# Enantioselective modification of sulfonamides and sulfonamide-containing drugs *via* carbene organic catalysis†

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A carbene-catalyzed method for highly enantioselective modification of sulfonamides is disclosed. The reaction proceeds under mild conditions with broad substrate scope, wide functional group tolerance, and good to excellent yields. When multiple sulfonamides or amines are present in the same molecule, the reaction occurs in a highly chemo-selective manner. Application of our method allows for selective modification of sulfonamide-containing drug molecules to form the corresponding phthalidyl derivatives as potential prodrugs. Experimental observations and DFT calculations suggest that the reaction proceeds *via* a stepwise addition pathway, assisted by $Li^+$ ions or protons. Non-covalent interactions, such as cation–π interactions, play important roles in enhancing the reactivity and controlling the enantioselectivity of the reaction.

## 1. Introduction

Sulfonamides are common functional moieties in organic molecules with applications in medicine and many other areas.[1] A sizeable number of top-selling pharmaceuticals and molecules in the WHO's list of essential drugs contain sulfonamide moieties. Shown in Fig. 1a are several examples of sulfonamide-containing drugs, including hydrochlorothiazide,[2] macitentan,[3] sulfamethoxazole,[4] pazopanib,[5] and gliclazide.[6] For instance, hydrochlorothiazide is a diuretic medication for the treatments of high blood pressure, congestive heart failure, diabetes insipidus, and renal tubular acidosis.[2] These sulfonamide moieties often behave as critical functional groups in bioactive molecules.[7] It is also established that further synthetic transformations of sulfonamides prepared from ammonia and primary amines can offer new structures and properties.[8] For medicinal molecules, synthetic modifications of the sulfonamide moieties can provide potential prodrugs with enhanced performance and/or altered pharmacological properties. One such method is to react sulfonamides with phthalaldehydic acid derivatives (such as 3-bromophthalides)

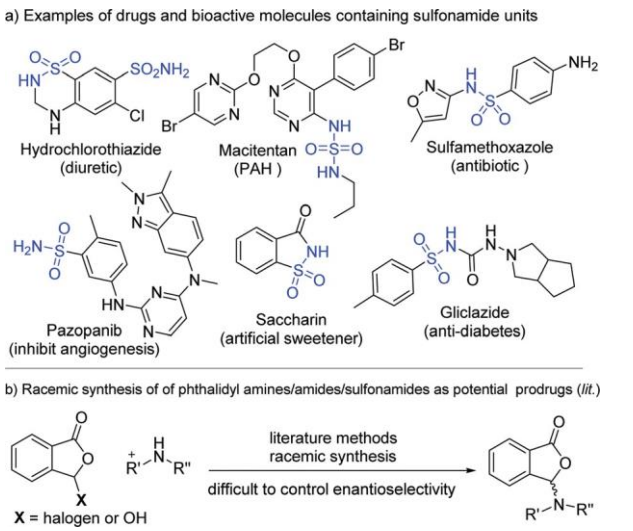


Fig. 1 Sulfonamide drugs and the common racemic modification.

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to form the corresponding phthalidyl sulfonamides (Fig. 1b).[9b] Unfortunately, with these present approaches it is difficult to control the enantioselectivity of the newly formed chiral center in the phthalidyl derivatives.[9]

Here we disclose an enantioselective modification of sulfonamides through a reaction with dialdehydes to afford optically enriched phthalidyl sulfonamides under N-heterocyclic carbene (NHC) organocatalysis (Fig. 2). DFT calculation suggests that this transformation proceeds *via* a stepwise process. Non-covalent interactions of the $Li^+$ ion with catalyst-activated substrates are believed to play important roles in facilitating this reaction and controlling its enantio-selectivity. The operationally stable while physiologically labile phthalidyl units in our products have found proven applications in prodrugs.[10] Our study constitutes the first enantioselective preparation of chiral phthalidyl amines/sulfonamides. It allows for facile modification of a diverse set of sulfonamides, including several commercial drug molecules.[11] Preliminary *in vitro* bioactivity evaluations show that phthalidyl sulfamethoxazole offers enhanced antibacterial activities, when compared to the unmodified sulfamethoxazole.

## 2. Results and discussion

We initiated our studies using phthalaldehyde 1a and *N*-phenylbenzene sulfonamide 2a as the model substrates in the presence of DQ oxidant[12] to search for suitable conditions (Table 1). We first used dichloromethane as the solvent and DBU as the base (entries 1–6). We examined amino acid-derived triazolium A [13] as the NHC pre-catalyst and found the formation of the proposed product 3a in 77% yield and 46 : 54 er (entry 1). We then examined aminoindanol-derived NHC pre-catalysts (B to F). The aminoindanol-derived pre-catalyst with an *N*-phenyl substituent (B)[14] led to 3a with an excellent yield, albeit with a very low 53 : 47 er value (entry 2). Introducing a methyoxyl unit on the *para*-position of the *N*-phenyl unit of B (to get catalyst C)[15] gave the product in 88% yield and a slightly improved er (60 : 40 er, entry 3). A large increase in er value (16 : 84 er) was obtained when the NHC pre-catalyst with a *N*-pentafluorophenyl substituent (D)[16] was used (entry 4). A slightly improved result (14 : 86 er) was obtained when a pre-catalyst (E)[17] with an *N*-mesityl substituent was used (entry 5). Both pre-catalysts D and E led to lower yields. When NHC pre-catalyst F [18] with a *N*-trichlorophenyl group was used, the reaction gave 3a in 92% yield and 86 : 14 er (entry 6). We next studied the effect of bases (entries 7 and 8) and found that the use of $LiOH{\cdot}H_2O$ as the base could significantly improve the er value of 3a to 99 : 1 with 92% yield (entry 8). Other solvents such as $PhCF_3$ and THF were also examined; a relatively small loss in yields or er values was observed (entries 9 and 10). The critical role of the $Li^+$ ion (LiOH as the base) in enhancing the reaction enantioselectivity is unravelled using DFT calculations (*vide infra*).

With the optimized conditions in hand, we move to explore the substrate scope with respect to different aryl amine-derived sulfonamides (Scheme 1). The absolute configuration of 3a was confirmed *via* single crystal X-ray analysis. Sulfonamide

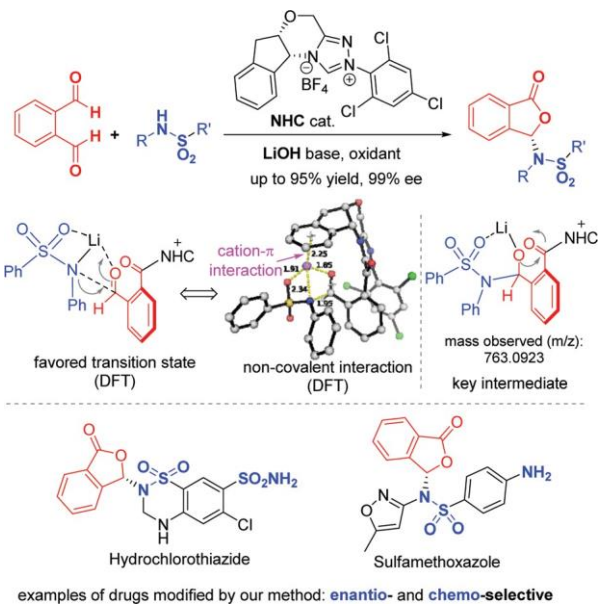
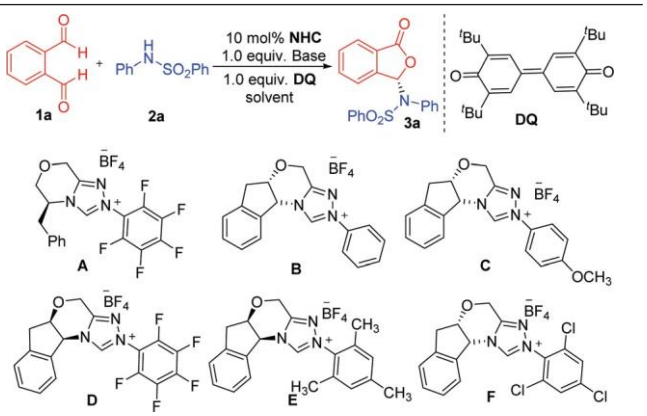


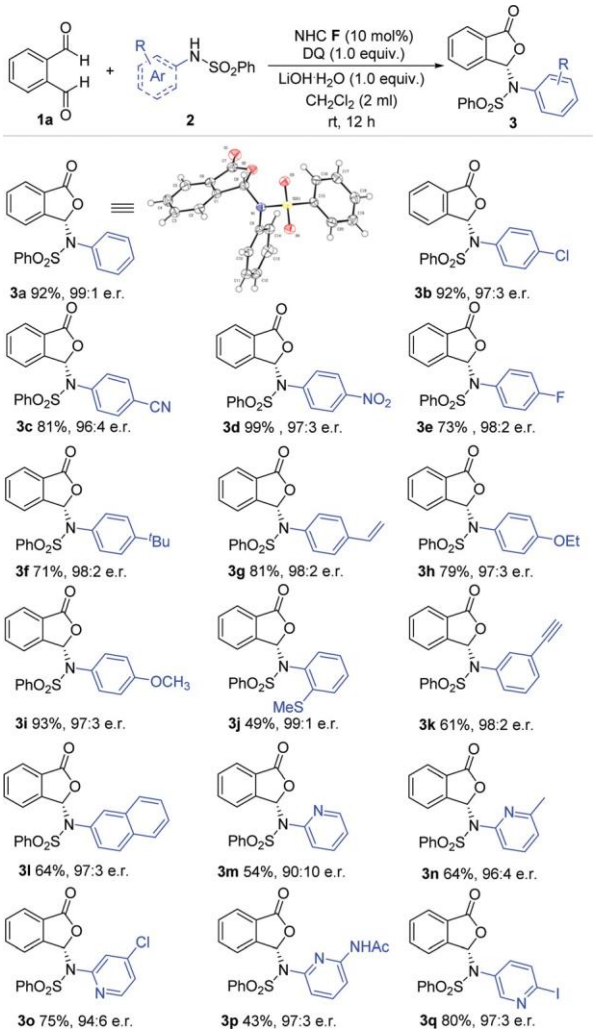

Fig. 2 NHC-catalyzed enantioselective synthesis of phthalidyl sulfonamides (this work).

Table 1 Optimization of reaction conditions[a]




| Entry | NHC | Base | Solvent | Yield (%) | er |
|---|---|---|---|---|---|
| 1 | A | DBU | $CH_2Cl_2$ | 77 | 46 : 54 |
| 2 | B | DBU | $CH_2Cl_2$ | 84 | 53 : 47 |
| 3 | C | DBU | $CH_2Cl_2$ | 88 | 60 : 40 |
| 4 | D | DBU | $CH_2Cl_2$ | 66 | 16 : 84 |
| 5 | E | DBU | $CH_2Cl_2$ | 68 | 14 : 86 |
| 6 | F | DBU | $CH_2Cl_2$ | 92 | 86 : 14 |
| 7 | F | $Cs_2CO_3$ | $CH_2Cl_2$ | 79 | 96 : 4 |
| 8 | F | $LiOH{\cdot}H_2O$ | $CH_2Cl_2$ | 92 | 99 : 1 |
| 9 | F | $LiOH{\cdot}H_2O$ | $PhCF_3$ | 80 | 97 : 3 |
| 10 | F | $LiOH{\cdot}H_2O$ | THF | 74 | 92 : 8 |

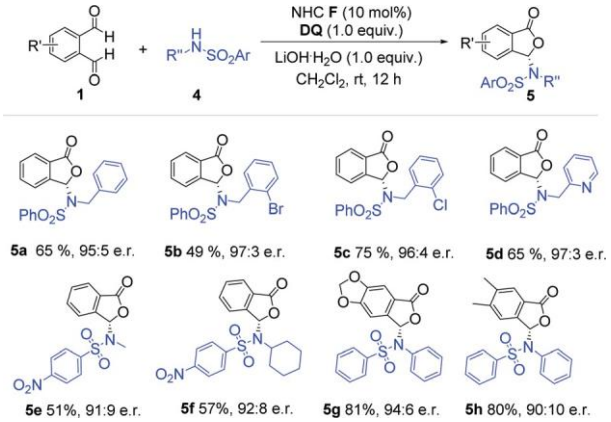
[a] Reaction conditions: 1a (1.0 equiv.), 2a (1.5 equiv.), NHC (0.1 equiv.), base (1.0 equiv.), DQ (1.0 equiv.) = 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone, solvent (2 mL). DBU = 1,8-diazabicyclo [5.4.0] undec-7-ene. Yields were isolated yields after $SiO_2$ column chromatography. The er was determined *via* chiral-phase HPLC analysis.




Scheme 1 Examples of aryl amine-derived sulfonamides. Reaction conditions: 1a (1.0 equiv.), sulfonamides (1.5 equiv.), NHC F (10 mol%), DQ (1.0 equiv.), $CH_2Cl_2$ (2 mL), 12 h. DQ = 3,3',5,5'-tetra-*tert*-butyldiphenoquinone. e.r. = enantiomeric ratio. Yields were isolated yields after $SiO_2$ column chromatography. The e.r. was determined *via* chiral-phase HPLC analysis. 3a: CCDC No. 2045331.†

containing different functional groups at the *para*-carbon of the phenyl ring were all well tolerated to furnish phthalidyl products (3b–i) with excellent enantiomeric ratios and good yields. These functional groups include halogen, cyano (–CN), nitro ($–NO_2$), alkoxy (–OR), alkyl, alkenyl and alkynyl units (3b–i). Installing substituents at both the *ortho* and *meta* positions ($–SCH_3$, –yne) of the phenyl ring led to a drop in the reaction yield but without diminishing the er value (3j, 3l). 2-Naphthylamine-derived sulfonamide was applied with 64% yield and 97 : 3 er (3m). It is also worth noting that pyridine amine-derived sulfonamides bearing various substituents and substitution patterns can fit in well with the present strategy (3n–3r).

We then moved to examine aliphatic amine-derived sulfonamides as substrates (Scheme 2). Aliphatic amine-based sulfonamides, especially *N*-benzyl substituted sulfonamides, afforded the desired product with high enantiomeric ratios

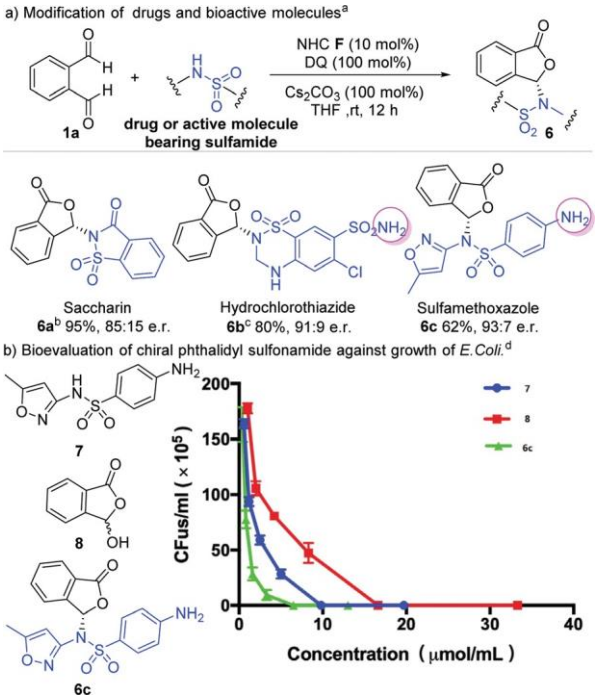



Scheme 2 Examples of alkyl amine-derived sulfonamides. Reaction conditions: 1 (1.0 equiv.), sulfonamides (1.5 equiv.), NHC F (10 mol%), DQ (1 equiv.), $CH_2Cl_2$ (2 mL), 12 h. DQ = 3,3',5,5'-tetra-*tert*-butyldiphenoquinone, er = enantiomeric ratio. Yields were isolated yields after $SiO_2$ column chromatography. The er was determined *via* chiral-phase HPLC analysis.

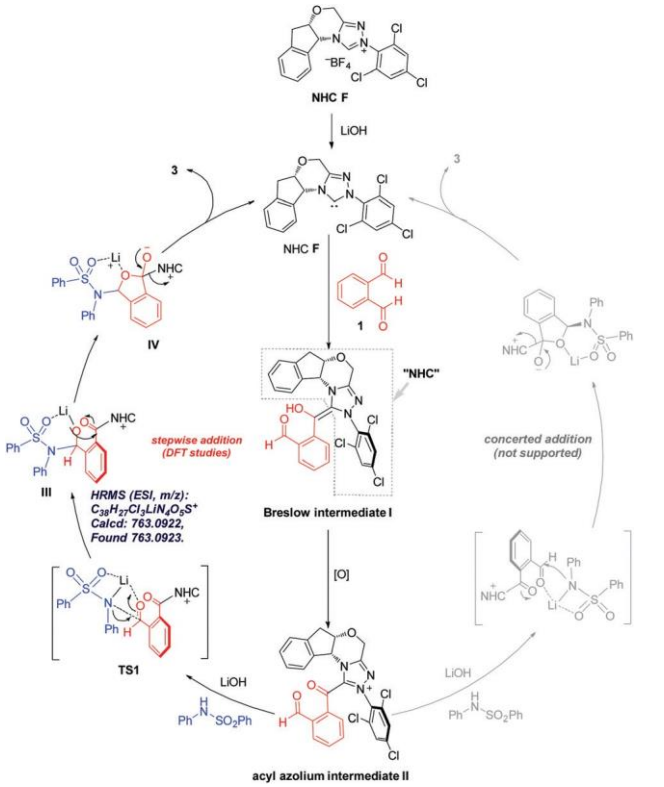
and good yields (5a–5d). Halogen atoms on the phenyl ring were tolerated under our reaction conditions (5b–5c). The sulfonamide derivative from 2-(aminomethyl) pyridine also gave the desired phthalide derivative (5d) with high er value and good yield. When sulfonamides derived from methylamine and cyclohexylamine were used, the corresponding products (5e and 5f) were obtained with suppressed yields and er values (51% yield, 91 : 9 er for 5e; 57% yield, 92 : 8 er for 5f). Phthalaldehyde bearing substituents (5g–5h) did not significantly affect the reaction outcome.

We next explored the use of our method for enantioselective modification of sulfonamide-containing food additives and drug molecules (Scheme 3). Saccharin is an artificial sweetener and could be modified with our method to give the corresponding phthalidyl sulfonamide 6a in 95% yield and 85 : 15 er. Hydrochlorothiazide is a diuretic medicine for the treatment of high blood pressure and swelling due to fluid buildup.[2] This drug molecule could be converted to the phthalidyl derivative 6b with 80% yield and 91 : 9 er. Similarly, the antibiotic sulfamethoxazole could be modified to give 6c with 62% yield and 93 : 7 er. Remarkably, pre-protection of free amino groups in these molecules (hydrochlorothiazide and sulfamethoxazole) is not required. Our reaction selectively proceeded on one sulfonamide moiety without affecting the amine group (6b and 6c). In addition, when two sulfonamide moieties were present in the same molecule (hydrochlorothiazide), a product with selective reaction on the secondary amine-derived sulfonamide was observed (6b). This unusual chemo-selectivity, resulting from a complicated process involving multiple reversible reactions of these amine/sulfonamide groups, further highlights the robust features of our strategy.

We performed a preliminary antibiotic evaluation of our modified phthalidyl sulfamethoxazole 6c against the growth of *E. coli*.[19] The hydroxyphthalide 7 and unmodified sulfamethoxazole 8 were tested as controls. The MIC (minimum inhibitory




Scheme 3 Modification of bioactive sulfonamides and preliminary bioactivity evaluation. Reaction conditions: 1a (1.0 equiv.), sulfonamides (1.5 equiv.), NHC F (10 mol%), DQ (1.0 equiv.), $Cs_2CO_3$ (1.0 equiv.), THF (2 mL), 12 h. DQ = 3,3',5,5'-tetra-*tert*-butyldiphenoquinone, er = enantiomeric ratio. Yields were isolated yields after $SiO_2$ column chromatography. The er was determined *via* chiral-phase HPLC analysis. [a] LiCl (1.0 equiv.) was added as the additive. [b] Replace $Cs_2CO_3$ with $Et_3N$, 0 °C, 24 h. [c] Bioevaluation of chiral phthalidyl sulfonamides against the growth of *E. coli* ($n$ = 3 biological replicates, mean ± SD). MIC values for 6c, 7 and 8 were 6.5 μmol $mL^{-1}$, 9.9 μmol $mL^{-1}$ and 16.7 μmol $mL^{-1}$, respectively.




Scheme 4 Postulated reaction mechanism.

concentration) value (6.5 μmol $mL^{-1}$) of our product 6c was found to be much lower than those of compounds 7 and 8 (MIC 9.9 μmol $mL^{-1}$ and 16.7 μmol $mL^{-1}$ respectively).

To elucidate the reaction pathway (Scheme 4) and unravel the origin of stereoselectivity of the present transformation, density functional theory (DFT) calculations were performed at the SMD($CH_2Cl_2$)-M06-2X/def2-TZVP//SMD($CH_2Cl_2$)-M06-2X/def2-SVP level of theory. The basis for the formation of Breslow intermediate (I) from the NHC catalyst F and the aldehyde substrate (1) has been previously established.[20] This intermediate (I) is then oxidized by DQ to generate acyl azolium intermediate II that can be detected experimentally *via* high-resolution mass spectrometry. Intermediate II can undergo either concerted addition (not supported) or stepwise addition (supported by DFT studies) to yield the cyclized product (*vide infra*).

Computational results pinpoint the importance of the $Li^+$ ion in affecting the observed enantioselectivity through the formation of cation–π interactions in key intermediates and transition states (Fig. 3). Two key conformers of acyl azolium intermediate II were found ((*Si*)-II and (*Re*)-II, Fig. 3; see ESI section V.1† for detailed conformational sampling). We note that for each conformer, only one face of the carbonyl group is open to attack by the incoming nucleophile as the other face is shielded from attack by forming π–π interactions between the aromatic ring of II and the 2,4,6-trichlorophenyl moiety of the NHC ligand. In the absence of the $Li^+$ ion (see ESI section V.2† for a detailed mechanism), the negatively charged N-atom of the deprotonated sulfonamide attacks the carbonyl group of acyl azolium intermediate II without any appreciable barrier and with concomitant cyclization as the resulting carboanion attacks the adjacent carbonyl group without any barrier (Fig. S4†). This implies that in the absence of the $Li^+$ ion, the cylization product forms immediately, whose product distribution will be determined by the thermodynamic stabilities of the reacting conformers of intermediate II ((*Si*)-II more stable). This mechanism predicts an er in favor of the (*R*)-phthalidyl sulfonamide product as 99.5 : 0.5 (Fig. S5†); thus, such a mechanism is unlikely in the present transformation. In the presence of the $Li^+$ ion, the addition proceeds in a stepwise manner.

According to the "energetic span model",[21] the $Li^+$ ion complexes with intermediate II to give the turnover frequency (TOF)-determining intermediate (TDI) (*Re*)-II···LiNR2 that is stabilized by the favorable $Li^+$ cation–π interaction (absent in (*Si*)-II···LiNR2; Fig. S7†), thus reversing the thermodynamic favorability for (*Si*)-II in the absence of cation coordination to (*Re*)-II in the presence of cation coordination. The addition to the *Re*-face is now favored by 5.3 kcal $mol^{-1}$ due to more favorable NCIs (non-covalent interactions) arising from the coordination of the $Li^+$ ion to the aromatic ring in (*Re*)-TS1. This cation–π interaction exists in all transition states and inter-

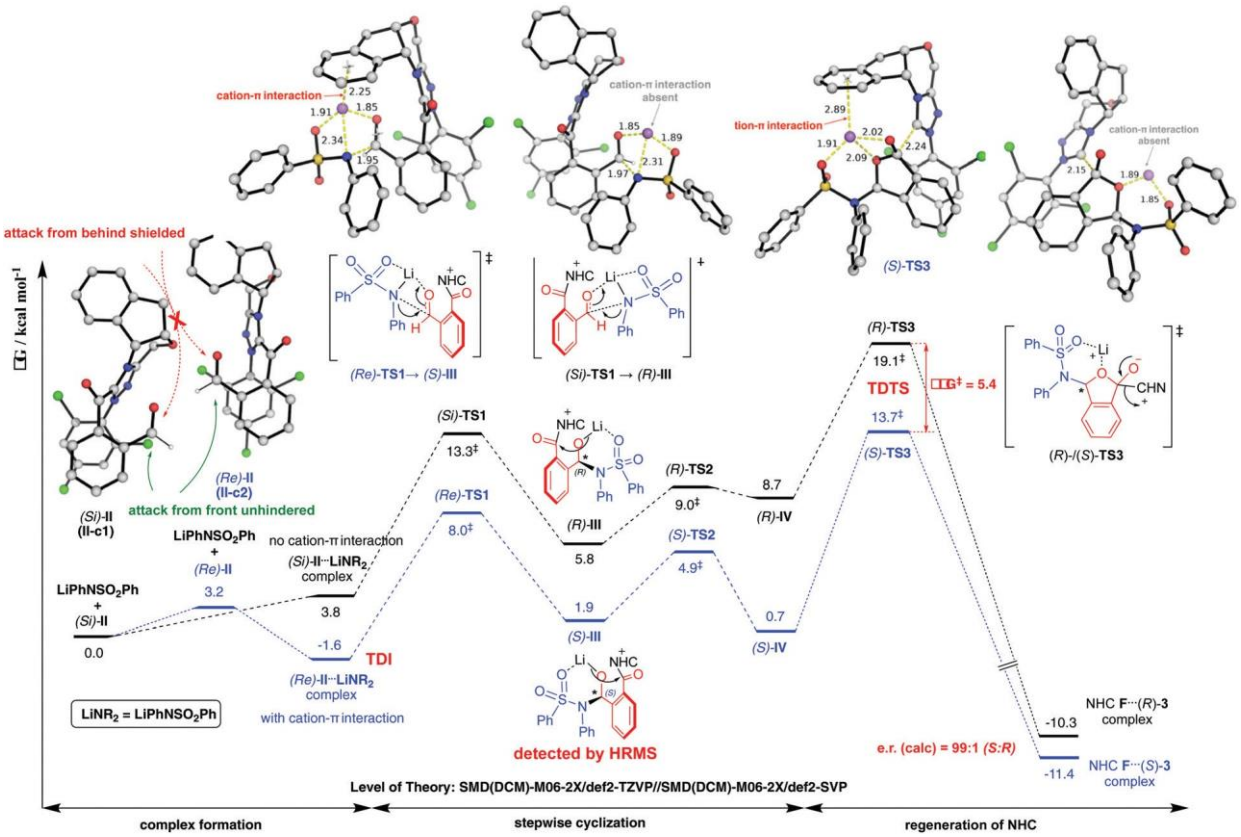



Fig. 3 Gibbs energy profile computed at the SMD($CH_2Cl_2$)-M06-2X/def2-TZVP//SMD($CH_2Cl_2$)-M06-2X/def2-SVP level of theory for the reaction between NHC-bound intermediate II and lithium sulfonamide. Key DFT-optimized structures are given with key bond distances in Å. TDI = turnover frequency-determining intermediate; TDTS = turnover frequency-determining transition state.

mediates for the favored pathway ((*Re*)-TS1, (*S*)-III/IV, (*S*)-TS2/TS3). The TDTSs are the regeneration of the NHC catalyst (*S*/*R*-TS3) with a barrier difference of 5.4 kcal $mol^{-1}$ in favor of the (*S*)-phthalidyl sulfonamide product formation (calculated er of 99.9 : 0.1; Fig. 3), in excellent quantitative agreement with the experimental observation (entry 8, Table 1). We highlight the important role of the $Li^+$ ion in facilitating a stepwise addition, allowing highly enantioselective cyclization to occur that could not be possible in the absence of cation participation (concerted, barrierless direct cyclization of the most thermodynamically stable (*Si*)-II conformer). We further note that the overall energetic span of 15.3 kcal $mol^{-1}$ is consistent with the high yield observed at room temperature. The important role of the $Li^+$ ion is further evidenced by the fact that its replacement by ( protonated) DBU reduces the enantioselectivity (entry 6, Table 1) due to DBU's less coordinating nature than the $Li^+$ ion (see ESI section V.5†).

## 3. Conclusions

In summary, we have developed a new approach for highly enantio- and chemo-selective modification of sulfonamides. The reaction starts with the addition of a carbene catalyst to one aldehyde moiety of phthalaldehyde as the initial step. The subsequent oxidation and a number of stepwise additions with sulfonamides furnish the corresponding phthalidyl sulfonamides with excellent yields and enantioselectivities. The possible reaction pathways were investigated *via* both experimental and DFT calculation methods, and non-covalent interactions (such as cation-π interactions) are believed to play crucial roles in promoting high enantioselectivities. Our new method uses mild conditions and tolerates various functional groups. Sulfonamide-containing drug molecules can be selectively modified to form the corresponding phthalidyl derivatives as potential prodrugs. Further explorations of our mechanistic observations for new catalysis development and applications of our methods in bioactive molecule modifications are in progress in our laboratories.

## Conflicts of interest

There are no conflicts to declare.

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