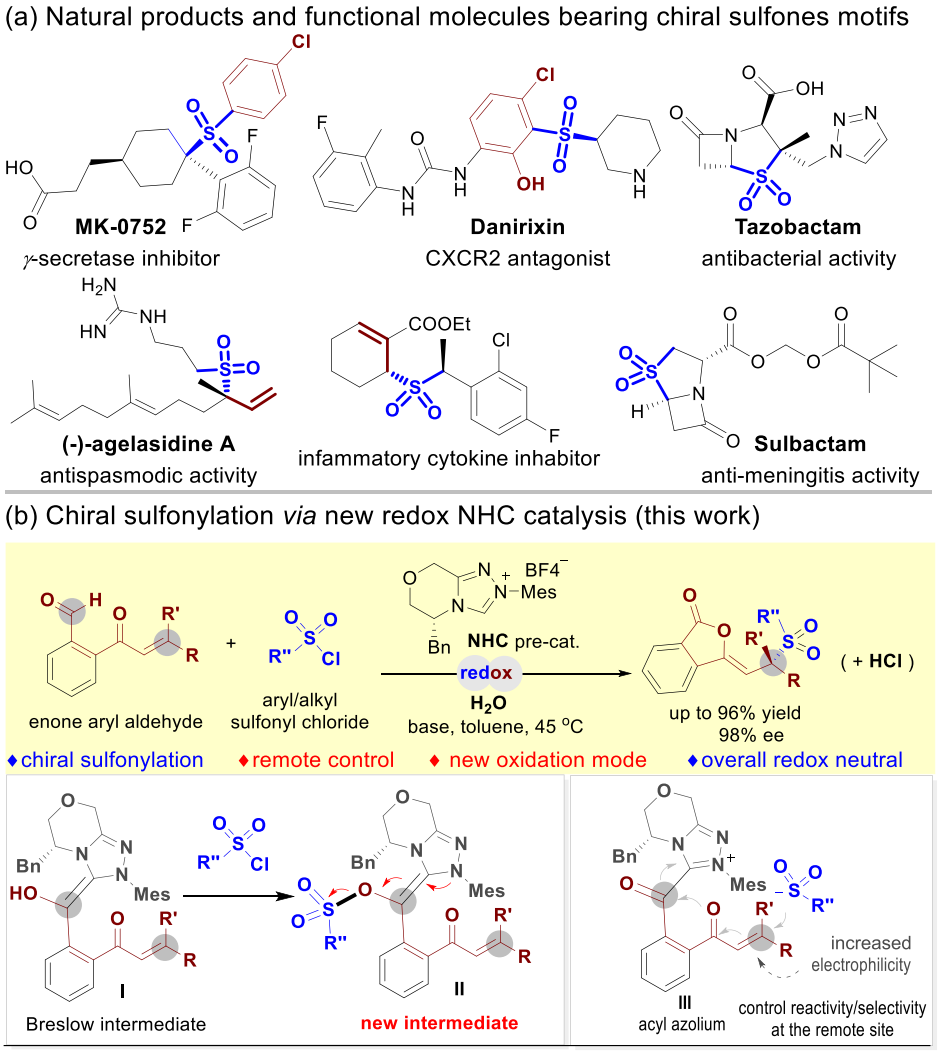

Figure 1. Functional molecules containing chiral sulfones and the new mode of Breslow intermediate oxidation.

RESULTS AND DISCUSSION

Reaction Development. We started by using enone aryl aldehyde **1a** and toluenesulfonyl chloride **2a** as model substrates to search for suitable conditions, with the key results summarized in Table 1. A typical condition involved the use of 0.10 mmol **1a**, 0.12 mmol of **2a**, 0.02 mmol of the NHC precatalyst, a base, and 2 mL of the solvent for the reaction to proceed at 45 °C for 12 h. To our delight, with the use of aminoindanol-derived triazolium **A**[16] as the NHC precatalyst, the desired product **3a** could be obtained with excellent enantioselectivity [96% enantiomeric excess (ee)] and a low but encouraging 13% yield (Table 1, entry 1).When 4 Å molecular sieves (MSs) (50 mg) were added to the reaction mixture, a sharp drop in the reaction yield was observed (from 13% to less than 5% yield, entries 1 and 2). When water (0.05 mmol) was added, the reaction gave a much improved 44% yield without much erosion on the product optical purity (entry 3). These results suggested that water played an important role in either promoting the desired reaction pathways or modulating some of the catalyst deactivation processes (see Figure 4b and the Supporting Information). We next performed the reactions in the presence of a small amount of water. After evaluating the NHC precatalysts **B**[17] and **C**[18] (Table 1, entries 4 and 5), using the triazolium precatalyst **C** gave product **3a** in 50% yield and 98% ee value (Table 1, entry 5). Several organic and inorganic bases were tested here, and we found that the yield was slightly improved using Cs_2CO_3, and **3a** was obtained in 52% yield and 97% ee (Table 1, entries 6 to 8). Solvents also had a clear impact on the reaction outcomes: toluene performed the best to give **3a** with 75% yield and 98% ee (Table 1, entries 9 to 11). The product yield was further improved to 90% when the amount of toluenesulfonyl chloride **2a** was increased from 0.12 mmol to 0.15 mmol, with no loss of enantioselectivity of the product (Table1, entry 12). It is worth noting that the reaction time could be decreased to 4 h without affecting both the product yield and ee value (Table1, entry 13). Based on entry 13, we performed additional studies on the effects of bases. It was found that weak bases performed better than strong bases. This is likely because that the use of strong bases disfavors the formation of the Breslow intermediate (proton transfer from the conjugated acid of a strong base such as *t*BuOK is unfavorable). Carbonates (such as K_2CO_3 and Cs_2CO_3) are optimal bases due to the readily formation of H-bonding networks that facilitate proton transfer. A detailed analysis on the role of bases is provided in the Supporting Information.

Reaction Scope. With an optimal reaction condition in hand, we explored the reaction scope of both enone aryl

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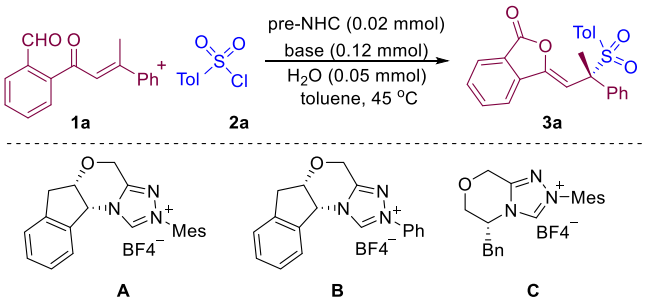
Table 1. Optimization of the Reaction Conditions[a]



entry	pre-NHC	base	solvent	yield(%)[b]	ee(%)[c]
1[d]	**A**	K_2CO_3	EA	13	96
2[e]	**A**	K_2CO_3	EA	< 5	96
3	**A**	K_2CO_3	EA	44	94
4	**B**	K_2CO_3	EA	29	77
5	**C**	K_2CO_3	EA	50	98
6	**C**	Cs_2CO_3	EA	52	97
7	**C**	DBU	EA	nr	nr
8	**C**	DABCO	EA	nr	nr
9	**C**	Cs_2CO_3	THF	64	97
10	**C**	Cs_2CO_3	Toluene	75	98
11	**C**	Cs_2CO_3	DME	nr	nr
12[f]	**C**	Cs_2CO_3	Toluene	90	98
13[f,g]	**C**	Cs_2CO_3	Toluene	90	98
14[f,g]	**C**	DBU	Toluene	21	98
15[f,g]	**C**	Et_3N	Toluene	15	98
16[f,g]	**C**	DABCO	Toluene	nr	nr
17[f,g]	**C**	K_3PO_4	Toluene	34	94
18[f,g]	**C**	KOAc	Toluene	< 10	98
19[f,g]	**C**	*t*BuOK	Toluene	22	90

[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), H_2O (0.05 mmol), and the solvent (2 mL) at 45 °C for 12 h. [b]Isolated yield of **3a**. [c]The ee values were determined via HPLC on the chiral stationary phase. [d]50 mg of 4 Å MSs. [e]No additive. [f]0.15 mmol **2a** was used. [g]Reaction time was 4 h, nr = no reaction.

aldehydes **1** and toluenesulfonyl chloride **2a**. Different substitution patterns of enone aryl aldehydes were examined (Table 2). Substituents with both electron-withdrawing groups (**3b**−**3f** and **3i**−**3k**) and electron-donating groups (**3g**−**3h** and **3l**) could be installed on the para- and meta-positions of the *β*-phenyl group of enone aryl aldehydes, with the corresponding desired products afforded in excellent yields and enantioselectivities. However, the yield of the desired product was decreased when a fluorine unit was introduced to the ortho-position of the *β*-phenyl group of the enone aryl aldehyde (**3m**). The *β*-phenyl group of the enone aryl aldehyde **1a** could be replaced with a naphthalene group, and the product could be obtained in excellent yield and enantioselectivity (**3n**). It is worth noting that the *β*-phenyl group could be replaced with isopropyl and methyl groups, and excellent yields were also obtained (**3o**−**3p**). Changing the methyl group of the enone aryl aldehyde to the ethyl group did not affect the corresponding product enantioselectivity (**3q**). The installation of either electron-withdrawing Cl/F or electron-donating methyl groups at the 4- or 5-position on the aromatic ring of enone aryl aldehydes did not affect the excellent yields and enantioselectivities (**3r**−**3v**). Taken together, these substrate scope screenings demonstrated that the electronic influences on the aryl groups of the substrates are highly amenable to modification and tuning, without suffering from the loss of yield or enantioselectivity.

The generality of different types of sulfonyl chlorides **2** was also examined (Table 2). Placing different substituents on the para- and meta-positions of sulfonyl chlorides resulted in excellent enantioselectivities (**4a**−**4j**). The naphthalene group of sulfonyl chloride could get the corresponding product with excellent enantioselectivity (**4k**). Under the current conditions, using heterocycle or alkane instead of phenyl groups led to decreased yields, with retention of excellent enantioselectivities (**4l**−**4q**).

Synthetic Applications. The sulfone-containing enol lactone product from our reactions could undergo further transformations using straightforward conditions. For example, the enol carbon−carbon double bond of **3a** could undergo dichlorination in a highly stereoselective manner to give **5** as essentially a single diastereomer with 97% ee.[19] This product **5** could react with ethanol to open its lactone ring with a subsequent elimination of the chloride anion to give chlorinated ketone adduct **6** as a single diastereomer with 97% ee. This carbon−carbon double bond of **3a** could also be epoxidized with *m*-CPBA to form epoxide product **7** as a single diastereomer without reduction of the optical purity[20] (Table 3).

Mechanistic Study. To understand the mechanism of our new catalytic reaction, density functional theory (DFT) calculations and multiple experiments were performed (Figures 2 and 3).

The DFT studies suggest that the reaction starts with stereoselective addition of the NHC catalyst to the aldehyde group of **1a**, followed by the formation of the Breslow intermediate **I** (Figure 2a). The addition of NHC to the (*Re*)-face of the aldehyde (***Re*-TS1**) has a barrier that is 4.4 kcal mol^{-1} lower than that to the (*Si*)-face (***Si*-TS1**). This barrier difference kinetically favors the (*Re*)-face addition by ∼1500 times at the reaction temperature using simple transition state theory (TST) (Supporting Information Section S4.1). We note that this (*Re*)-face selectivity for the addition of NHC to aldehyde is different from the (*Si*)-face selectivity for a similar reaction previously reported,[21] potentially due to the different interactions between the side groups of the substrate and the different NHC molecules used. The NHC-adduct **S-INT2** can be converted to the Breslow intermediate **I** under a protonated base assistance, in accordance with previous reports.[21] Concerted 1,2-proton transfer via a seven-membered cyclic transition structure **S-TS2** has the lowest barrier (22.4 kcal mol^{-1}) compared to other modes of Breslow intermediate formation (Supporting Information Section S4.2). The mechanistic alternative for the direct tosylation at the oxyanion of **S-INT2** (via **S-TS2a**, at 24.5 kcal mol^{-1}, Figure 2a) was computationally considered but was found to be much less kinetically favorable, by a factor of about 1:33, than **S-TS2** (Supporting Information Section S4.3).

Although thermodynamically uphill as compared to the reactants, the Breslow intermediate **I** can undergo a base-assisted, barrierless deprotonation (Supporting Information Section S4.4) to give enolate **I-a**, which further undergoes O-tosylation via **TS3** (barrier of 22.3 kcal mol^{-1}) to give tosylated species **II** (Figure 2b). This process is highly thermodynamically favorable and irreversible as the forward reaction has a much lower barrier than the reverse reaction.

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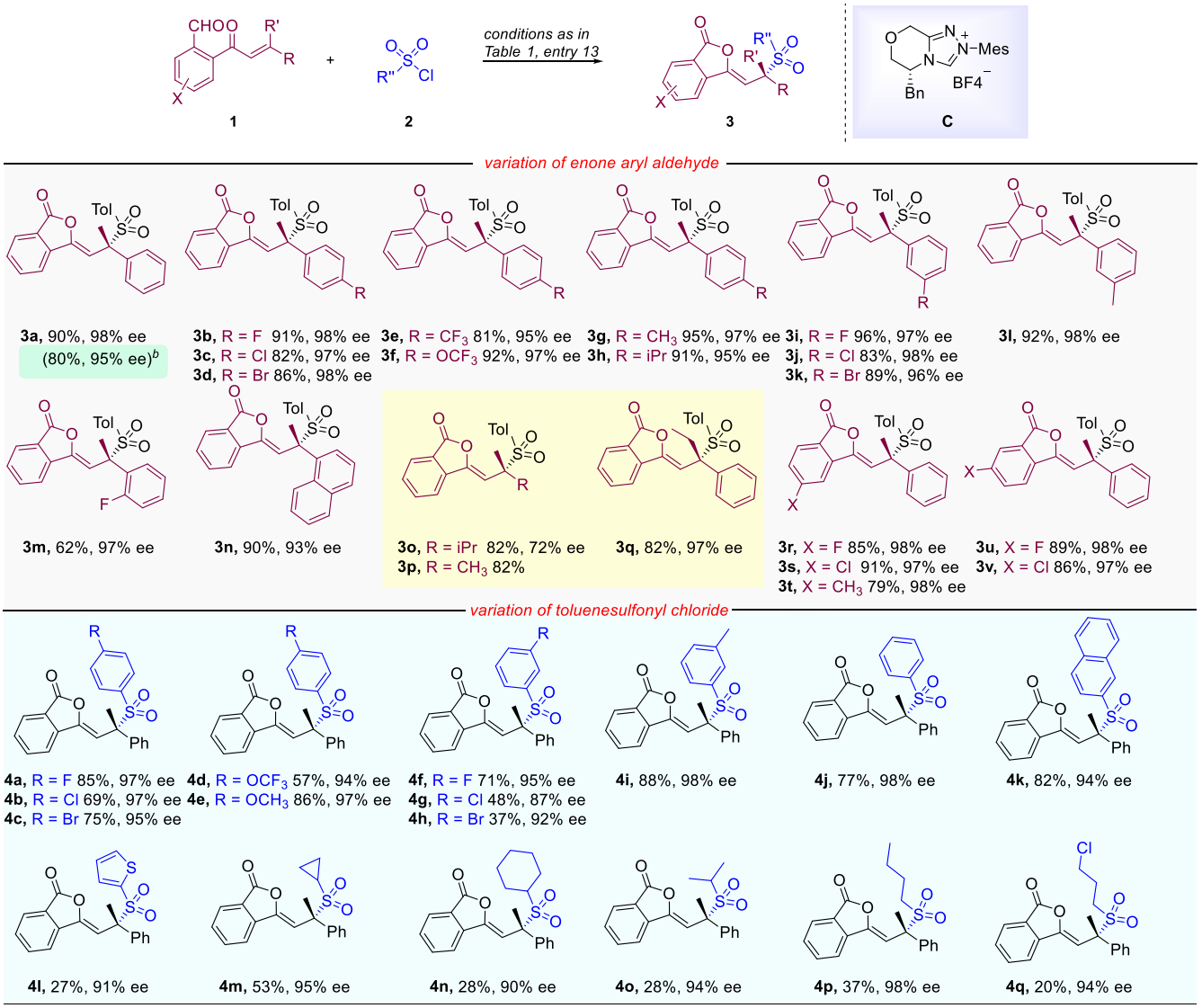
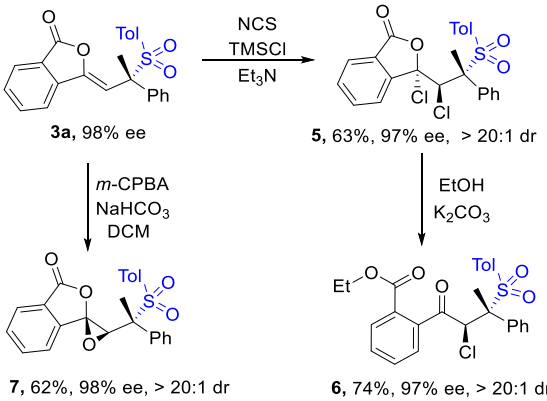
Table 2. Scope of Enone Aryl Aldehyde 1a and Toluenesulfonyl Chloride 2a[a]



[a]Reaction conditions as stated in Table 1, entry 13. Yields are isolated yields after purification by column chromatography. The ee values were determined via HPLC on the chiral stationary phase. [b]The reaction was carried out at 4.0 mmol scale based on **1a**.

Table 3. Synthetic Transformation of 3a



From the tosylated species **II**, the tosyl anion Ts^- can be generated via **TS4** with a barrier of 22.7 kcal mol^{-1} (Figure 2c). This gave the acyl azolim intermediate **III**, to which the nascently generated Ts^- can be added in a stereoselective manner. We found that the addition of Ts^- to the (*Re*)-face of the *β*-carbon of the enone aryl aldehyde substrate (***Re*-TS5**, $\Delta G^{\ddagger}$ = 12.6 kcal mol^{-1}) has a lower barrier than that to the (*Si*)-face (***Si*-TS5**, $\Delta G^{\ddagger}$ = 14.3 kcal mol^{-1}). This $\Delta\Delta G^{\ddagger}$ of 1.7 kcal mol^{-1} favors the observed enantioselectivity by 17:1 and translates to an ee value of about 89%, in good agreement with the experimental observations. We found that ***Re*-TS5** has a lower activation barrier due to the favorable noncovalent interactions (NCIs) between the C−H bonds on the aryl ring of the NHC and the O-atoms of Ts^- anion, which stabilize the transition state (TS). These CH−O NCIs are absent in ***Si*-TS5** (Figures 2d and S13).

We note that the energies for the key TSs (**S-TS2**, **TS3**, and **TS4**) are all very close to each other (within 0.3 kcal mol^{-1}), suggesting that any one of these steps may be possible as the rate-limiting step. Nevertheless, all these barriers (22.3−22.7 kcal mol^{-1}) are consistent with ambient temperature reactivity.

We additionally ruled out the alternative mechanism for the generation of acyl azolium intermediate **III** from the Breslow

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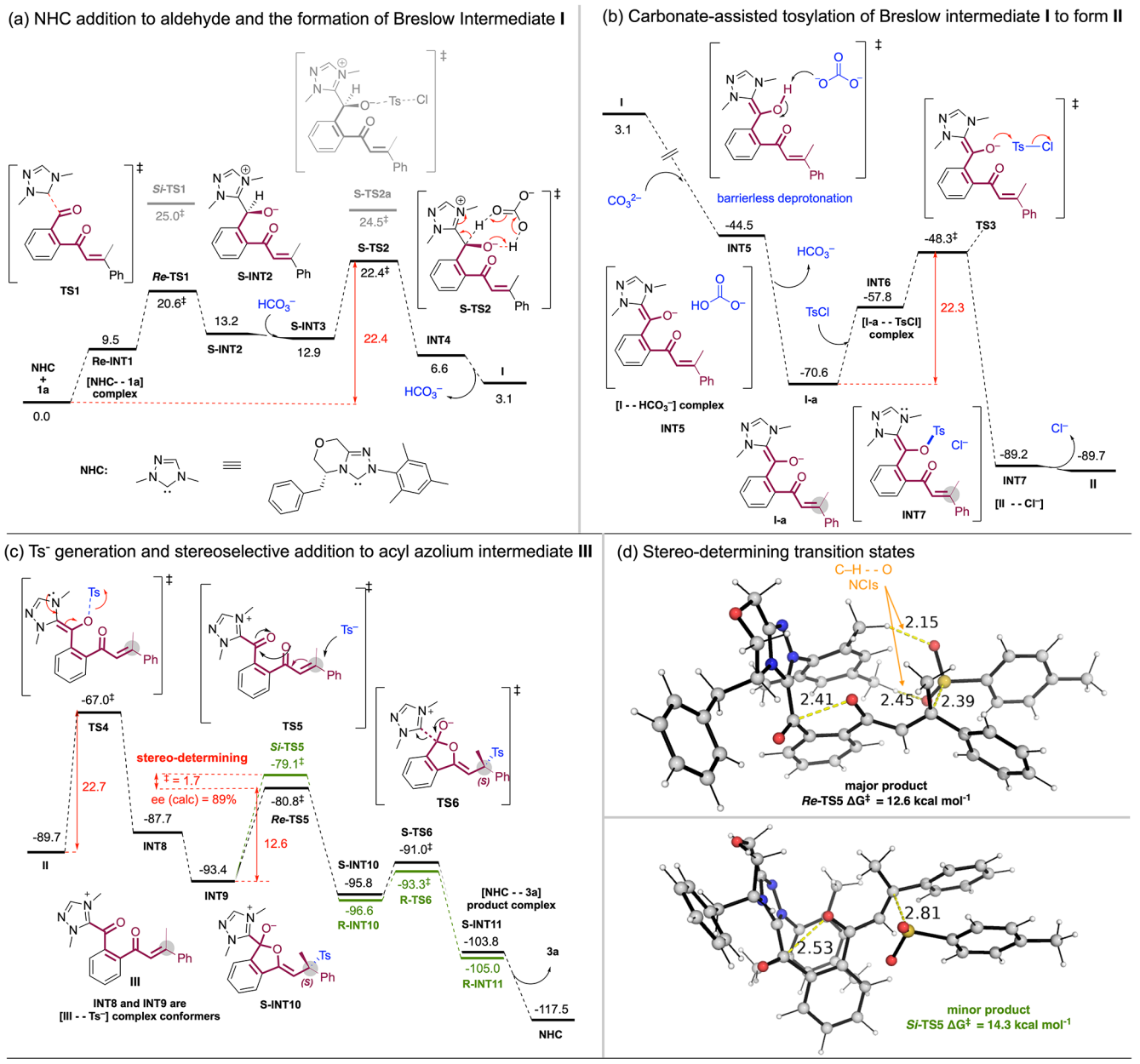

Figure 2. Gibbs energy profile for the full reaction (a–c) and the DFT-optimized structures for the stereodetermining transition states (d). Gibbs energies are computed at the SMD (toluene)-M06-2X/def2-TZVP//M06-2X/def2-SVP level of theory and are quoted in kcal mol^{-1}.

intermediate **I** via direct hydride transfer to toluenesulfonyl chloride (Figure 3). These TSs (Figure S20) have much higher barriers (>45 kcal mol^{-1}) that are thermally challenging to overcome under the reaction conditions used.

Additional mechanistic possibilities involving single-electron redox processes/radical intermediates were computationally investigated (Supporting Information Section S3). These are ruled out based on much less favorable activation barriers and unfavorable redox potentials.

Based on the combined experimental and computational mechanistic studies, we propose that the current transformation proceeds via the catalytic cycle shown in Figure 4a. To understand the role of water on the mechanistic outcome, several control experiments were carried out (Figure 4b). When using 4 Å MSs as the additive and anhydrous toluene as the solvent, it was found that NHC directly reacted with toluenesulfonyl chloride **2a** to form adduct **8**. This adduct **8** was determined via liquid chromatography–high resolution mass spectroscopy (LC-HRMS). Under this anhydrous condition, product **3a** was nearly unobservable, suggesting a strong deactivation of the NHC catalyst. When a small amount water was added (as the condition in Table 1, entry 13), only a trace amount of adduct **8** was detected by LC-HRMS. Our current attempts in detecting the exact intensity of adduct **8** in the reaction mixture were not successful because this adduct was short-lived and highly reactive. A semiquantitative analysis was performed, and the intensity of adduct **8** in the absence of water was found to be 30–130 times higher than that in the presence of water (Figure 4b, see the Supporting Information for more details). These observations suggested that water plays an important role in releasing the NHC catalyst from adduct **8**, thus recovering the deactivated NHC-TS complex to regenerate the NHC for a productive catalytic cycle. We also found that without NHC activation of the substrate **1a**,

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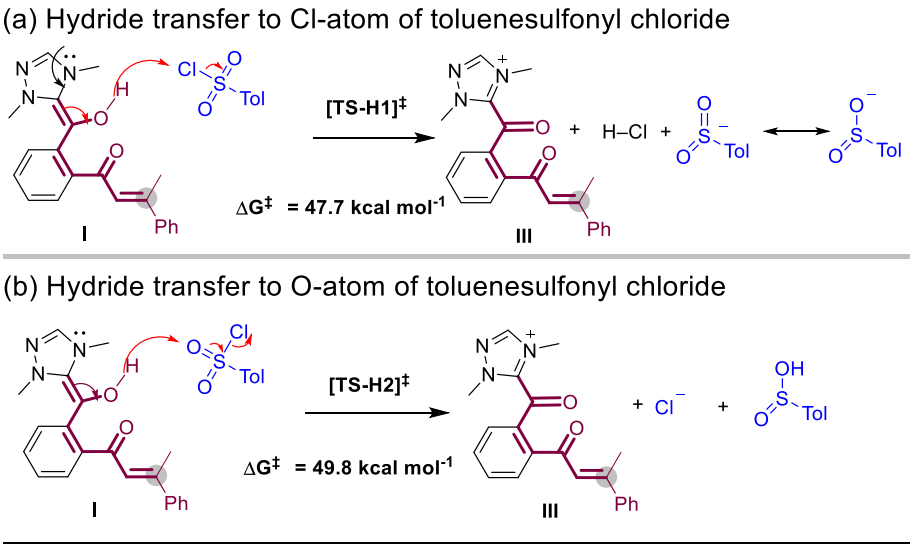

Figure 3. Alternative mechanism for the generation of acyl azolium intermediate **III** from Breslow intermediate **I** via direct hydride transfer to toluenesulfonyl chloride.

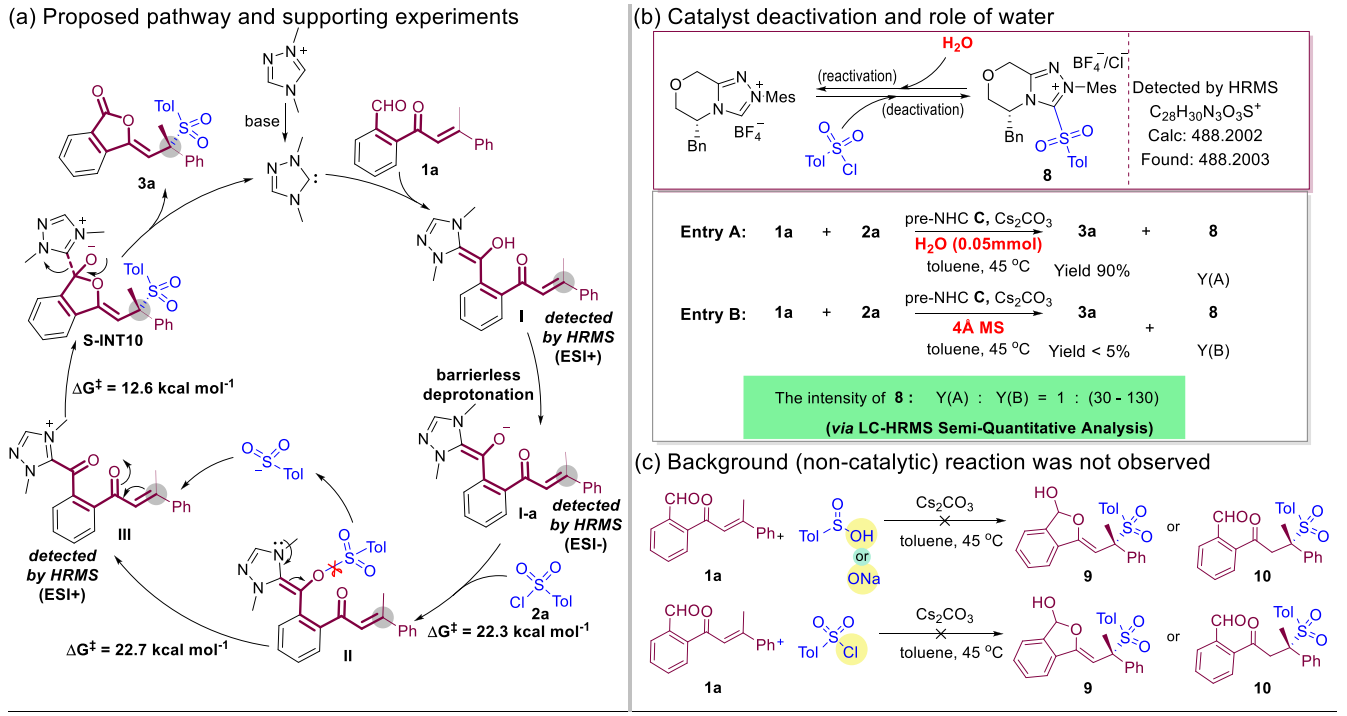

Figure 4. Proposed catalytic cycle and additional supporting mechanistic experiments.

addition of the sulfonate anion to the enone moiety of **1a** did not occur (Figure 4c). These results (Figure 4c) suggested that both the reactivity and stereoselectivity of the enone β-carbon are controlled via the NHC catalyst that adds to an aldehyde moiety at a very remote site.

CONCLUSIONS

In summary, we have developed an NHC-catalyzed enantioselective strategy for the sulfonylation of enone aryl aldehydes by sulfonyl chlorides. The sulfonyl chloride behaves as an oxidant, and its reduced form (the resulting sulfinate anion) functions as a nucleophilic substrate to provide the sulfone moiety. The overall reaction is a redox-neutral process (without the need for external oxidants) that features a new intermediate and a new mode of oxidation under NHC catalysis. Through addition to the aryl aldehyde carbon that is very remote from the substrate reaction site, the NHC catalyst provides both reaction activations and stereoselectivity controls. Both experiments and DFT calculations were performed to elucidate the mechanistic pathway of our reactions. Water was found to play an important role in modulating the activation/deactivation routes of the NHC catalyst. Inspired by these findings, the ongoing studies in our laboratories include the development of new NHC-bound intermediates and their reactions and construction of chiral sulfone-containing bioactive molecules for applications in medicines and agrochemicals.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c13384.

X-ray crystallographic data for compound **3a**, **7**, and **6-1** from the Cambridge Crystallographic Data Centre under CCDC 2026198, 2127890, and 2127891, respectively; full experimental details for the preparation of all new compounds and their spectroscopic and chromatographic data; and geometries of all DFT-optimized structures. All these data have been deposited with this Supporting Information and uploaded to zenodo.org (DOI: 10.5281/zenodo.5889602) (PDF)

Accession Codes

CCDC 2026198 and 2127890−2127891 contain 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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Author Contributions

[⊥]R.D., S.W., and C.M. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. Identification of 4-Substituted 1,2,3-Triazoles as Novel Oxazolidinone Antibacterial Agents with Reduced Activity against Monoamine Oxidase A. *J. Med. Chem.* **2005**, *48*, 499−506. (b) Yamada, M.; Ichikawa, T.; Ii, M.; Itoh, K.; Tamura, N.; Kitazaki, T. Novel Cyclohexene Derivatives as Anti-Sepsis Agents: Synthetic Studies and Inhibition of NO and Cytokine Production. *Bioorg. Med. Chem.* **2008**, *16*, 3941−3958. (c) Liu, K. G.; Robichaud, A. J.; Bernotas, R. C.; Yan, Y.; Lo, J. R.; Zhang, M.-Y.; Hughes, Z. A.; Huselton, C.; Zhang, G. M.; Zhang, J. Y.; Kowal, D. M.; Smith, D. L.; Schechter, L. E.; Comery, T. A. 5-Piperazinyl-3-Sulfonylindazoles as Potent and Selective 5-Hydroxytryptamine-6 Antagonists. *J. Med. Chem.* **2010**, *53*, 7639−7646. (d) Ivachtchenko, A. V.; Golovina, E. S.; Kadieva, M. G.; Kysil, V. M.; Mitkin, O. D.; Tkachenko, S. E.; Okun, I. M. Synthesis and Structure-Activity Relationship (SAR) of (5,7-Disubstituted 3-Phenylsulfonyl-Pyrazolo-[1,5-α]Pyrimidin-2-yl)-Methylamines as Potent Serotonin 5-HT_6 Receptor (5-HT_6R) Antagonists. *J. Med. Chem.* **2011**, *54*, 8161−8173. (e) Pero, J. E.; Matthews, J. M.; Behm, D. J.; Brnardic, E. J.; Brooks, C.; Budzik, B. W.; Costell, M. H.; Donatelli, C. A.; Eisennagel, S. H.; Erhard, K.; Fischer, M. C.; Holt, D. A.; Jolivette, L. J.; Li, H.; Li, P.; McAtee, J. J.; McCleland, B. W.; Pendrak, I.; Posobiec, L. M.; Rivera, K. L. K.; Rivero, R. A.; Roethke, T. J.; Sender, M. R.; Shu, A.; Terrell, L. R.; Vaidya, K.; Xu, X.; Lawhorn, B. G. Design and Optimization of Sulfone Pyrrolidine Sulfonamide Antagonists of Transient Receptor Potential Vanilloid-4 with in Vivo Activity in a Pulmonary Edema Model. *J. Med. Chem.* **2018**, *61*, 11209−11220. (f) Scott, K. A.; Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. *Top. Curr. Chem.* **2018**, *376*, 5. (g) Feng, M.; Tang, B.; Liang, S.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synsthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2016**, *16*, 1200−1216.

(2) (a) Fouladi, M.; Stewart, C. F.; Olson, J.; Wagner, L. M.; Onar-Thomas, A.; Kocak, M.; Packer, R. J.; Goldman, S.; Gururangan, S.; Gajjar, A.; Demuth, T.; Kun, L. E.; Boyett, J. M.; Gilbertson, R. J. Phase I Trial of MK-0752 in Children with Refractory CNS Malignancies: A Pediatric Brain Tumor Consortium Study. *J. Clin. Oncol.* **2011**, *29*, 3529−3534. (b) Krop, I.; Demuth, T.; Guthrie, T.; Wen, P. Y.; Mason, W. P.; Chinnaiyan, P.; Butowski, N.; Groves, M. D.; Kesari, S.; Freedman, S. J.; Blackman, S.; Watters, J.; Loboda, A.; Podtelezhnikov, A.; Lunceford, J.; Chen, C.; Giannotti, M.; Hing, J.; Beckman, R.; Lorusso, P. Phase I Pharmacologic and Pharmacodynamic Study of the Gamma Secretase (Notch) Inhibitor MK-0752 in Adult Patients with Advanced Solid Tumors. *J. Clin. Oncol.* **2012**, *30*, 2307−2313.

(3) Lazaar, A. L.; Miller, B. E.; Tabberer, M.; Yonchuk, J.; Leidy, N.; Ambery, C.; Bloomer, J.; Watz, H.; Tal-Singer, R. Effect of the CXCR2 Antagonist Danirixin on Symptoms and Health Status in COPD. *Eur. Respir. J.* **2018**, *52*, 1801020.

(4) (a) Cai, A.; Kleij, A. W. Regio- and Enantioselective Preparation of Chiral Allylic Sulfones Featuring Elusive Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2019**, *58*, 14944−14949. (b) Khan, A.; Zhao, H.; Zhang, M.; Khan, S.; Zhao, D. Regio- and Enantioselective Synthesis of Sulfone-Bearing Quaternary Carbon Stereocenters by Pd-Catalyzed Allylic Substitution. *Angew. Chem., Int. Ed.* **2020**, *59*, 1340−1345. (c) Nakamura, H.; Wu, H.; Kobayashi, J. i.; Ohizumi, Y.; Hirata, Y.; Higashijima, T.; Miyazawa, T. Agelasidine-A, a novel sesquiterpene possessing antispasmodic activity from the okinawa sea sponge. *Tetrahedron Lett.* **1983**, *24*, 4105−4108.

(5) Lodise, T. P., Jr.; Lomaestro, B.; Drusano, G. L. Piperacillin-Tazobactam for Pseudomonas Aeruginosa Infection: Clinical Implications of an Extended-Infusion Dosing Strategy. *Clin. Infect. Dis.* **2007**, *44*, 357−363.

(6) Williams, J. D. β-Lactamase Inhibition and in Vitro Antivity Sulbactam and Sulbactam/Cefoperazone. *Clin. Infect. Dis.* **1997**, *24*, 494−497.

(7) (a) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixão, M. W.; Jørgensen, K. A. Asymmetric Organocatalysis with Sulfones. *Angew. Chem., Int. Ed.* **2010**, *49*, 2668−2679. (b) Huang, Y.; Li, J.; Chen, H.; He, Z.; Zeng, Q. Recent Progress on the Synthesis of Chiral Sulfones. *Chem. Rec.* **2021**, *21*, 1216−1239. (c) Zhu, C.; Cai, Y.; Jiang, H. Recent Advances for the Synthesis of Chiral Sulfones with the Sulfone Moiety Directly Connected to the Chiral Center. *Org. Chem. Front.* **2021**, *8*, 5574−5589.

(8) (a) Ding, Z.; Yang, J.; Wang, T.; Shen, Z.; Zhang, Y. Dynamic Kinetic Resolution of β-Keto Sulfones via Asymmetric Transfer Hydrogenation. *Chem. Commun.* **2009**, 571−573. (b) Ueda, M.; Hartwig, J. F. Iridium-Catalyzed, Regio- and Enantioselective Allylic Substitution with Aromatic and Aliphatic Sulfinates. *Org. Lett.* **2010**, *12*, 92−94. (c) García-Domínguez, A.; Muller, S.; Nevado, C. Nickel-Catalyzed Intermolecular Carbosulfonylation of Alkynes via Sulfonyl Radicals. *Angew. Chem., Int. Ed.* **2017**, *56*, 9949−9952. (d) Long, J.; Shi, L.; Li, X.; Lv, H.; Zhang, X. Rhodium-Catalyzed Highly Regio- and Enantioselective Hydrogenation of Tetrasubstituted Allenyl Sulfones: An Efficient Access to Chiral Allylic Sulfones. *Angew. Chem., Int. Ed.* **2018**, *57*, 13248−13251. (e) Chang, F.; Wang, S.; Zhao, Z.; Wang, L.; Cheng, T.; Liu, G. Enantioselective Dual-Catalysis: A Sequential Michael Addition/Asymmetric Transfer Hydrogenation of α-Nitrosulfone and Enones. *ACS Catal.* **2020**, *10*, 10381−10389. (f) Hell, S. M.; Meyer, C. F.; Laudadio, G.; Misale, A.; Willis, M. C.; Noël, T.; Trabanco, A. A.; Gouverneur, V. Silyl Radical-Mediated Activation of Sulfamoyl Chlorides Enables Direct Access to Aliphatic Sulfonamides from Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 720−725. (g) Hell, S. M.; Meyer, C. F.; Misale, A.; Sap, J. B. I.; Christensen, K. E.; Willis, M. C.; Trabanco, A. A.; Gouverneur, V. Hydrosulfonylation of Alkenes with Sulfonyl Chlorides under Visible Light Activation. *Angew. Chem., Int. Ed.* **2020**, *59*, 11620−11626. (h) Li, W.; Wagener, T.; Hellmann, L.; Daniliuc, C. G.; Mück-Lichtenfeld, C.; Neugebauer, J.; Glorius, F. Design of Ru(II)-NHC-Diamine Precatalysts Directed by Ligand Cooperation: Applications and Mechanistic Investigations for Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2020**, *142*, 7100−7107. (i) Cao, S.; Hong, W.; Ye, Z.; Gong, L. Photocatalytic Three-Component Asymmetric Sulfonylation via Direct C(sp^3)-H Functionalization. *Nat. Commun.* **2021**, *12*, 2377. (j) Liu, G.; Yin, C.; Yang, X.; Li, A.; Wang, M.; Zhang, X.; Dong, X.-Q. Highly Chemo- and Enantioselective Rh-Catalyzed Hydrogenation of β-Sulfonyl-α,β-Unsaturated Ketones: Access to Chiral γ-Ketosulfones. *Org. Lett.* **2021**, *23*, 19−24.

(9) (a) Mossé, S.; Alexakis, A. First Organocatalyzed Asymmetric Michael Addition of Aldehydes to Vinyl Sulfones. *Org. Lett.* **2005**, *7*, 4361−4364. (b) Moteki, S. A.; Xu, S.; Arimitsu, S.; Maruoka, K. Design of Structurally Rigid Trans-Diamine-Based Tf-Amide Organocatalysts with a Dihydroanthracene Framework for Asymmetric Conjugate Additions of Heterosubstituted Aldehydes to Vinyl Sulfones. *J. Am. Chem. Soc.* **2010**, *132*, 17074−17076. (c) Bera, K.; Namboothiri, I. N. N. Enantioselective Synthesis of α-Nitro-δ-Ketosulfones via a Quinine-Squaramide Catalyzed Conjugate Addition of α-Nitrosulfones to Enones. *Chem. Commun.* **2013**, *49*, 10632−10634. (d) Li, L.; Liu, Y.; Peng, Y.; Yu, L.; Wu, X.; Yan, H. Kinetic Resolution of β-Sulfonyl Ketones through Enantioselective β-Elimination Using a Cation-Binding Polyether Catalyst. *Angew. Chem., Int. Ed.* **2016**, *55*, 331−335. (e) Chen, P.; Wang, K.; Guo, W.; Liu, X.; Liu, Y.; Li, C. Enantioselective Reactions of 2-Sulfonylalkyl Phenols with Allenic Esters: Dynamic Kinetic Resolution and [4+2] Cycloaddition Involving Ortho-Quinone Methide Intermediates. *Angew. Chem., Int. Ed.* **2017**, *56*, 3689−3693. (f) Li, D.; Tan, Y.; Peng, L.; Li, S.; Zhang, N.; Liu, Y.; Yan, H. Asymmetric Mannich Reaction and Construction of Axially Chiral Sulfone-Containing Styrenes in One Pot from α-Amido Sulfones Based on the Waste-Reuse Strategy. *Org. Lett.* **2018**, *20*, 4959−4963. (g) Zhang, N.; He, T.; Liu, Y.; Li, S.; Tan, Y.; Peng, L.; Li, D.; Shan, C.; Yan, H. Organocatalytic Atropo- and E/Z-Selective Michael Addition Reaction of Ynones with α-Amido Sulfones as Sulfone-Type Nucleophile. *Org. Chem. Front.* **2019**, *6*, 451−455.

(10) (a) Wu, X.-S.; Chen, Y.; Li, M.-B.; Zhou, M.-G.; Tian, S.-K. Direct Substitution of Primary Allylic Amines with Sulfinate Salts. *J. Am. Chem. Soc.* **2012**, *134*, 14694−14697. (b) Choi, J.; Martín-Gago, P.; Fu, G. C. Stereoconvergent Arylations and Alkenylations of Unactivated Alkyl Electrophiles: Catalytic Enantioselective Synthesis of Secondary Sulfonamides and Sulfones. *J. Am. Chem. Soc.* **2014**, *136*, 12161−12165. (c) Gómez, J. E.; Cristòfol, À.; Kleij, A. W. Copper-Catalyzed Enantioselective Construction of Tertiary Propargylic Sulfones. *Angew. Chem., Int. Ed.* **2019**, *58*, 3903−3907.

(11) (a) Pritzius, A. B.; Breit, B. Asymmetric Rhodium-Catalyzed Addition of Thiols to Allenes: Synthesis of Branched Allylic Thioethers and Sulfones. *Angew. Chem., Int. Ed.* **2015**, *54*, 3121−3125. (b) Pritzius, A. B.; Breit, B. Z-Selective Hydrothiolation of Racemic 1,3-Disubstituted Allenes: An Atom-Economic Rhodium-Catalyzed Dynamic Kinetic Resolution. *Angew. Chem., Int. Ed.* **2015**, *54*, 15818−15822.

(12) (a) Yan, Q.; Xiao, G.; Wang, Y.; Zi, G.; Zhang, Z.; Hou, G. Highly Efficient Enantioselective Synthesis of Chiral Sulfones by Rh-Catalyzed Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2019**, *141*, 1749−1756. (b) Vyas, V. K.; Clarkson, G. J.; Wills, M. Sulfone Group as a Versatile and Removable Directing Group for Asymmetric Transfer Hydrogenation of Ketones. *Angew. Chem., Int. Ed.* **2020**, *59*, 14265−14269.

(13) (a) Jia, S.; Chen, Z.; Zhang, N.; Tan, Y.; Liu, Y.; Deng, J.; Yan, H. Organocatalytic Enantioselective Construction of Axially Chiral Sulfone-Containing Styrenes. *J. Am. Chem. Soc.* **2018**, *140*, 7056−7060. (b) Zhang, Q.; Dong, D.; Zi, W. Palladium-Catalyzed Regio- and Enantioselective Hydrosulfonylation of 1,3-Dienes with Sulfinic Acids: Scope, Mechanism, and Origin of Selectivity. *J. Am. Chem. Soc.* **2020**, *142*, 15860−15869. (c) Li, M. M.; Cheng, L.; Xiao, L. J.; Xie, J. H.; Zhou, Q. L. Palladium-Catalyzed Asymmetric Hydrosulfonylation of 1,3-Dienes with Sulfonyl Hydrazides. *Angew. Chem., Int. Ed.* **2021**, *60*, 2948−2951.

(14) (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by N-Heterocyclic Carbenes. *Chem. Rev.* **2007**, *107*, 5606−5655. (b) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190−

https://doi.org/10.1021/jacs.1c13384
J. Am. Chem. Soc. 2022, 144, 5441−5449

1191. (c) Jin, Z.; Xu, J.; Yang, S.; Song, B.-A.; Chi, Y. R. Enantioselective Sulfonation of Enones with Sulfonyl Imines by Cooperative N-Heterocyclic-Carbene/Thiourea/Tertiary-Amine Multicatalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 12354−12358. (d) Ryan, S. J.; Candish, L.; Lupton, D. W. Acyl Anion Free N-Heterocyclic Carbene Organocatalysis. *Chem. Soc. Rev.* **2013**, *42*, 4906−4917. (e) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485−496. (f) Mahatthananchai, J.; Bode, J. W. On the Mechanism of N-Heterocyclic Carbene-Catalyzed Reactions Involving Acyl Azoliums. *Acc. Chem. Res.* **2014**, *47*, 696−707. (g) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307−9387. (h) Menon, R. S.; Biju, A. T.; Nair, V. Recent Advances in Employing Homoenolates Generated by N-Heterocyclic Carbene (NHC) Catalysis in Carbon-Carbon Bond-Forming Reactions. *Chem. Soc. Rev.* **2015**, *44*, 5040−5052. (i) Murauski, K. J. R.; Jaworski, A. A.; Scheidt, K. A. A Continuing Challenge: N-Heterocyclic Carbene-Catalyzed Syntheses of γ-Butyrolactones. *Chem. Soc. Rev.* **2018**, *47*, 1773−1782. (j) Dai, L.; Xia, Z. H.; Gao, Y. Y.; Gao, Z. H.; Ye, S. Visible-Light-Driven N-Heterocyclic Carbene Catalyzed γ- and ε-Alkylation with Alkyl Radicals. *Angew. Chem., Int. Ed.* **2019**, *58*, 18124−18130. (k) Dai, L.; Ye, S. NHC-Catalyzed ε-Umpolung via p-Quinodimethanes and Its Nucleophilic Addition to Ketones. *ACS Catal.* **2019**, *10*, 994−998. (l) Jin, S.; Fang, S.; Ma, R.; Liang, Z.; Xu, Y.; Lu, T.; Du, D. β-Sulfonylation of α-Bromoenals Enabled by N-Heterocyclic Carbene Catalysis. *Org. Chem. Front.* **2019**, *6*, 3392−3396. (m) Ishii, T.; Kakeno, Y.; Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2019**, *141*, 3854−3858. (n) Ishii, T.; Ota, K.; Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 14073−14077. (o) Chen, X.; Wang, H.; Jin, Z.; Chi, Y. R. N-Heterocyclic Carbene Organocatalysis: Activation Modes and Typical Reactive Intermediates. *Chin. J. Chem.* **2020**, *38*, 1167−1202. (p) Yang, X.; Wang, H.; Jin, Z.; Chi, Y. R. Development of Green and Low-Cost Chiral Oxidants for Asymmetric Catalytic Hydroxylation of Enals. *Green Synth. Catal.* **2021**, *2*, 295−298. (q) Wu, X.; Witzig, R. M.; Beaud, R.; Fischer, C.; Häussinger, D.; Sparr, C. Catalyst Control over Sixfold Stereogenicity. *Nat. Catal.* **2021**, *4*, 457−462.

(15) (a) Satpathi, B.; Ramasastry, S. S. V. Morita-Baylis-Hillman Reaction of β,β-Disubstituted Enones: An Enantioselective Organocatalytic Approach for the Synthesis of Cyclopenta[b]Annulated Arenes and Heteroarenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 1777−1781. (b) Ghosh, A.; Patra, A.; Mukherjee, S.; Biju, A. T. Synthesis of 2-Aryl Naphthoquinones by the Cross-Dehydrogenative Coupling Involving an NHC-Catalyzed endo-Stetter Reaction. *J. Org. Chem.* **2019**, *84*, 1103−1110. (c) Mishra, U. K.; Patel, K.; Ramasastry, S. S. V. Synthesis of Cyclopropanoids via Substrate-Based Cyclization Pathways. *Org. Lett.* **2019**, *21*, 175−179.

(16) (a) He, M.; Struble, J. R.; Bode, J. W. Highly Enantioselective Azadiene Diels-Alder Reactions Catalyzed by Chiral N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2006**, *128*, 8418−8420. (b) Chiang, P.-C.; Rommel, M.; Bode, J. W. α'-Hydroxyenones as Mechanistic Probes and Scope-Expanding Surrogates for α,β-Unsaturated Aldehydes in N-Heterocyclic Carbene-Catalyzed Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 8714−8718.

(17) (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. A Highly Enantioselective Catalytic Intramolecular Stetter Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. (b) Kerr, M. S.; Rovis, T. Enantioselective Synthesis of Quaternary Stereocenters via a Catalytic Asymmetric Stetter Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 8876−8877. (c) Mahatthananchai, J.; Bode, J. W. The Effect of the N-Mesityl Group in NHC-Catalyzed Reactions. *Chem. Sci.* **2012**, *3*, 192−197. (d) Massey, R. S.; Collett, C. J.; Lindsay, A. G.; Smith, A. D.; O'Donoghue, A. C. Proton Transfer Reactions of Triazol-3-ylidenes: Kinetic Acidities and Carbon Acid Pk_a Values for Twenty Triazolium Salts in Aqueous Solution. *J. Am. Chem. Soc.* **2012**, *134*, 20421−20432. (e) Collett, C. J.; Massey, R. S.; Maguire, O. R.; Batsanov, A. S.; O'Donoghue, A. C.; Smith, A. D. Mechanistic Insights into the Triazolylidene-Catalysed Stetter and Benzoin Reactions: Role of the N-Aryl Substituent. *Chem. Sci.* **2013**, *4*, 1514−1522. (f) Collett, C. J.; Massey, R. S.; Taylor, J. E.; Maguire, O. R.; O'Donoghue, A. C.; Smith, A. D. Rate and Equilibrium Constants for the Addition of N-Heterocyclic Carbenes into Benzaldehydes: A Remarkable 2-Substituent Effect. *Angew. Chem., Int. Ed.* **2015**, *54*, 6887−6892.

(18) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. Enantioseletive Synthesis of α,α-Disubstituted Cyclopentenes by an N-Heterocyclic Carbene-Catalyzed Desymmetrization of 1,3-Diketones. *J. Am. Chem. Soc.* **2007**, *129*, 10098−10099.

(19) Kang, L.; Wang, F.; Zhang, J.; Yang, H.; Xia, C.; Qian, J.; Jiang, G. High Chemo-/Stereoselectivity for Synthesis of Polysubstituted Monofluorinated Pyrimidyl Enol Ether Derivatives. *Org. Lett.* **2021**, *23*, 1669−1674.

(20) (a) Iovan, D. A.; Wilding, M. J. T.; Baek, Y.; Hennessy, E. T.; Betley, T. A. Diastereoselective C-H Bond Amination for Disubstituted Pyrrolidines. *Angew. Chem., Int. Ed.* **2017**, *56*, 15599−15602. (b) Murray, S. A.; Liang, M. Z.; Meek, S. J. Stereoselective Tandem Bis-Electrophile Couplings of Diborylmethane. *J. Am. Chem. Soc.* **2017**, *139*, 14061−14064.

(21) (a) Zhang, M.; Wang, X.; Yang, T.; Qiao, Y.; Wei, D. Theoretical Model for N-Heterocyclic Carbene-Catalyzed Decarboxylation Reactions. *Org. Chem. Front.* **2021**, *8*, 3268−3273. (b) Zhang, M.; Wang, Y.; Li, S.-J.; Wang, X.; Shi, Q.; Li, X.; Qu, L.-B.; Wei, D.; Lan, Y. Multiple Functional Organocatalyst-Promoted Inert C-C Activation: Mechanism and Origin of Selectivities. *ACS Catal.* **2021**, *11*, 3443−3454.

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