Desymmetrization of Cyclic 1,3-Diketones under N-Heterocyclic Carbene Organocatalysis: Access to Organofluorines with Multiple Stereogenic Centers

Guanjie Wang, Min Zhang, Yezhi Guan, Ye Zhang, Xianfang Hong, Chenlong Wei, Pengcheng Zheng, Donghui Wei, Zhenqian Fu, Yonggui Robin Chi, and Wei Huang

1Key Laboratory of Flexible Electronics (KLOFE) & Institute of Advanced Materials (IAM) Nanjing Tech University (NanjingTech), 30 South Puzhu Road, Nanjing 211816, China
2College of Chemistry and Green Catalysis Center, Zhengzhou University, Zhengzhou, Henan 450001, China
3School of Chemistry and Molecular Engineering, Nanjing Tech University (NanjingTech), 30 South Puzhu Road, Nanjing 211816, China
4Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China
5Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore, Singapore 637371
6Frontiers Science Center for Flexible Electronics (FSCFE) & Shaanxi Institute of Flexible Electronics (SIFE), Northwestern Polytechnical University (NPU), 127 West Youyi Road, Xi’an 710072, China

Correspondence should be addressed to Pengcheng Zheng; zhengpc1986@163.com, Donghui Wei; donghuiwei@zzu.edu.cn, Zhenqian Fu; iamzqfu@njtech.edu.cn, and Wei Huang; iamwhuang@njtech.edu.cn

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Symmetric 1,3-diketones with fluorine or fluorinated substituents on the prochiral carbon remain to be established. Herein, we have developed a novel prochiral fluorinated oxindanyl 1,3-diketone and successfully applied these substrates in carbene-catalyzed asymmetric desymmetrization. Accordingly, a versatile strategy for asymmetric generation of organofluorines with fluorine or fluorinated methyl groups has been developed. Multiple stereogenic centers were selectively constructed with satisfactory outcomes. Structurally diverse enantioenriched organofluorines were generated with excellent results in terms of yields, diastereoselectivities, and enantioselectivities. Notably, exchanging fluorinated methyl groups to fluorine for this prochiral 1,3-diketones leads to switchable stereoselectivity. Mechanistic aspects and origin of stereoselectivity were studied by DFT calculations. Notably, some of the prepared organofluorines demonstrated competitive antibacterial activities.

1. Introduction

Asymmetric desymmetrization represents one of the most facile and efficient methods for the generation of enantioenriched organic compounds, especially with multiple stereogenic centers, from meso or prochiral raw materials [1–4]. In this area, catalytic desymmetrization of prochiral 1,3-diketones has been investigated widely, including asymmetric reduction, intramolecular adol-type reactions, and others [5–21]. Furthermore, this desymmetric strategy as the key step has shown wide application in diverse natural product synthesis associated with diverse promising biological activities [22, 23]. Owing to privileged structural characters of prochiral 1,3-diketones, such as containing unique and versatile carbonyl groups, and easily introducing substituents, further development of novel diverse prochiral diketones and their desymmetric strategies is still of high importance. Organic molecules with fluorine or fluorinated substituents can...
significantly change their physical, chemical, and biological properties [24–29]. For example, fluorocortisone, the first fluorine-containing pharmaceutical, possesses remarkable glucocorticoid activity that exceeds the activities of the parent hormones by a factor of 10 [30]. Although fluorine is the 13th most common element in the earth’s crust, it mainly exists as inorganic salts. Indeed, the number of biogenic organofluorines is extremely limited (around 20) [31]. Therefore, organofluorine synthesis and application have received tremendous attention in organic chemistry and achieved great advances [32–36]. Currently, a large number of pharmaceuticals and agrochemicals involve at least one fluorine atom. Surprisingly, symmetric 1,3-diketones with fluorine or fluorinated substituents on the prochiral carbon are largely overlooked and remain to be established (Figure 1(a)).

Notably, prochiral 1,3-diketones possess several privileged advantages, including the following: (i) The acidic
Prochiral carbon can be easily functionalized by deprotonation with various commercially available fluorination reagents (F, CF₃, CF₂H, CH₂F, etc.) [37–42]. Catalytic asymmetric desymmetrization of these substrates ensures a versatile method for the synthesis of enantioenriched organofluorines. Actually, it is challenging to be compatible with fluorine and fluorinated substituents in one asymmetric reaction due to their distinct properties. (ii) Asymmetrically modifying one of the two ketone carbonyl groups leads to the formation of fluorine-containing multiple stereogenic centers. Notably, the synthesis of such great challenging motifs has been largely underdeveloped, although they have already appeared in several invaluable pharmaceuticals (Figure 1(c)) [36].

Given the significant success of asymmetric N-heterocyclic carbene (NHC) catalysis [43–52] and privileged structural characters of prochiral 1,3-diketones, based on our ongoing interest in organocatalysis [53–57], we envisioned that a versatile method for the synthesis of enantioenriched organofluorines with multiple stereogenic centers might be established based on NHC-catalyzed asymmetric desymmetrization of novel prochiral fluorinated or fluoromethylated oxindolyl 1,3-ketones. Notably, asymmetric synthesis of spirocycle compounds has attracted a lot of synthetic attention [58–61]. Among them, spiro compounds containing oxindole moieties are proven among the important scaffolds in natural products and bioactive molecules exemplified by those in Figure 1(d) [61, 62]. These easily available prochiral 1,3-diketones could react with unsaturated acyl triazolium intermediates [63–65] obtained from bromoenals with NHC to construct spiropolycyclic organofluorines with five stereogenic centers, including three quaternary stereocenters. While one requirement would be to achieve intermolecular domino desymmetrization, the connection of the reactive site (carbonyl group) to a sterically hindered quaternary carbon center may impede this process. Furthermore, the ability to

**Table 1: Optimized conditions**

| Entry | NHC-HX | Base | Solvent | Yield (%) | dr<sup>[c]</sup> | ee<sup>[d]</sup> |
|-------|--------|------|---------|-----------|---------------|-----------|
| 1     | A      | K₂CO₃| Toluene | 11        | —             | —         |
| 2     | A      | Cs₂CO₃| Toluene | <10       | —             | —         |
| 3     | A      | Na₂CO₃| Toluene | <10       | —             | —         |
| 4     | A      | NaHCO₃| Toluene | <10       | —             | —         |
| 5     | A      | DBU  | Toluene | <10       | —             | —         |
| 6     | A      | KOAc | Toluene | 80        | >20:1         | >99       |
| 7     | A      | NaOAc| Toluene | 82        | >20:1         | >99       |
| 8     | A      | Et₃N | Toluene | 19        | —             | —         |
| 9     | B      | NaOAc| Toluene | 88        | >20:1         | >99       |
| 10    | C      | NaOAc| Toluene | 84        | >20:1         | >99       |
| 11    | D      | NaOAc| Toluene | 81        | >20:1         | >99       |
| 12    | E      | NaOAc| Toluene | 80        | >20:1         | >99       |
| 13    | B      | NaOAc| DCM     | 81        | >20:1         | >99       |
| 14    | B      | NaOAc| THF     | <10       | —             | —         |
| 15    | B      | NaOAc| Mesitylene | 93    | >20:1         | >99       |
| 16    | B      | NaOAc| o-Xylene| 90        | >20:1         | >99       |
| 17<sup>[e]</sup> | B | NaOAc| Mesitylene | 78 | >20:1 | >99 |

<sup>[a]</sup>Standard condition: 1a (0.1 mmol), 2a (1.2 equiv), NHC-HX (10 mol%), solvent (0.1 M), 30°C, 24 h. <sup>[b]</sup>Yield of the product after column chromatography. <sup>[c]</sup>Determined via ¹H NMR spectroscopy. <sup>[d]</sup>Determined by chiral HPLC, %ee = [(R-S)/(R+S)] × 100. <sup>[e]</sup>5 mol% catalyst, 60 h.
achieve satisfactory diastereoselectivity and enantioselectivity would remain important. Importantly, organocatalyzed generation of enantioenriched organofluorines prevents heavy metal residues, considerably increasing the potential utilities. We herein have developed a novel prochiral fluoroated oxindanyl 1,3-diketone and successfully applied these substrates in carbene-catalyzed asymmetric desymmetrization. Accordingly, a versatile and practical strategy for asymmetric generation of organofluorines with fluorine or fluorinated methyl groups (CF$_3$, CF$_2$H, or CH$_2$F) has been developed. Multiple stereogenic centers were selectively constructed with satisfactory outcomes. It may be mentioned that enantioselective synthesis of tricyclic β-lactones by NHC-catalyzed desymmetrization of cyclic 1,3-diketones has been demonstrated recently by Shee and coworkers [66].

2. Results

We initially attempted this synthetic approach with prochiral trifluoromethylated oxindolyl 1,3-diketone 1a and (Z)-2-bromo-3-phenylacrylaldehyde 2a under NHC organocatalysis. Trifluoromethylated spiropolycyclic compound 3a was obtained in 11% yield when sterically hindered aminoindanol-derived triazolium precatalyst A was employed in the presence of K$_2$CO$_3$ in toluene at room temperature (Table 1, entry 1). Subsequently, several bases were screened, and sodium acetate was the best base, giving the product 3a in good yield (82%) with >20:1 dr and >99% ee (entries 2–8). Several NHC catalysts were next investigated, with NHC precatalyst B, with a Br atom on the indane moiety, proving to be the better choice to deliver the product 3a in...
Figure 3: Scope of reactions.
high yield without any loss in dr or ee (entries 9–12). The yield could be further improved to 93% by using mesitylene as the solvent (entries 13–16). 5 mol% catalyst ensured this transformation to give the product in 78% yield (entry 17).

Under optimal conditions (Table 1, entry 15), the scope of this desymmetrization domino reaction was examined (Figure 2). For trifluoromethylated oxindolyl 1,3-diketones, several substituents at the 4-, 5-, 6-, and 7-positions on the oxindole ring were well tolerated to form 3a–3f in good to excellent yields (81–93%) with excellent diastereoselectivities (>20:1 dr values) and enantioselectivities (>99% ee values). Substrates with N-benzyl, N-allyl, and N-isopropyl groups reacted efficiently to form products 3g–3i in 83%–93% yields and without any erosion of dr values and ee values. For the indane motif, substrate 1 with a naphthalene unit gave 3j in 83% yield with >20:1 dr and >99% ee. Introducing two symmetrical chloride atoms to the indane ring did not influence the efficiency, furnishing the product 3k in 86% yield with >20:1 dr and >99% ee. Subsequently, the generality of 2-bromoenals was evaluated. For 2-bromoenals associated with electron-donating or electron-withdrawing groups on the aromatic ring, the reactions worked efficiently to afford the products 3l–3w in good to excellent yields with good to excellent diastereoselectivities and excellent enantioselectivities. Bromoenals with a naphthalene or heteroaryl unit (such as 2-furyl and 2-thienyl) were also compatible with the reaction. Unfortunately, β-alkyl-substituted enals failed to deliver the product in our reaction.

To further investigate the scope and limitations of this organocatalytic strategy, other fluorinated methyl groups, such as difluoromethyl, and monofluoromethyl groups were introduced into the prochiral substrates (Figure 3). Notably, for these substrates, the release of CO₂ could not be completely avoided under the reaction conditions and in the purification step that followed. Thus, one more decarbonation operation was performed for these substrates. Delightfully, all reactions proceeded smoothly, forming the products 6 and 8 with acceptable results. On the other hand, the intermediate underwent ring opening with a nucleophile, such as methanol, delivering products 5 and 7, respectively. We consider that

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**Figure 4: Scope of reactions. Reaction conditions: 9 (0.1 mmol), 2 (1.2 mmol), NHC-HBF₄ B (2 mol%), NaOAc (1.5 mmol), mesitylene (1 mL), 4 Å MS (50 mg), 30 °C, 24 h.**

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| Entry | R     | Yield (%) | ee   | dr    |
|-------|-------|-----------|------|-------|
| 10a   | 4-H   | 93        | 98   | 5:1   |
| 10b   | 4-F   | 88        | >99  | 6:1   |
| 10c   | 4-OMe| 96        | >99  | 5:1   |
| 10d   | 4-OMe| 93        | >99  | 2:1   |
| 10e   | 4-Br  | 91        | >99  | 1.0:1 |
| 10f   | 4-Cl  | 89        | >99  | 1.0:1 |
| 10g   | 4-Cl  | 89        | >99  | 1.0:1 |
| 10h   | 4-NO₂| 83        | >99  | 6:1   |
| 10i   | 4-NO₂| 83        | >99  | 6:1   |
| 10j   | 4-Me  | 89        | >99  | 1.0:1 |
| 10k   | 4-Me  | 89        | >99  | 1.0:1 |
| 10l   | 4-Me  | 89        | >99  | 1.0:1 |
| 10m   | 4-Me  | 89        | >99  | 1.0:1 |
| 10n   | 4-Me  | 89        | >99  | 1.0:1 |
| 10o   | 4-Me  | 89        | >99  | 1.0:1 |
| 10p   | 4-Me  | 89        | >99  | 1.0:1 |
| 10q   | 4-Me  | 89        | >99  | 1.0:1 |
| 10r   | 4-Me  | 89        | >99  | 1.0:1 |
| 10s   | 4-Me  | 89        | >99  | 1.0:1 |
| 10t   | 4-Me  | 89        | >99  | 1.0:1 |
| 10u   | 4-Me  | 89        | >99  | 1.0:1 |
| 10v   | 4-Me  | 89        | >99  | 1.0:1 |
| 10w   | 4-Me  | 89        | >99  | 1.0:1 |

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asymmetric synthesis of important organofluorines containing CF₂H and CFH₂ has been overlooked to date [34, 67–69]. Our novel strategy for asymmetric synthesis of these organofluorines by carbene-catalyzed desymmetrization is effective.

After successfully documenting the synthesis of fluoromethylated molecules with five stereogenic centers under NHC organocatalysis, the generality of this desymmetrization strategy was further explored to construct fluorinated molecules (Figure 4). Different from the above-obtained products 3, 5, 6, 7, and 8, which featured the more sterically hindered fluorinated methyl groups, the resulting product 10 featured the relatively small fluorine atom and showed the opposite absolute configuration under the identical reaction conditions. In all the cases, the desymmetrization cascade process proceeded smoothly by using just 2 mol% carbene catalyst, delivering spirocyclohexene products in 86-93% yields with 2.6:1-11:1 dr and 90-99% ee values. Under 10 mol% of NHC precatalyst B catalysis, the reaction worked efficiently on a gram scale to generate 3 g in 88% yield with >20:1 dr and >99% ee (Figure 5(a)). To demonstrate the practicality of the present strategy, further synthetic transformation of the resulting product was performed as shown in Figure 2. The substrates 1a with CF₃ and 9a with F underwent intramolecular desymmetrical cyclisation, followed by decarbonation to generate the corresponding products 11 and 12 in good yields with excellent dr and ee values, respectively. Impressively, our method reported here is also effective to prepare enantioenriched trifluoromethylthiolated spirocyclohexene product, leading to product 14 with excellent yields, dr and ee values (Figure 5(c)). Ring opening of the product 3a was achieved by treatment with nucleophiles such as methanol and benzylamine at room temperature and led to the formation of amides 15a and 15b in excellent outcomes. More importantly, for the

![Figure 5: Synthetic application: (a) gram scale synthesis; (b) one pot process to enantioenriched spirocyclohexene product; (c) synthesis of enantioenriched trifluoromethylthiolated spirocyclohexene product; (d) one pot process to cycle-open product; (e) Baeyer-Villiger oxidation of the enantioenriched product.](image-url)
alcohols with promising biological activities, such as cholesterol, fluphenazine, and adapalene-derived alcohol, the ring-opened products 15c-e were formed in good yields with excellent dr and ee (or de) values. The treatment of 10a with methanol under basic conditions followed by oxygen insertion converted the carbonyl moiety into a carboxylic moiety, leading to product 17 in good yield with the retention of dr and ee.

DFT calculations were conducted to explore the possible pathway. As shown in Figure 6, the carbonyl carbon of reactant 1a is susceptible to nucleophilic attack by the carbene carbon of the actual NHC catalyst via transition state TS1, which is followed by an acetic acid-mediated [1, 2]-proton transfer via transition state TS2 for the formation of Breslow intermediate M2. The third step is a bromide removal process via transition state TS3. Deprotonation can then be mediated by bromide ion, coupled with protonation by acetic acid via transition state TS4. The fifth step involves diastereoselective transition state TS5SS (or TS5RR) for Cβ–C1 bond formation between intermediate M4 and deprotonated achiral 1,3-diketone 2a', which is followed by an intramolecular [2 + 2] cycloaddition to complete the six-membered ring closure via transition state TS6SS. The two letters after the names of the stationary points represent the chirality of the molecules associated with the centrally chiral C1 and Cβ atoms. The last step is the dissociation of catalyst NHC from the main product PSS via transition state TS7SS. The Gibbs free energy barriers of the seven steps via transition states TS1-7 are 4.3, 6.3, 1.7, 18.2, 9.5 (or 12.6 for RR-configured isomer), 8.8, and 5.4 kcal/mol, respectively.

To further examine the origin of enantioselectivity, quantitative Bader atoms-in-molecules analyses were carried out. The energy barrier of transition state TS5RR is 3.1 kcal/mol higher than that of transition state TS5SS, whereas the energy barrier of the transition state TS5RR' (Figure 7(a)), meaning that the enantioselectivity can be switched by exchanging the -CF3 substituent with -F. As shown in Figures 3(b) and 3(c), there are no C-H…F hydrogen bond [70] and (long pair) LP…π interaction in the TS5RR (RR-configured transition state), which is due to the long distance between the -CF3 substituent and NHC catalyst in the RR-configuration. This is why TS5SS is more stable than TS5RR. While the -CF3 substituent is replaced by the small -F group, although there is still not C-H…F interaction, the C-H…O hydrogen bond interactions between the substrate and NHC catalyst in TS5RR' become significantly stronger than those of C-H…O and C-H…F hydrogen bond interactions in transition state

![Figure 6: Gibbs free energy profile of the entire catalytic cycle computed at the M06-2X/6-31G(d, p)/IEFPCM mesitylene level.](image-url)
Figure 7: (a) The Gibbs free energy barrier differences (\(\Delta G^0\), energy in kcal/mol), (b) AIM analyses for transition states TS5SS, TS5RR, TS5SS', and TS5RR' with different substitutes (distance in Å), and (c) summary of the values of Laplacian electron density (\(\nabla^2 \rho\) in eÅ\(^{-3}\)).

TS5SS', which is the key factor in strengthening the stability of the RR-configured transition state TS5RR' and leads to the switchable stereoselectivity for the reaction. Noteworthily, 20 possible conformations for TS5SS, TS5RR, TS5SS', and TS5RR' were proposed and optimized to ensure that the conformation with the lowest energy was selected. The calculated results were provided in Figure S1 of the SI.

To show the practical value of the resulting enantiomer-enriched fluorinated and fluoromethylated molecules, their antibacterial activities were initially examined by using Xanthomonas oryzae, Xanthomonas axonopodis, and Ralstonia solanacearum as target bacteria [71–73]. These bacteria are widespread plant pathogens that can cause serious plant diseases and huge economic losses in agricultural production [74]. Some of the chiral organofluorines from the current study exhibited superior antibacterial activities, as shown in Table 2. For example, compounds 10a and 8b showed higher inhibitory rates against Xoo than the commercial bactericide bismethiazol when used at 50 \(\mu\)g/mL. Similarly, compounds 6b and 16 showed inhibitory rates against Xal that were similar to thiodiazole-copper. Under the same conditions, compounds 12 and 15a showed better inhibitory rates against Rs than thiodiazole-copper. These promising results indicated that the organofluorines produced in the current study have potential use as agrochemicals.

### 3. Discussion

In summary, asymmetric desymmetrization of a novel prochiral 1,3-diketone with a fluorine or fluorinated methyl group has been demonstrated under NHC organocatalysis. Accordingly, a versatile and practical strategy for the construction of diverse organofluorines featuring fluorine or fluoromethyl groups (CF\(_3\), CF\(_2\)H, or CH\(_2\)F) has been successfully developed by the current strategy. Notably, products featuring five stereogenic centers, including three quaternary centers and two rings, have been efficiently constructed in this transformation. Mechanism studies and DFT calculations demonstrated that the first C-C bond formation is the
| Compound               | Xanthomonas oryzae pv. oryzae (Xoo) inhibition rate 50 ppm | Xanthomonas axonopodis pv. citri (Xal) inhibition rate 50 ppm | Ralstonia solanacearum (Rs) inhibition rate 50 ppm |
|-----------------------|----------------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------|
| 3a                    | 0.00% ± 9.86%                                            | 44.30% ± 3.66%                                              | 0.00% ± 4.53%                                   |
| 6b                    | 74.71% ± 10.22%                                          | 73.14% ± 6.77%                                              | 78.26% ± 4.53%                                  |
| 8b                    | 99.69% ± 7.57%                                            | 64.75% ± 3.60%                                              | 38.90% ± 13.88%                                 |
| 10a                   | 93.40% ± 21.20%                                           | 41.87% ± 4.98%                                              | 58.95% ± 4.70%                                  |
| 11                    | 21.46% ± 1.91%                                            | 35.69% ± 11.07%                                             | 47.03% ± 6.87%                                  |
| 12                    | 0.00% ± 19.67%                                            | 41.28% ± 2.90%                                              | 94.57% ± 0.55%                                  |
| 15a                   | 3.90% ± 0.11%                                             | 41.65% ± 6.29%                                              | 99.69% ± 18.24%                                 |
| 16                    | 0.00% ± 5.79%                                             | 70.42% ± 12.69%                                             | 0.00% ± 5.57%                                   |
| Thiodiazole-copper    | 89.29% ± 10.69%                                           | 79.32% ± 0.64%                                              | 93.29% ± 1.19%                                  |
| Bismerthiazol         | 94.39% ± 22.58%                                           | 54.67% ± 1.22%                                              | 47.40% ± 7.43%                                  |

Table 2: The antibacterial activity of the products.
stereoselectivity-determining step as well as C-H...O and C-H...F interactions are the key factors to control and even switch the enantioselectivity of the reaction by exchanging the fluoromethyl substituents. The initial test indicated that some of the obtained enantoenriched organofluorines showed competitive antibacterial activities. Further investigations and exploration of this catalytic process and the resulting enantoenriched organofluorines are underway in our laboratory.

4. Materials and Methods

4.1. General Procedure for the Synthesis of Organofluorine 3
To an oven-dried screw-capped test tube equipped with a magnetic stir bar, the prochiral 1,3-diketones 1 (0.1 mmol), 2-bromoenals 2 (0.12 mmol), triazolium salt NHC B (5.0 mg, 10 mol %), NaOAc (12.3 mg, 1.5 equiv.), and 4 Å MS (50 mg) were added. To this mixture was added anhydrous mesitylene (0.1 M). After completion of the reaction, purification of the crude residue gave the desired product 3.

Data Availability
The data that support the finding of this study are available from the corresponding authors upon reasonable request.

Conflicts of Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

Authors’ Contributions
Z.F. conceived the idea and designed the experiments. Z.F., D.W., R.Y.C., and W.H. supervised the work. G.W. conducted most of the experiments. Y.Z., X.H., and C.W. prepared some of starting materials. M.Z. performed the DFT study. Y.G. and P.Z. performed antibacterial activity tests. Z.F. drafted the manuscript with assistance from all coauthors. All authors contributed to discussions.

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Supplementary Materials
Preparation of substrates. Characterization of reaction substrates. General procedures. Characterization of reaction products. X-ray crystallographic data of 3f and 10j. Computational details. In vitro antibacterial bioassay. Copies of NMR spectra and HPLC chromatographs. Energies, Cartesian coordinates, and frequencies of all the optimized stationary points in DFT studies. (Supplementary Materials)

References
[1] A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson, and D. J. Dixon, “Organocatalytic enantioselective desymmetrisation,” Chemical Society Reviews, vol. 45, no. 20, pp. 5474–5540, 2016.
[2] X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou, and J. Zhou, “Catalytic enantioselective desymmetrisation reactions to all-carbon quaternary stereocenters,” Chemical Reviews, vol. 116, no. 12, pp. 7330–7396, 2016.
[3] T. Das, “Desymmetrization of cyclopentene-1,3-diones via alkylation, arylation, amidation and cycloadition reactions,” ChemistrySelect, vol. 5, no. 45, pp. 14484–14509, 2020.
[4] T. Shu and J. Cossey, “Asymmetric desymmetrization of alkene-, alkyne- and allene-tethered cyclohexadienones using transition metal catalysis,” Chemical Society Reviews, vol. 50, no. 1, pp. 658–666, 2021.
[5] B. M. Bocknack, L.-C. Wang, and M. J. Krische, “Desymmetrisation of enone-diones via rhodium-catalyzed diastereo- and enantioselective tandem conjugate addition-aldol cyclization,” Proceedings of the National Academy of Sciences of the United States of America, vol. 101, no. 15, pp. 5421–5424, 2004.
[6] M. Wadamoto, E. M. Phillips, T. E. Reynolds, and K. A. Scheidt, “Enantioselective synthesis of a,a-disubstituted cyclopentenes by anN-Heterocyclic carbene-catalyzed desymmetrization of 1,3-diketones,” Journal of the American Chemical Society, vol. 129, no. 33, pp. 10098–10099, 2007.
[7] B. M. Partridge, J. Solana González, and H. W. Lam, “Iridium-catalyzed arylative cyclization of alkynes by 1,4-iridium migration,” Angewandte Chemie International Edition, vol. 53, no. 25, pp. 6523–6527, 2014.
[8] X. Wu, Z. Chen, Y.-B. Bai, and V. M. Dong, “Diastereodivergent construction of bicyclic y-lactones via enantioselective ketone hydroacylation,” Journal of the American Chemical Society, vol. 138, no. 37, pp. 12013–12016, 2016.
[9] C. Zhu, D. Wang, Y. Zhao, W.-Y. Sun, and Z. Shi, “Enantioselective palladium-catalyzed intramolecular α-arylative desymmetrization of 1,3-diketones,” Journal of the American Chemical Society, vol. 139, no. 46, pp. 16486–16489, 2017.
[10] S. Cuadros, L. Dell’Amico, and P. Melchiorre, “Forging fluorine-containing quaternary stereocenters by a light-driven organocatalytic aldol desymmetrization process,” Angewandte Chemie International Edition, vol. 56, no. 39, pp. 11875–11879, 2017.
[11] L. Cai, K. Zhang, S. Chen et al., “Catalytic asymmetric Staedinger-azaWittig reaction for the synthesis of heterocyclic amines,” Journal of the American Chemical Society, vol. 141, no. 24, pp. 9537–9542, 2019.
[12] X. Chen, H. Zhang, M. A. Maria-Solano et al., “Efficient reductive desymmetrization of bulky 1,3-cyclo- diketones enabled by structure-guided directed evolution of a carbonyl reductase,” Nature Catalysis, vol. 2, no. 10, pp. 931–941, 2019.
[13] Q. Gong, J. Wen, and X. Zhang, “Desymmetrization of cyclic 1,3-diketones via catalyzed hydrogenation: an efficient approach to cyclic hydroxy ketones with a chiral quaternary carbon,” Chemical Science, vol. 10, no. 25, pp. 6350–6353, 2019.
[14] C.-B. Yu, B. Song, M.-W. Chen, H.-Q. Shen, and Y.-G. Zhou, “Construction of multiple-substituted chiral cyclohexanes through hydrogenative desymmetrization of 2,2,5-trisubstituted 1,3-cyclohexanediones,” Organic Letters, vol. 21, no. 23, pp. 9401–9404, 2019.
T. Zhu, Y. Liu, M. Smetanko et al., "Carbene-catalyzed desymmetrization and direct construction of arenes with all-carbon quaternary chiral center," Angewandte Chemie International Edition, vol. 58, no. 44, pp. 15778–15782, 2019.

J. M. Zanghi, S. Liu, and S. J. Meek, "Enantio- and diastereoselective synthesis of functionalized carboxylic acids by Cucatalyzed borylative cyclization of alkynes with ketones," Organic Letters, vol. 21, no. 13, pp. 5172–5177, 2019.

J. Chen, Y. Wang, Z. Ding, and W. Kong, "Synthesis of bridged tricyclo[5.2.1.0]-decanes via nickel-catalyzed asymmetric domino cyclization of enynes," Nature Communications, vol. 11, no. 1, pp. 1882–1890, 2020.

Y.-X. Ding, Z.-H. Zhu, H. Wang, C.-B. Yu, and Y.-G. Zhou, "Construction of three stereocenters via hydrogenation desymmetrization of 2,2,5-trisubstituted cyclohexane-1,3-diones," Science China: Chemistry, vol. 64, no. 2, pp. 232–237, 2021.

B. Yang, J. Dai, Y. Luo et al., "Desymmetrization of 1,3-diones by catalytic enantioselective condensation with hydrazine," Journal of the American Chemical Society, vol. 143, no. 11, pp. 4179–4186, 2021.

X.-L. Qin, A. Li, and F.-S. Han, "Desymmetric enantioselective reduction of cyclic 1,3-diketones catalyzed by a recyclableP-chiral phosphinamide organocatalyst," Journal of the American Chemical Society, vol. 143, no. 7, pp. 2994–3002, 2021.

B. Ghosh, R. Balhara, G. Jindal, and S. Mukherjee, "Catalytic enantioselective desymmetrizing Fischer indolization through dynamic kinetic resolution," Angewandte Chemie International Edition, vol. 60, no. 16, pp. 9086–9092, 2021.

S. Prevo, N. Dupre, M. Leutzh, Q. Wang, V. Wachauer, and B. List, "Catalytic asymmetric Torgov cyclization: a concise total synthesis of (+)-estrone," Angewandte Chemie International Edition, vol. 53, no. 33, pp. 8770–8773, 2014.

M. Wang, M. Feng, B. Tang, and X. Jiang, "Recent advances of desymmetrization protocol applied in natural product total synthesis," Tetrahedron Letters, vol. 55, no. 52, pp. 7147–7155, 2014.

P. Kirsch, Modern Fluoroorganic Chemistry, Wiley-VCH, Weinheim, 2013.

K. Muller, C. Faeh, and F. Diederich, "Fluorine in pharmaceuticals: looking beyond intuition," Science, vol. 317, no. 5846, pp. 1881–1886, 2007.

S. Purser, P. R. Moore, S. Swallow, and V. Gouverneur, "Fluorine in medicinal chemistry," Chemical Society Reviews, vol. 37, no. 2, pp. 320–330, 2008.

J. Wang, M. Sanchez-Roselló, J. L. Aceña et al., "Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001-2011)," Chemical Reviews, vol. 114, no. 4, pp. 2432–2506, 2014.

Q. A. Huchet, B. Kuhn, B. Wagner et al., "Fluorination pattern: a study of structural motifs that impact physicochemical properties of relevance to drug discovery," Journal of Medicinal Chemistry, vol. 58, no. 22, pp. 9041–9060, 2015.

E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, and N. A. Meanwell, "Applications of fluorine in medicinal chemistry," Journal of Medicinal Chemistry, vol. 58, no. 21, pp. 8315–8359, 2015.

J. Fried and E. F. Sabo, "9α-Fluoro derivatives of cortisol and hydrocortisone," Journal of the American Chemical Society, vol. 76, no. 5, pp. 1455–1456, 1954.

D. O’Hagan and D. B. Harper, "Fluorine-containing natural products," Journal of Fluorine Chemistry, vol. 100, no. 1-2, pp. 127–133, 1999.

T. Furuya, A. S. Kamlet, and T. Ritter, "Catalysis for fluorination and trifluoromethylation," Nature, vol. 473, no. 7348, pp. 470–477, 2011.

V. Gouverneur and K. Seppelt, "Introduction: fluorine chemistry," Chemical Reviews, vol. 115, no. 2, pp. 563–565, 2015.

Y. X. Yang, T. Wu, R. J. Phipps, and F. D. Toiste, "Advances in catalytic enantioselective fluorination, mono-, di-, and trifluoromethylation, and trifluoromethylthiolation reactions," Chemical Reviews, vol. 115, no. 2, pp. 826–870, 2015.

H. Groult, F. Leroux, and A. Tressaud, Modern Synthesis Processes and Reactivity of Fluorinated Compounds, Academic Press, London, 2017.

Y. Zhu, J. Han, J. Wang et al., "Modern approaches for asymmetric construction of carbon-fluorine quaternary stereogenic centers: synthetic challenges and pharmaceutical needs," Chemical Reviews, vol. 118, no. 7, pp. 3887–3964, 2018.

N. Shibata, A. Matsnev, and D. Cahard, "Shelf-stable electrophilic trifluoromethylating reagents: a brief historical perspective," Beilstein Journal of Organic Chemistry, vol. 6, p. 65, 2010.

P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, and J.-F. Faquin, "Monofluorination of organic compounds: 10 years of innovation," Chemical Reviews, vol. 115, no. 17, pp. 9073–9174, 2015.

C. Ni, M. Hu, and J. Hu, "Good partnership between sulfur and fluorine: sulfur-based fluorination and fluoroalkylation reagents for organic synthesis," Chemical Reviews, vol. 115, no. 2, pp. 765–825, 2015.

J. Charpentier, F. Früh, and A. Togni, "Electrophilic trifluoromethylation by use of hypervalent iodine reagents," Chemical Reviews, vol. 115, no. 2, pp. 650–682, 2015.

J. Kalim, T. Duhail, T.-N. Le et al., "Merging hypervalent iodine and sulfoximine chemistry: a new electrophilic trifluoromethylation reagent," Chemical Science, vol. 10, no. 45, pp. 10516–10523, 2019.

M. Li, X.-S. Xue, and J.-P. Cheng, "Establishing cation and radical donor ability scales of electrophilic F, CF3, and SCF3 trans-fluorination, mono-, di-, and tri-fluoromethylation, and trifluoromethylthiolation reactions," Accounts of Chemical Research, vol. 53, no. 1, pp. 182–197, 2020.

D. Enders, O. Niemeier, and A. Henseler, "Organocatalysis by N-heterocyclic carbene catalysis: a new electrophilic trifluoromethylation reagent," Chemical Reviews, vol. 107, no. 12, pp. 5606–5655, 2007.

X. Bugaut and F. Glorius, "Organocatalytic umpolung: N-heterocyclic carbens and beyond," Chemical Society Reviews, vol. 41, no. 9, pp. 3511–3522, 2012.

D. T. Cohen and K. A. Scheidt, "Cooperative Lewis acid/N-heterocyclic carbene catalysis," Chemical Science, vol. 3, no. 1, pp. 53–57, 2012.

S. De Sarkar, A. Biswas, R. C. Samanta, and A. Studer, "Catalysis with N-heterocyclic carbens under oxidative conditions," Chemistry - A European Journal, vol. 19, no. 15, pp. 4664–4678, 2013.

S. J. Ryan, L. Candish, and D. W. Lupton, "Acyl anion free N-heterocyclic carbene organocatalysis," Chemical Society Reviews, vol. 42, no. 12, pp. 4906–4917, 2013.

M. N. Hopkinson, C. Richter, M. Schedler, and F. Glorius, "An overview of N-heterocyclic carbens," Nature, vol. 510, no. 7506, pp. 485–496, 2014.
[49] D. M. Flanigan, F. Romanov-Michailidis, N. A. White, and T. Rovis, “Organocatalytic reactions enabled by N-heterocyclic carbene,” *Chemical Reviews*, vol. 115, no. 17, pp. 9307–9387, 2015.

[50] X. Y. Chen, Z. H. Gao, and S. Ye, “Bifunctional N-heterocyclic carbene derived from L-proglutamic acid and their applications in enantioselective organocatalysis,” *Accounts of Chemical Research*, vol. 53, no. 3, pp. 690–702, 2020.

[51] H. Ohmiya, “N-Heterocyclic carbene-based catalysis enabling cross-coupling reactions,” *ACS Catalysis*, vol. 10, no. 12, pp. 6862–6869, 2020.

[52] Y. Zhang, J. Huang, Y. Guo, L. Li, Z. Fu, and W. Huang, “Access to enantioenriched organosilanes from enals and β-silyl enones: carbene organocatalysis,” *Angewandte Chemie, International Edition*, vol. 57, no. 17, pp. 4594–4598, 2018.

[53] Y. Gao, D. Liu, Z. Fu, and W. Huang, “Facile synthesis of 2,2-diacyl spirocyclohexanones via an N-heterocyclic carbene-catalyzed formal [3C + 3C] annulation,” *Organic Letters*, vol. 21, no. 4, pp. 926–930, 2019.

[54] G. Wang, Q. Shi, W. Hu et al., “Organocatalytic asymmetric α,N-sulfonyl amide C-N bond activation to access axially chiral biaryl amino acids,” *Nature Communications*, vol. 11, no. 1, p. 946, 2020.

[55] Y. Zhang, X. Huang, J. Guo, C. Wei, M. Gong, and Z. Fu, “Carbene-catalyzed enantioselective synthesis of γ-keto-β-silyl esters and amides,” *Organic Letters*, vol. 22, no. 24, pp. 9545–9550, 2020.

[56] G. Wang, Q.-C. Zhang, C. Wei et al., “Asymmetric carbene-catalyzed oxidation of functionalized aldimines as 1,4-dipoles,” *Angewandte Chemie, International Edition*, vol. 60, no. 14, pp. 7913–7919, 2021.

[57] A. Ding, M. Meazza, H. Guo, J. W. Yang, and R. Rios, “New development in the enantioselective synthesis of spiro compounds,” *Chemical Society Reviews*, vol. 47, no. 15, pp. 5946–5996, 2018.

[58] P.-W. Xu, J.-S. Yu, C. Chen, Z.-Y. Cao, F. Zhou, and J. Zhou, “Catalytic enantioselective construction of spiro quaternary carbon stereocenters,” *ACS Catalysis*, vol. 9, no. 3, pp. 1820–1882, 2019.

[59] L. Hong and R. Wang, “Recent advances in asymmetric organocatalytic construction of 3,3′-spirocyclic oxindoles,” *Advanced Synthesis & Catalysis*, vol. 355, no. 6, pp. 1023–1052, 2013.

[60] D. Cheng, Y. Ishihara, B. Tan, and C. F. Barbas III, “Organocatalytic asymmetric assembly reactions: synthesis of spirooxindoles via organocascade strategies,” *ACS Catalysis*, vol. 4, no. 3, pp. 743–762, 2014.

[61] B. Yu, D.-Q. Yu, and H.-M. Liu, “Spirooxindoles: promising scaffolds for anticancer agents,” *European Journal of Medicinal Chemistry*, vol. 97, pp. 673–698, 2015.

[62] J. Mahatthananchai and J. W. Bode, “On the mechanism of N-heterocyclic carbene-catalyzed reactions involving acyl azoliums,” *Accounts of Chemical Research*, vol. 47, no. 2, pp. 696–707, 2014.

[63] S. Mondal, S. R. Yetra, S. Mukherjee, and A. T. Biju, “NHCl-catalyzed generation of α,β-unsaturated acylazoliums for the enantioselective synthesis of heterocycles and carbocycles,” *Accounts of Chemical Research*, vol. 52, no. 2, pp. 425–436, 2019.

[64] A. Ghosh and A. T. Biju, “Revealing the similarities of α,β-unsaturated iminiums and acylazoliums in organocatalysis,” *Angewandte Chemie International Edition*, vol. 60, no. 25, pp. 13712–13724, 2021.

[65] S. Shee, S. Mukherjee, R. G. Gonnade, and A. T. Biju, “Enantioselective synthesis of tricyclic β-lactones by NHCl-catalyzed desymmetrization of cyclic 1,3-diketones,” *Organic Letters*, vol. 22, no. 14, pp. 5407–5411, 2020.

[66] J.-A. Ma and D. Cahard, “Asymmetric fluorination, trifluoromethylation, and perfluoroalkylation reactions,” *Chemical Reviews*, vol. 104, no. 12, pp. 6119–6164, 2004.

[67] Z. Feng, Y.-L. Xiao, and X. Zhang, “Transition-metal (Cu, Pd, Ni)-catalyzed difluoroalkylation via cross-coupling with difluoroalkyl halides,” *Accounts of Chemical Research*, vol. 51, no. 9, pp. 2264–2278, 2018.

[68] X.-S. Hu, J.-S. Yu, and J. Zhou, “Catalytic selective mono- and difluoroalkylation using fluorinated silyl enol ethers,” *Chemical Communications*, vol. 55, no. 91, pp. 13638–13648, 2019.

[69] Y.-J. Hao, J. S. Yu, Y. Zhou, X. Wang, and J. Zhou, “Influence of C–F...H–X interactions on organic reactions,” *Acta Chimica Sinica*, vol. 76, no. 12, pp. 925–939, 2018.

[70] T. R. Gottwald, G. Hughes, J. H. Graham, X. Sun, and T. Riley, “The citrus canker epidemic in Florida: the scientific basis of regulatory eradication policy for an invasive species,” *Phytopathology*, vol. 91, no. 1, pp. 30–34, 2001.

[71] P. Li, D. Hu, D. Xie, J. Chen, L. Jin, and B. Song, “Design, synthesis, and evaluation of new sulfone derivatives containing a 1,3,4-oxadiazole moiety as active antibacterial agents,” *Journal of Agricultural and Food Chemistry*, vol. 66, no. 12, pp. 3093–3100, 2018.

[72] P. Y. Wang, M. W. Wang, D. Zeng et al., “Rational optimization and action mechanism of novel imidazole (or imidazolium)-labeled 1,3,4-oxadiazole thioethers as promising antibacterial agents against plant bacterial diseases,” *Journal of Agricultural and Food Chemistry*, vol. 67, no. 13, pp. 3535–3545, 2019.

[73] Q. L. Dang, W. K. Kim, C. M. Nguyen et al., “Nematicidal and antifungal activities of Annonaceous acetogenins from Annona squamosa against various plant pathogens,” *Journal of Agricultural and Food Chemistry*, vol. 59, no. 20, pp. 11160–11167, 2011.