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Sulfinylimidates as Chiral Amide Equivalents for Irreversible, Asymmetric Aldol Reactions

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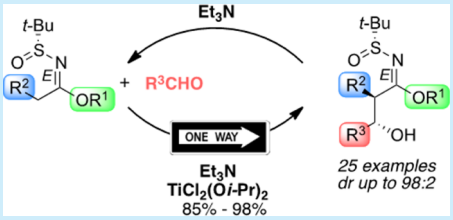
Supporting Information

ABSTRACT: A highly selective *N*-sulfinylimidate aldolization has been developed under mildly basic conditions leading to diastereopure products of high synthetic potential. The innate reversibility of this aldolization was suppressed by the use of titanium as the Lewis acid. An application of this methodology via the synthesis of a potential neurotransmitter reuptake inhibitor is illustrated.



tert-Butanesulfinamide, a chiral ammonia equivalent, exhibits very high levels of diastereocontrol in the addition of a large variety of nucleophiles to *tert*-butylsulfinylimines, which has led to numerous synthetic applications.[1] Conversely, the α-functionalization of *tert*-butylsulfinylimines has been less successful. Indeed, *N*-sulfinylaldimines are unsuitable for this transformation due to competing autocondensation during the deprotonation step.[2] This limitation was partially overcome using *N*-sulfinylimidates which undergo highly diastereoselective α-functionalization, so far limited to alkylation, Mannich-type, and Michael addition reactions under strong basic conditions.[3] Strikingly, the obvious and much more applicable condensation with an aldehyde has not been reported to date, despite the potential of these compounds as chiral amide equivalents to be complementary to e.g. chiral oxazolidinones (Figure 1).[4] The functionalized imidates produced from such a

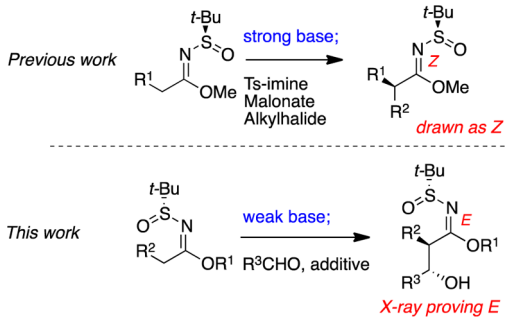


Figure 1. Context of this work.

reaction would represent versatile synthetic intermediates, readily converted into the corresponding esters or amides. Derivatives of this type of product are currently of significant interest for their potential activity as selective neurotransmitter reuptake inhibitors.[5] In addition, oxidation of the *N*-sulfinyl group yields *N*-sulfonylimidates, potentially useful pro-drugs,[6] and *N*-deprotection gives chiral imidate intermediates used in heterocycle synthesis.[7] Herein the development of a highly diastereoselective *N*-sulfinylimidate aldolization under mild conditions is reported.

Initially, the reaction of methyl (R_s)-*N*-*tert*-butylsulfinyl-2-phenylethanimidate[8] **1a** with benzaldehyde was studied. Deprotonation of the imidate **1a** with LiHMDS followed by the addition of benzaldehyde at low temperature gave very low conversion (Table 1, entry 1). Longer reaction times had no influence on the conversion, and raising the temperature resulted in complete recovery of the starting imidate **1a** (Table 1, entry 2). A range of different bases were then employed (KHMDS, *n*-BuLi, DBU, Et_3N, entries 3−6), but no improvement was observed. It was apparent at this stage that development of an *N*-sulfinylimidate aldolization would not be possible by simple extension of previous work.[3] The innate reversibility of the reaction and need for efficient control in the formation of two new stereocenters render it a significant challenge. Attempts to improve the nucleophilicity of the metalloenamine (DMPU, Table 1, entry 7), or the electrophilicity of the aldehyde ($BF_3{\cdot}OEt_2$, Table 1, entry 8), were unsuccessful. To prevent the reversibility of the reaction, stabilization of the aldol product by coordination to an oxophilic center was investigated: use of TMSOTf resulted only in degradation (Table 1, entry 9), but when $TiCl_4$ was employed trace formation of the desired product was observed (Table 1, entry 10). This titanium-promoted reaction turned out to be very sensitive to the amine base, and significant improvement in the efficiency of the reaction was gained by employing a milder base (triethylamine, Table 1, entry 11). Under these conditions the reaction proceeded with moderate diastereoselectivity to give two diastereoisomers (out of a potential four) in a 66% combined yield. The yield was further improved when $TiCl_2(O\textit{i}\text{-Pr})_2$ was utilized in the place of $TiCl_4$

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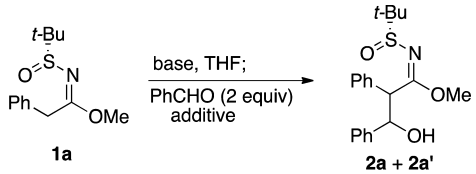
Table 1. Initial Aldol Reaction Attempts



entry	base[a]	additive (equiv)	t (°C)	result
1	LiHMDS	–	−78	*b*
2	LiHMDS	–	−78 to rt	NR[f]
3	KHMDS	–	−78 to rt	NR[f]
4	*n*-BuLi	–	−78 to rt	NR[f]
5	DBU[c]	–	rt	NR[f]
6	Et_3N[d]	–	rt	NR[f]
7	LiHMDS	DMPU (1)	−78 to rt	NR[f]
8	LiHMDS	$BF_3{\cdot}OEt_2$ (1.3)	−78 to rt	degradation
9	LiHMDS	TMSOTf (2)	−78 to rt	degradation
10	LiHMDS	$TiCl_4$ (1.5)	−78	trace product
11	Et_3N[e]	$TiCl_4$ (2)	0 to rt	66%, 60:40 dr
12	Et_3N[e]	$TiCl_2(Oi\text{-}Pr)_2$ (2)	rt	90%, 57:43 dr

[a]Unless otherwise indicated reactions employed 1.5 equiv of base. [b]20% conversion after 4 h; presumably a mixture of the four diastereoisomers (4:2:2:1). [c]0.05 equiv and 1.5 equiv of base tested. [d]3 equiv of base. [e]4 equiv of base. [f]No reaction, recovery of the starting imidate.

(Table 1, entry 12), although the moderate diastereoselectivity was unaltered.

Separation of the two crystalline diastereoisomers by column chromatography allowed assignment of their relative configuration by X-ray crystallography (Figure 2).[9] This analysis

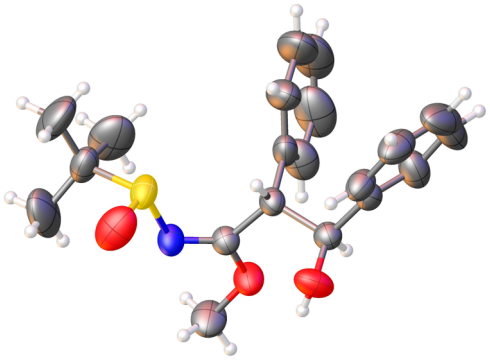
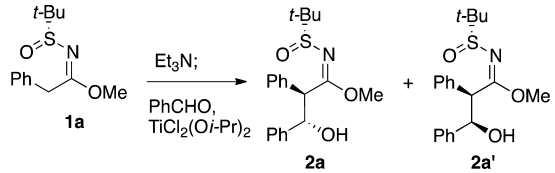


Figure 2. ORTEP of *E-N*-sulfinylimidate adduct **2a**.

indicated that the reaction proceeded with complete control of the face of attack of the imidate, as diastereoisomers **2a** and **2a′** possess the same configuration at the center α to the C=N bond. Interestingly, the X-ray analysis also showed an *E*-configuration for the sulfinylimidate, which has been shown as a *Z*-isomer in previous reports.[10] To the best of our knowledge, this is the first crystal structure of a *N*-sulfinylimidate derivative.[11]

Systematic optimization of the reaction parameters was undertaken in order to improve the diastereocontrol of the reaction (Table 2). The ratio of $TiCl_2(Oi\text{-}Pr)_2$ to benzaldehyde was highly important: changing from a 1:2 to 1:1 ratio substantially improved the diastereomeric ratio from 57:43 to 91:9 (Table 2, entries 1 and 2). Solvent screening revealed that the transformation proceeded at a faster rate in diethyl ether,

Table 2. Optimization of the Reaction Diastereoselectivity[a]



entry	PhCHO (equiv)	Ti[b] (equiv)	solvent	t (h)	conv[c] (yield)	dr (**2a**/**2a′**)
1	4	2	THF	18	100% (90%)	57:43
2	3	3	THF	18	100% (94%)	91:9
3	″	″	Et_2O	1	100%	86:14[d]
4	″	″	toluene	1	100%	89:11[d]
5	″	″	CH_2Cl_2	1	100% (96%)	91:9
6[e]	″	″	CH_2Cl_2	4	100%	91:9
7[f]	″	″	CH_2Cl_2	2 + 1	100%	91:9
8	1.5	3	CH_2Cl_2	2	100% (94%)	97:3

[a]All reactions run with 5.0 equiv of Et_3N except for entry 8, which was run with 4.0 equiv. [b]Ti = $TiCl_2(Oi\text{-}Pr)_2$. [c]Determined by ^1H NMR analysis of the crude reaction mixture. [d]Presence of four diastereoisomers in ^1H NMR spectrum of the crude reaction mixture; dr refers to major diastereoisomer/combined minor diastereoisomers. [e]Reaction performed at 0 °C. [f]Slow addition of a dichloromethane solution of $TiCl_2(Oi\text{-}Pr)_2$ and PhCHO *via* syringe pump over 2 h.

toluene, or dichloromethane (complete conversion after 1 h, Table 2, entries 3−5) than in tetrahydrofuran (complete conversion after 18 h, Table 2, entry 2). The reaction in dichloromethane gave the best selectivity, comparable to that of the reaction in tetrahydrofuran. Performing the reaction at 0 °C, or undertaking a slow addition of the aldehyde/$TiCl_2(Oi\text{-}Pr)_2$ solution, resulted in no further improvement in the selectivity (Table 2, entries 6 and 7). Finally, the best results were obtained in dichloromethane using a 2:1 ratio of $TiCl_2(Oi\text{-}Pr)_2$/PhCHO (Table 2, entry 8), which resulted in high diastereoselectivity (97:3) and enabled isolation of the major diastereoisomer in a 94% yield. Attempts to reduce the triethylamine, or $TiCl_2(Oi\text{-}Pr)_2$, to stoichiometic or substoichiometric quantities were unsuccessful, resulting in incomplete conversion of the starting imidate **1a**.

The scope of the reaction was next investigated (Table 3). Variation of the imidate[8] (R^1 or R^2) was successfully tolerated, and reactions with ethyl imidate **1b** (R^1 = Et), imidate **1c** (R^2 = *p*-MeO-C_6H_4), and imidate **1d** (R^2 = *p*-F-C_6H_4) proceeded with similar diastereoselectivities to those obtained with the methyl imidate **1a** to give comparable yields of the desired products **2** (Table 3, entries 2−6). The chloroalkylsubstituted imidate **1e** (R^2 = Cl) also reacted efficiently, with high diastereoselectivity,[12] although the formation of three diastereoisomers was observed (Table 3, entries 4, 10, and 13). The relative stereochemistry of **2c** was secured by X-ray analysis, as variation of the facial selectivity has been reported in the alkylation of α-alkyl and α-chloro imidates.[3b,d] A range of aldehydes were also well tolerated: reactions with aromatic aldehydes containing electron-withdrawing or -donating groups proceeded equally efficiently and with high diastereoselectivities (Table 3, entries 7−14). More sterically hindered aromatic aldehydes, bearing ortho substituents on the ring, were good substrates (Table 3, entries 14−16) as were those bearing halogens (Table 3, entries 17−21). Heterocyclic aldehydes

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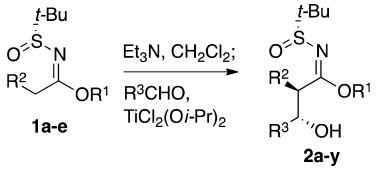
Table 3. Scope of the Sulfinylimidate Aldolization



entry	R^1	R^2	R^3	dr	yield[a]	2
1	Me	Ph	Ph	97:3	94%	**2a**
2[b]	Me	Ph	Ph	97:3	92%	***ent*-2a**
3	Et	Ph	Ph	97:3	92%[c]	**2b**
4[b]	Me	Cl	Ph	93:7	96%[c,d]	***ent*-2c**
5	Me	*p*-MeO-Ph	Ph	96:4	91%	**2d**
6	Me	*p*-F- Ph	Ph	95:5	90%	**2e**
7	Me	Ph	*m*-MeO-Ph	96:4	96%	**2f**
8[b]	Me	Ph	*m*-MeO-Ph	96:4	92%	***ent*-2f**
9	Et	Ph	*m*-MeO-Ph	97:3	97%	**2g**
10[b]	Me	Cl	*m*-MeO-Ph	94:6	94%[c,d]	***ent*-2h**
11	Me	Ph	*p*-NO_2-Ph	>98:2	96%	**2i**
12	Et	Ph	*p*- NO_2-Ph	>98:2	91%	**2j**
13[b]	Me	Cl	*p*- NO_2-Ph	92:8	96%[c,d]	***ent*-2k**
14	Me	Ph	*o*- NO_2-Ph	>98:2	94%	**2l**
15	Me	Ph	*o*-Me-Ph	95:5	93%	**2m**
16	Me	*p*-F- Ph	*o*-Me-Ph	94:6	89%	**2n**
17	Me	Ph	*m*-Br-Ph	93:7	91%	**2o**
18	Me	Ph	*p*-Br-Ph	93:7	89%	**2p**
19	Me	Ph	*m*-F-Ph	96:4	92%	**2q**
20	Me	*p*-MeO-Ph	*m*-F-Ph	97:3	89%	**2r**
21	Me	Ph	*p*- F-Ph	94:6	90%	**2s**
22	Me	Ph	1-napthyl	95:5	85%[c]	**2t**
23	Me	Ph	2-furyl	91:9	85%	**2u**
24	Me	Ph	2-thiophene	92:8	90%	**2v**
25	Me	Ph	PhCH=CH	89:11	84%	**2w**
26	Me	Ph	*t*-Bu	>98:2	98%	**2x**
27	Et	Ph	*t*-Bu	>98:2	96%	**2y**

[a]Yield refers to a single isolated diastereoisomer (>99:1). [b]*S*[s] enantiomer of *N*-sulfinylimidate used. [c]Yield refers to a mixture of the diastereoisomers. [d]Three diastereoisomers observed; major diastereoisomer: combined minor diastereoisomers.

were also compatible with the reaction conditions in addition to α,β-unsaturated aldehydes (Table 3, entries 23−25) and pivaldehyde (Table 3, entries 26 and 27), but not enolizable aldehydes.

In all cases, the same complete facial selectivity of the imidate is observed, regardless of the α-substituent of the imidate. This feature can be explained by the selective formation of an *E*-enolate upon deprotonation of the *N*-sulfinylimidate with triethylamine (with the bulky NSO*t*-Bu group and the R^2 group at opposite sides of the C−C bond).[11] Steric shielding of the face of the enolate occupied by the bulky *tert*-butylsulfinyl group forces the reaction with the aldehyde to occur from the opposite face.[14] Given the steric repulsion between the R^3 group of the aldehyde and both the R^2 group of the imidate and the OR^1 group of the imidate in transition state **B**, it is proposed that the reaction proceeds *via* transition state **A**, giving the desired *anti* product (Figure 3). Although a complete mechanistic understanding of the reaction is not yet possible, some insight into the role of the titanium, which must be important in templating the reaction, has been gained. For example, treatment of *N*-sulfinylimidate **1a** with triethylamine in the presence of MeOD resulted in its complete conversion to

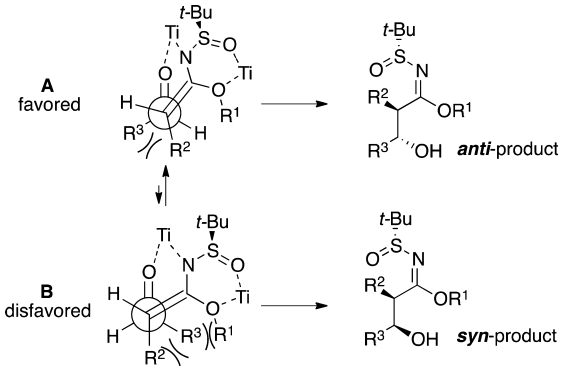
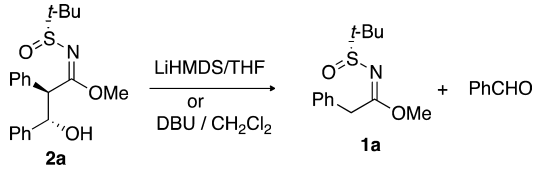


Figure 3. Stereochemical rationalization.

the dideuterated analogue after 3 h. The aldol reaction of the same imidate **1a** with benzaldehyde was complete in only half that time, strongly suggesting that the titanium facilitates deprotonation of the imidate **1a**. Assuming that 1 equiv of the titanium is also required to activate the aldehyde, this would explain the necessity for a 2:1 ratio of $TiCl_2(Oi\text{-}Pr)_2$ to benzaldehyde.

In addition to its role in templating the reaction, it is of course highly likely that the titanium remains coordinated to the final product, preventing the retro-aldol reaction. Indeed, treatment of the aldol product **2a** with triethylamine at rt resulted in 10% retro-aldolization, whereas treatment with DBU or LiHMDS resulted in complete reversal of the reaction (Scheme 1).[15]

Scheme 1. Retroaldolization in the Presence of Strong or Weak Base



The synthesis of amine **3** was next undertaken. This molecule (and a number of similar compounds) has recently been patented for its potential use as a selective neurotransmitter reuptake inhibitor. The current synthetic method suffers from low yields, and poor diastereoselectivities, and access to enantiopure versions relies on optical resolution of the racemate.[5] From the diastereomerically and enantiomerically pure product **2s** (Table 3, entry 21), amine **3** was obtained in only four steps in excellent yield (89%). Quantitative protection of the free hydroxyl group as a triethylsilyl ether followed by reduction gave the sulfinamide, which was *N*-methylated, and the protecting groups were then removed concurrently to give the desired amine hydrochloride **3** (Scheme 2). This novel imidate aldol reaction can thus provide an efficient entry to a range of compounds of this type in enantiopure form.

In summary, we have developed a mild and efficient method for the unprecedented and challenging aldol reaction of a variety of *N*-sulfinylimidates with a range of aldehydes. In most cases, the transformation affords diastereomerically and enantiomerically pure products **2a−y** in excellent yields. This method allows access to *anti*-aldol imidate derivatives containing both α- and β-aromatic groups, which are not readily available by other methods. Further investigations are

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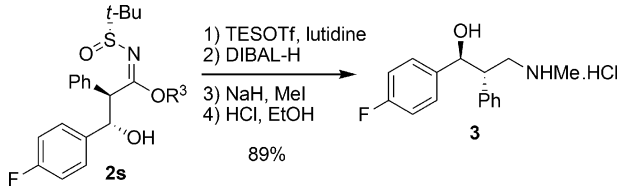
Scheme 2. Transformation of Aldol Product 2s into Potential Neurotransmitter Reuptake Inhibitor 3



ongoing to expand the scope of this transformation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data, full experimental procedures, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and crystallographic data for compounds **2a**, **2a′**, and **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) Crystal data for **2a**: $C_{20}H_{25}NO_3S$, M_r: 359.47 g·mol^{-1}, crystal dimensions (mm^3): 0.38 × 0.36 × 0.35, crystal system: monoclinic, space group: $P2_1$, unit-cell dimensions and volume: a = 11.057(2) Å, b = 7.2132(14) Å, c = 13.515(3) Å, β = 106.23(3)°, V = 1035.0(4) Å^3, no. of formula units in the unit cell Z = 2, calculated density r_{calcd}: 1.153 mg/m^3, linear absorption coefficient m: 0.173 mm^{-1}, radiation and wavelength: l Mo Kα = 0.71073 Å, temperature of measurement: 296.0 K, 2 Q_{max} 60°, no. of measured and independent reflections: 14674 and 5480 (including Friedel pairs), R_{int}: 0.0313, R = 0.0463, wR = 0.1027, residual electron density: 0.305. The crystallographic information file (CIF) has been deposited at the Cambridge Crystallographic Data Centre as CCDC 981802. For the ORTEP of **2a** and **2a′** (CCDC 981801), see the Supporting Information.

(10) Previous reports of both alkylation and Mannich-type reaction of *N*-sulfinylimidates have suggested a *Z*-configuration; however crystal structures of the products were not provided: see ref 3.

(11) The crystal structure of a compound derived from a Mannich reaction of a *N*-sulfonylimidate reveals a similar *E*-configuration: Matsubara, R.; Berthiol, F.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 1804.

(12) X-ray crystallographic analysis confirmed the stereochemistry of the major diastereoisomer **2c** (CCDC 981803). The ORTEP is included in the Supporting Information.

(13) It has been postulated that the α-substituent of the imidate can influence the *E*/*Z* ratio of the corresponding enolate, and this could explain the presence of the third diastereoisomer: see ref 3d.

(14) The observed facial selectivity is in agreement with that previously observed for the alkylation of *N*-sulfinylimidates: see ref 3a.

(15) Treatment of the aldol product **2s** derived from the reaction of *p*-fluorobenzaldehyde with triethylamine under the same conditions resulted in 30% retro-aldolization.