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Graphical Abstract

HBF_4•DEE-catalyzed formation of sulfinyl imines: synthesis and mechanistic studies

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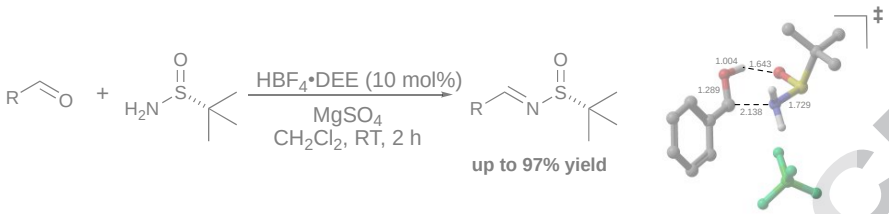

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HBF_4•DEE-catalyzed formation of sulfinyl imines: synthesis and mechanistic studies

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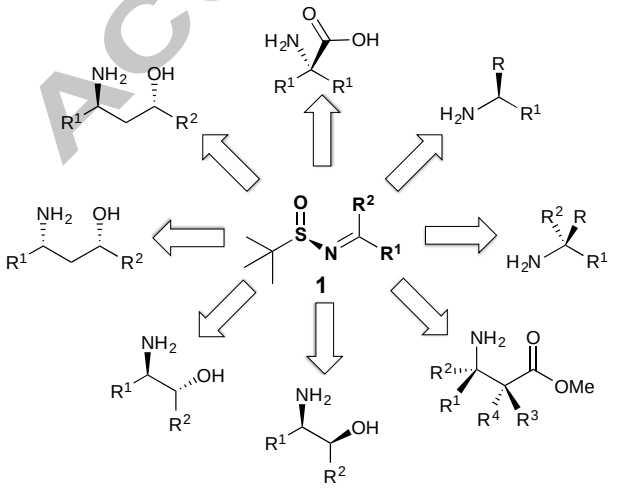
ABSTRACT

A mild acid-catalysed method is reported for the formation of sulfinyl imines from *tert*-butanesulfinamide and aromatic or aliphatic aldehydes using tetrafluoroboric acid diethyletherate (10 mol%) in dichloromethane. Reactions were performed at room temperature and gave the corresponding sulfinyl imines in excellent yield after 2 hours. A DFT study was performed and a mechanism for the reaction is postulated.

1. Introduction

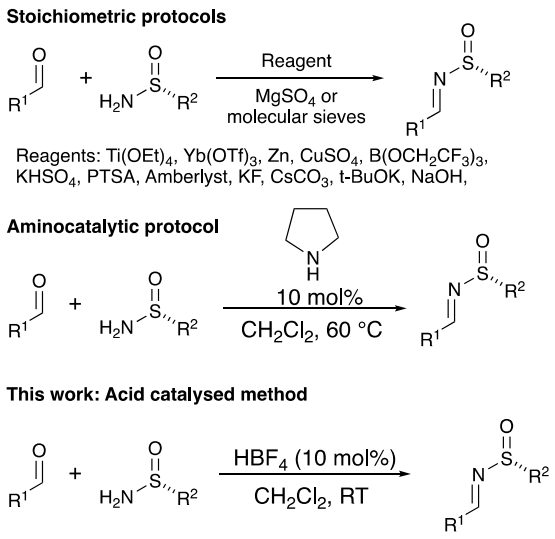
Chiral sulfinamides function as amine equivalents and have been used as versatile chiral auxiliaries in asymmetric synthesis.[1-3] The sulfinamide reagent, usually *tert*-butanesulfinamide, reacts with aldehydes and ketones to provide *tert*-butanesulfinyl imines in high yields. These imines can then react with different classes of nucleophiles where the *tert*-butanesulfinyl moiety acts as a chiral directing group giving products with high stereoselectivity. *tert*-Butanesulfinyl imines have been used in the asymmetric synthesis of many versatile building blocks, including *syn*- and *anti*- 1,2- or 1,3-amino alcohols,[4-8] α-branched and α,α-dibranched amines,[9,10] and α- or β-amino acids and esters.[11-14]



Scheme 1. Overview of strategies utilising the *tert*-butanesulfinyl moiety as a chiral auxillilary.[4-14]

As a result, *tert*-butanesulfinyl imine based strategies have recently been utilized in several total syntheses, providing high levels of stereoselectivies.[15-18]

The most common method to prepare sulfinyl imines from aldehydes and ketones is to use an excess of titanium(IV) alkoxide.[19,10] Alternative methods applying weak protic or Lewis acids, such as Amberlyst,[20] pyridinium *p*-toluene sulfonate,[21] $Yb(OTf)_3$,[22] and $CuSO_4$,[3] have been developed for the synthesis of aldimines, however they usually require stoichiometric amounts of reagent, extensive heating or a large excess of the reacting aldehyde (Scheme 2).



Scheme 2. Lewis acid, aminocatalytic and Brönsted acid promoted protocols for the formation of *tert*-butanesulfinyl imines.

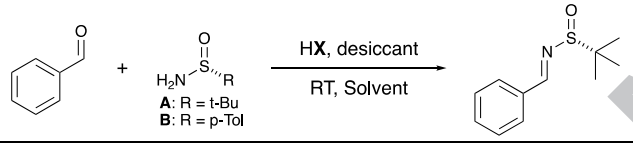
Recently, Cid and co-workers reported an aminocatalytic method for the formation of sulfinyl imines from aldehydes.[23] The use of catalytic pyrrolidine and equimolar amounts of the sulfinamide and aldehyde at 60 °C, provided the corresponding sulfinyl imine in excellent yield (Scheme 2).

In an effort to expand the applicability of the use of sulfinyl imines in asymmetric synthesis, we aimed to develop a mild and highly efficient acid-catalyzed protocol for the formation of sulfinyl imines from sulfinamides and aldehydes which operates with short reaction times and at room-temperature.

2. Results and Discussion

Since the N-S bond of the *N*-sulfinyl group is commonly cleaved by treatment with strong acids such as hydrochloric acid in the presence of water,[3] most of the previous acid promoted transformations have used weak acids, often in stoichiometric amounts and under reflux conditions, in order to form sulfinyl imines from aldehydes (Scheme 2).

Table 1.
Screening of different acids and additives for the formation of the sulfinyl imine from benzaldehyde and *tert*-butanesulfinamide.[a]



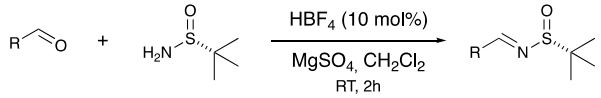
Entry	HX (mol %)	R	Desiccant (equiv.)	Solvent	Conv. (%)
1	HBF_4 (10)	A	4Å MS	Toluene[b]	66
2	AcOH (10)	A	4Å MS	Toluene[b]	0
3	$MeSO_3H$ (10)	A	4Å MS	Toluene[b]	46
4	*p*-NO_2-$PhCO_2H$ (10)	A	4Å MS	Toluene[b]	0
5	HBF_4 (10)	A	$MgSO_4$ (1)	Toluene[b]	69
6	HBF_4 (10)	A	$MgSO_4$ (1)	Toluene[c]	80
7	$MeSO_3H$ (10)	A	$MgSO_4$ (1)	Toluene[c]	61
8	HBF_4 (10)	A	$MgSO_4$ (1)	CH_2Cl_2	89
9	HBF_4 (10)	A	$MgSO_4$ (1)	Et_2O[c]	68
10	HBF_4 (10)	A	$MgSO_4$ (1)	EtOH[c]	17
11	HBF_4 (10)	A	$MgSO_4$ (1)	MeCN[c]	38
12	HBF_4 (5)	A	$MgSO_4$ (1)	CH_2Cl_2	71
13	HBF_4 (2.5)	A	$MgSO_4$ (1)	CH_2Cl_2	50
14	HBF_4 (1)	A	$MgSO_4$ (1)	CH_2Cl_2	21
15	HBF_4 (5)	A	$MgSO_4$ (3)	CH_2Cl_2	61
16	HBF_4 (10)	A	$MgSO_4$ (3)	CH_2Cl_2	88
17	HBF_4 (5)	A	$MgSO_4$ (5)	CH_2Cl_2	68
18[d]	HBF_4 (10)	A	$MgSO_4$ (1)	CH_2Cl_2	94
19[e]	HBF_4 (10)	B	$MgSO_4$ (1)	CH_2Cl_2	37 (48)[e]

[a] Reagents and conditions: benzaldehyde (0.25 mmol, 0.25 M), (*R*)-*tert*-butanesulfinamide (0.275 mmol), magnesium sulphate (0.25 mmol), HBF_4•DEE (10 mol%), 2 h, rt. [b] 5% THF as co-solvent. [c] 5% CH_2Cl_2 as co-solvent. [d] Benzaldehyde (1.0 M). [e] After 18 h.

Therefore, we were delighted to note that catalytic amounts of tetrafluoroboric acid diethyletherate (HBF_4•DEE, 10 mol%, 25 µl from a 0.5 M stock solution in THF) in the presence of molecular sieves (4 Å) promoted the reaction between benzaldehyde and *tert*-butanesulfinamide to form **1a** (66% conv.) at room temperature in only 2 h (Table 1, entry 1). Weaker organic acids, such as acetic acid or *p*-nitrobenzoic acid, did not promote the reaction (Table 1, entries 2 and 4), while methane sulfonic acid promoted the reaction with lower conversion (46%, Table 1, entry 3). The molecular sieves could be replaced with magnesium sulfate giving similar conversion (69%, Table 1, entry 5). With a stock solution in CH_2Cl_2, the conversion was increased significantly (80% conv., Table 1, entry 6) and changing the solvent completely to CH_2Cl_2 led to a further increase of the conversion (89%, Table 1, entry 8). The use of other solvents (Et_2O, EtOH, MeCN, Table 1, entries 9-11) led to a decrease in conversion compared to toluene and CH_2Cl_2. Lower catalyst loading (1, 2.5 and 5 mol%, Table 1, entries 12-14) led to a significantly lower conversion after two hours. An increased amount of $MgSO_4$ was added in order to drive the reaction to completion, but no noteworthy change in conversion was observed (Table 1, entries 15-17). At higher concentration of the reaction mixture (1.0 M compared to 0.25 M) an increase in conversion to the sulfinyl imine was achieved (94%, Table 1, entry 18). The formation of the sulfinyl imine from *p*-toluenesulfinamide was less effective compared to the *tert*-butanesulfinamide, giving the product in only 37% yield after two hours and only 48% yield after extended reaction time (Table 1, entry 19). Unfortunately, the reaction between *tert*-butanesulfinamide and ketones (e.g. acetophenone) did not yield the corresponding sulfinyl imine.

With the optimized reaction conditions in hand, we set out to investigate the synthetic utility and substrate scope of the reaction. The parent benzaldehyde was easily converted to sulfinyl imine **1a** (93%) in excellent isolated yield after two hours at room temperature and a similar result was obtained for the bulkier 1-naphthaldehyde (Table 2, entries 1 and 2).

Table 2.
Substrate scope for sulfinyl imine formation from aliphatic and aromatic aldehydes and *tert*-butanesulfinamide.[a]



Entry	R	Product	Isolated yield (%)
1	Ph	**1a**	93
2	1-naphthyl	**1b**	88
3	4-nitrophenyl	**1c**	94
4	3-nitrophenyl	**1d**	97
5	4-cyanophenyl	**1e**	91
6	3-methoxyphenyl	**1f**	92
7	salicyl	**1g**	93
8	3-bromophenyl	**1h**	97
9	2-furyl	**1i**	82
10	3-phenylpropionyl	**1j**	94
11	cyclohexyl	**1k**	91
12	*tert*-butyl	**1l**	92
13	1-cyclohexene	**1m**	94

14	(*S*)-*N*-Boc-2-phenethyl	**1o**	83

[a] Reagents and conditions: benzaldehyde (0.25 mmol, 1.0 M), (*R*)-*tert*-butanesulfinamide (0.275 mmol), magnesium sulphate (0.25 mmol), HBF_4•DEE (10 mol%), CH_2Cl_2 (0.25 mL), 2 h, rt.

Aromatic aldehydes with electron withdrawing substituents, such as nitro and cyano groups, in the *para*- and *meta*-position, and electron donating substituents, such as 3-methoxy and 2-hydroxy, were also converted to the corresponding imine products in excellent yields (Table 2, entries 3-7). The bromo-substituted substrate gave sulfinyl imine **1h** in excellent yield, while a slightly lower yield was observed for the more electron-rich, heteroaromatic furfural (82%, Table 2, entries 8 and 9). On the other hand, the aliphatic 3-phenylpropionaldehyde gave an excellent yield (Table 2, entry 10), showing that the potential side-reaction of enolization is not interfering in formation of the product. Aliphatic secondary, tertiary and α,β-unsaturated aldehydes gave the corresponding sulfinyl imines in excellent yields (Table 2, entries 11-13), which contrasts with the amino catalytic method by Cid and co-workers[23] for aliphatic aldehydes that requires extended reaction times and excess aldehydes. Finally, the sulfinyl imine from *N*-Boc-L-phenylalaninal (Table 2, entry 14) was successfully isolated in 83% yield without epimerization of the stereocenter in the α-position (see ESI). In addition, it has previously been reported that acids in the presence of the tetrafluoroborate counterion can cause epimerization on the stereogenic sulfur.[24] However, no epimerization was observed during the reaction as confirmed *via* chiral column HPLC (see ESI).

1.1. Computational studies of the mechanism of the HBF_4•DEE-catalyzed formation of sulfinyl imines.

In order to understand the mechanism of the HBF_4•DEE-catalyzed formation of sulfinyl imines, we performed a computational study using DFT. To begin with, we investigated the initial state of HBF_4•DEE in order to understand the activation mode of the acid. The optimization of HBF_4•DEE at the M062X/6-311+(d,p) level of theory, with the inclusion of solvent effects (CPCM, UFF, dichloromethane), show that the proton is significantly shifted towards the oxygen on the diethyl ether, which indicates that the initial acid in dichloromethane is the protonated diethyl ether with tetrafluoroborate as the counterion (Fig. 1A). In order to determine the initial state of the different components of the reaction mixture, we optimized and compared the stability (ΔΔG) of HBF_4•DEE-protonated benzaldehyde (Fig. 2B) and protonated *tert*-butanesulfinamide (Fig. 1C and D). The result show that protonation of the benzaldehyde by HBF_4•DEE is an unfavored process (+4.67 kcal mol^{-1}, Fig. 1B), while protonation on the sulfinamide nitrogen is only slightly favored (-1.38 kcal mol^{-1}, Fig. 1C). The most stable species on the Gibbs free energy surface, and presumably in the reaction mixture, was the *O*-protonated sulfinamide (Fig. 1D), which was stabilized with -10.5 kcal mol^{-1} compared to the HBF_4•DEE. This suggests that *O*-protonated sulfinamide is the initial state in the reaction mixture.

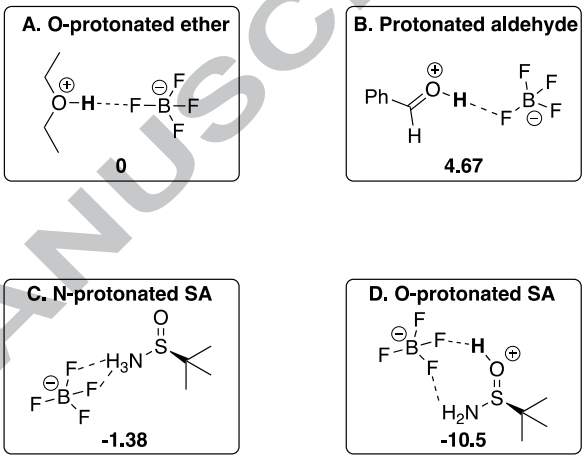


Figure 1. Gibb's free energies of the different protonated species; A) HBF_4•DEE; B) protonated aldehyde, C) *N*-protonated sulfinamide; D) *O*-protonated sulfinamide in dichloromethane at the M062X/6-311+G(d,p)–CPCM (CH_2Cl_2, UFF) level of theory.

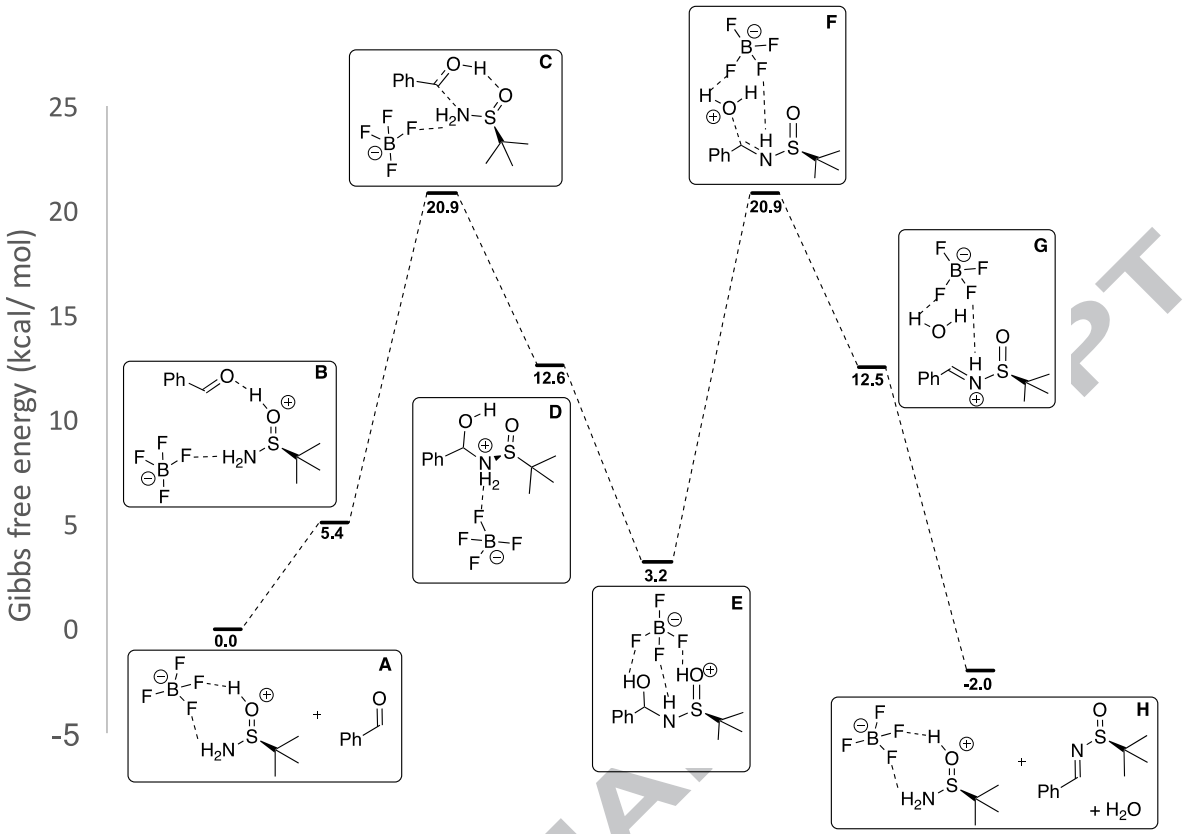


Figure 2. Gibbs free energy diagram for HBF4•DEE-catalyzed formation of the sulfinyl imine at the M062X/6-311+G(d,p)–CPCM (CH_2Cl_2, UFF) level of theory.

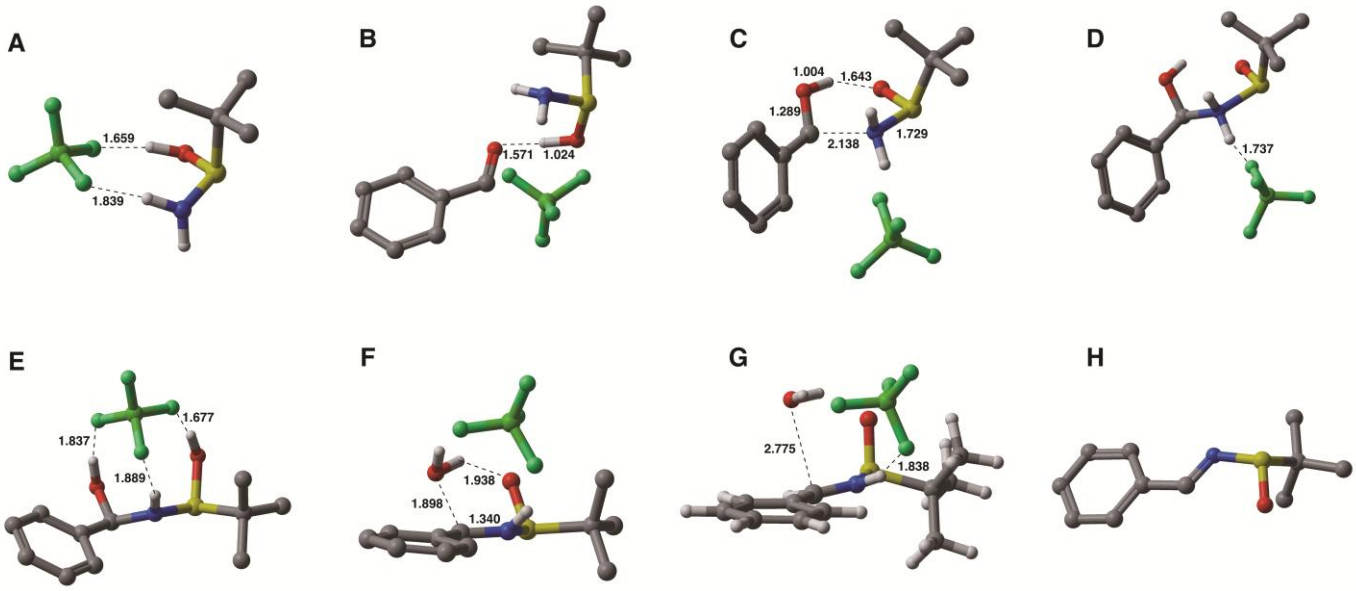


Figure 3. Geometries of minima and transitions states (A-F) on the M062X/6-311+G(d,p) –CPCM (CH_2Cl_2,UFF) level of theory.

Next, we investigated the potential energy surface for the formation *tert*-butanesulfinyl imine from benzaldehyde and the *O*-protonated sulfinamide (Fig. 2). Starting from the protonated sulfinamide, we were able to locate the transition state (**C**) for the formation of the hemiaminal intermediate (**E**) that is 20.9 kcal mol^{-1} higher in Gibbs free energy than the free reactants (Fig. 2, **A** and **C**). In the six-membered chair-like transition state (**C**), the proton from the *O*-protonated sulfinamide is completely transferred to the aldehyde oxygen, while the C-N bond still is not formed (2.138 Å). Following the intrinsic reaction coordinate (IRC) to the reactant side leads to an unstable complex **B** (+5.4 kcal mol^{-1}) between the protonated sulfinamide, BF_4^-, and benzaldehyde. On the product side of the transition state, the *N*-protonated hemiaminal intermediate (**D**) is formed in an endothermic reaction (+12.6 kcal mol^{-1}). Proton transfer from the nitrogen to the more electronegative oxygen of the sulfinamide moiety leads to a large stabilization (from +12.6 to +3.2 kcal mol^{-1}), which is due to the three hydrogen bonds that are formed between the polar hydrogens and the BF_4^-–counterion (**E**). From complex **E**, dehydration occurs in a concerted transition state that suggests that the water molecule is leaving without the formation of an intermediate when the proton is transferred from the sulfinamide oxygen. In the transition state, the proton is completely transferred to the leaving water molecule as the C–O-

bond is breaking (1.898 Å) leading to the protonated sulfinyl imine and water (**G**, +12.5 kcal mol^{-1}). The last step in the catalytic cycle involves proton transfer from the protonated sulfinyl imine to the oxygen of another sulfinamide yielding the product in an overall exothermic process (-2.0 kcal mol^{-1}).

3. Conclusion

A rapid and convenient method was developed for the synthesis of *tert*-butanesulfinyl imines from aldehydes and *tert*-butanesulfinamide, catalyzed by HBF_4•DEE (10 mol%) in CH_2Cl_2 at room temperature in 2 h. Sulfinyl imines obtained from both aliphatic, differently substituted aromatic and α,β-unsaturated aldehydes were obtained in high isolated yields. A DFT-investigation suggests that the sulfinamide is protonated by HBF_4•DEE and the addition of sulfinamide occurs *via* a six-membered chair-like transition state. The Gibbs free energy of activation for this process is 20.5 kcal mol^{-1} and the overall reaction is exothermic with 2.0 kcal mol^{-1}.

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Research highlights

• A mild, efficient and catalytic method for the formation of sulfinyl imines is reported.

• A computational investigation gave insight into the mechanism of the reaction.

• Sulfinamide addition to aldehyde occurs via a six-membered transition state.