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Asymmetric Synthesis of α-Alkylated *N*-Sulfinyl Imidates as New Chiral Building Blocks

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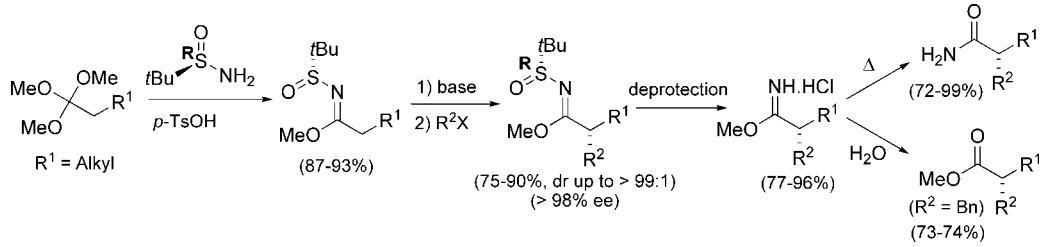

α-Alkylation of *N*-sulfinyl imidates, prepared via condensation of *tert*-butanesulfinamide with ortho esters, led to α-substituted *N*-sulfinyl imidates in good-to-excellent diastereomeric ratios (dr up to >99:1) and yields. Deprotection of the alkylated *N*-sulfinyl imidates gave access to the corresponding imidate hydrochlorides in outstanding yields. These imidate hydrochlorides proved to be excellent intermediates for an easy transformation to chiral amides in good yields and enantiomeric excess upon simple heating in chloroform. Hydrolysis of the α-benzylated imidate hydrochlorides afforded the corresponding chiral esters with >95% ee.

Introduction

Since their introduction three decades ago, sulfinimines have played an important role in the asymmetric synthesis of a variety of structurally diverse nitrogen containing compounds.[1] *N-tert*-butanesulfinamide, as pioneered by Ellman and co-workers, has drawn great attention in the auxiliary-aided asymmetric synthesis of a broad range of chiral amines, which are present in numerous pharmaceutical agents, natural products, and synthetic materials.[2] The electron-withdrawing *N*-sulfinyl auxiliary activates the imino function for nucleophilic addition, allowing reactions to proceed at a lower temperature, and exerts a powerful stereodirecting effect, which results in the addition of enolates and organometallic reagents to both steric and enolizable sulfinimines with high and predictable asymmetric induction. Recently our research group prepared chiral aziridines and cyclopropylamines starting from α-chlorinated *N-tert*-butanesulfinyl imines.[3] Unfortunately, it has been shown in the literature that attempts to further functionalize *N-tert*-butanesulfinyl imines via α-alkylation with alkyl halides were unsuccessful. Indeed, the electron-withdrawing character of the sulfinyl moiety strongly attenuates the nucleophilicity of the metalloenamine. In contrast, a highly diastereoselective α-alkylation of *N-tert*-butanesulfinyl amidines has been reported earlier.[4] Therefore, it was envisioned that the significantly more nucleophilic metalloenamines derived from *N*-sulfinyl imidates would be sufficiently reactive to enable α-alkylation. Herein the highly diastereoselective α-alkylation of chiral *N-tert*-butanesulfinyl imidates, that is, the precursors of the aforementioned *N-tert*-butanesulfinyl amidines,[4] used to prepare α-alkylated *N*-sulfinyl imidates as new chiral building blocks, is described. The interest in the synthesis of chiral α-alkylated *N*-sulfinyl imidates arises from the fact that *N*-sulfinyl imidates can be oxidized to the corresponding *N*-sulfonyl imidates, which are known as potentially useful prodrugs for drugs containing an ester function as well as for drugs containing

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a primary sulfonamide group.[5] Furthermore, N-deprotection of *N*-sulfinyl imidates leads to the corresponding imidates and their salts which have been known for nearly a century but for which only one general direct preparative method exists. This method of Pinner involves the synthesis of the imidate hydrochloride salt from the appropriate nitrile and alcohol with anhydrous hydrogen chloride.[6] Several other synthetic methods of specific imidates have been reported.[7] Until now, the Pinner synthesis was the only method used to prepare chiral α-alkylated imidates,[8] but this synthesis suffers from some limitations, such as long reaction times and poor yields.[6] In our hands, in most cases the Pinner reaction was accompanied by the formation of small quantities of the corresponding amides and methyl esters as side products.[9] It should be noted that N-unsubstituted imidates are useful intermediates for the synthesis of a variety of compounds, as recently demonstrated in the preparation of imidazoles and imidazolinones as intermediates in the synthesis of the angiotensin II antagonist Losartan,[10] imidazolines as precursors of 2,4(5)-connected imidazole crown ethers,[11] benzimidazoles as smooth muscle cell proliferation inhibitors,[12] and oxazoles as intermediates in the total synthesis of (−)-Hennoxazole A[13] and as mGluR5 antagonists with applications in the treatment of drug abuse.[14] Furthermore, N-unsubstituted imidates are useful in the preparation of oxazolines as efficient ligands for the iridium catalyzed enantioselective hydrogenation of unfunctionalized tetrasubstituted olefins,[15] benzoxazoles as modulators of metabotropic glutamate receptors,[16] thiazolines as starting material for the total synthesis of cystothiazoles A and C,[17] triazoles for the treatment of breathing disorders,[18] and several other interesting heterocycles like quinazolines,[19] pyrimidines,[20] and *N*-acyllactams.[21]

Results and Discussion

After optimization of a literature procedure, the condensation of (R_s)-*tert*-butanesulfinamide **1** and ortho esters **2** with a catalytic amount of *p*-TsOH without solvent afforded chiral *N*-sulfinyl imidates **3a**−**c** in excellent yields (Scheme 1).[4,22]

SCHEME 1. Synthesis of *N*-Sulfinyl Imidates 3 via Condensation of (R_s)-*tert*-Butanesulfinamide 1 with Ortho Esters 2

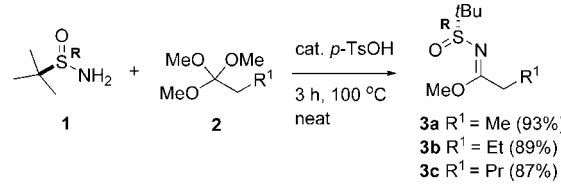
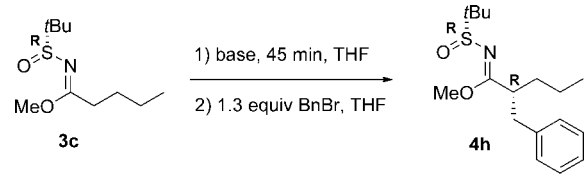


TABLE 1. Optimization of the α-Alkylation of *N*-Sulfinyl Imidate 3c with Benzyl Bromide



entry	base	temp (°C), time (h)	conversion of **3c** into **4h** (%)	dr[a]	yield[b] (%)
1	1.2 equiv LDA[c]	0 to rt, 28	63	73:27	
2	1.4 equiv LDA[c]	0 to rt, 2	69[f]	71:29	
3	1.6 equiv LDA[c]	0 to rt, 2	57[f]	69:31	36
4	1.5 equiv LDA[d]	−78, 1	49[f]	71:29	
5	1.5 equiv LiHMDS[d]	−78, 1.5	100	71:29	42[g]
6	1.5 equiv LiHMDS[c]	0 to rt, 1.5	100	63:37	
7	1.6 equiv KHMDS[c,e]	0 to rt, 1.5	100	96:4	63
8	1.5 equiv KHMDS[d,e]	−78, 1.5	100	95:5	79
9	1.2 equiv KHMDS[d,e]	−78, 1.5	100	98:2	84

[a] Diastereomeric ratio determined via ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of (R_s,*R*)-**4h** after flash chromatography. [c] Deprotonation was performed at 0 °C. [d] Deprotonation was performed at −78 °C. [e] A 0.5 M solution of KHMDS in toluene was used (2:3 THF/0.5 M solution of KHMDS in toluene (v/v)). [f] Some unidentified side products were also detected by ^{1}H NMR analysis of the crude reaction mixture. [g] (R_s,*S*)-**4h** was isolated in 21% yield.

The α-alkylation of *N*-*tert*-butanesulfinyl imidates **3** with alkyl halides was optimized by systematically changing the reaction conditions in the α-alkylation of *N*-sulfinyl imidate **3c** with benzyl bromide for the synthesis of (R_s,*R*)-imidate **4h** (Table 1). All initial attempts using LDA to deprotonate *N*-sulfinyl imidate **3c** resulted in incomplete conversion to the α-alkylated imidate **4h** because of the formation of unidentified side products and moderate diastereoselectivity leading to low yields of **4h** (Table 1, entries 1−4).

The use of LiHMDS (lithium bis(trimethylsilyl)amide) as a base gave full conversion at −78 °C in 1.5 h and resulted in a better yield of (R_s,*R*)-**4h** (42%, entry 5). It was also possible to isolate the other diastereomer (R_s,*S*)-**4h** (21%) because of the moderate diastereoselectivity of the reaction (dr 71:29). Repeating the reaction at room temperature led, not surprisingly, to an even lower stereoselectivity (Table 1, entry 6). The best results were obtained when KHMDS was used as a base leading to enhanced diastereoselectivities and yields at lower temperature or upon the use of less equivalents of KHMDS (Table 1, entry 7−9). Finally, treating *N*-sulfinyl imidate **3c** with 1.2 equiv of KHMDS for 45 min at −78 °C followed by a reaction with 1.3 equiv of benzyl bromide at −78 °C for 1.5 h afforded *N*-*tert*-butanesulfinyl imidate **4h** with excellent diastereoselectivity (dr

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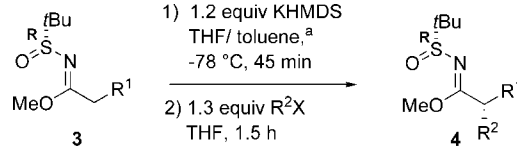
TABLE 2. Asymmetric α-Alkylation of *N*-Sulfinyl Imidates 3 with Alkyl Halides



entry	R^1	R^2X	temp (°C)	product **4**	dr[c]	yield[d] (%)
1	Me	BnBr	−78	(R_s,*R*)-**4a**	98:2	77
2	Me	EtI	−78 to rt	(R_s,*R*)- and (R_s,*S*)-**4b**	70:30	*e*
3	Me	allyl Br	−78	(R_s,*R*)-**4c**	98:2	75
4	Me	PrI	−78 to rt	(R_s,*R*)-**4d**	76:24	49[f]
5	Et	BnBr	−78	(R_s,*R*)-**4e**	96:4	90
6	Et	MeI	−78	(R_s,*S*)- and (R_s,*R*)-**4b**	78:22	*g*
7	Et	allyl Br	−78	(R_s,*R*)-**4f**	>99:1	88
8	Et	PrI	−78 to rt	(R_s,*R*)-**4g**	>99:1	78
9	Pr	BnBr	−78	(R_s,*R*)-**4h**	98:2	84
10	Pr	EtI	−78 to rt	(R_s,*S*)-**4g**	>99:1	79
11	Pr	allyl Br	−78	(R_s,*R*)-**4i**	>99:1	85
12	Pr	MeI	−78	(R_s,*S*)-**4d**	79:21	34[h]

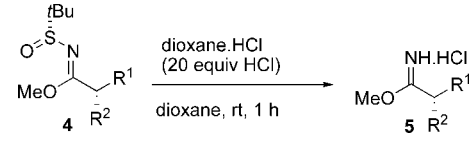
[a] 2:3 THF/0.5 M solution of KHMDS in toluene (v/v). [b] Determined by ^{1}H NMR analysis with Pirkle's alcohol. [c] Diastereomeric ratio determined via ^{1}H NMR analysis of the crude reaction mixture. [d] Yield of a single diastereomer **4** after flash chromatography. [e] The diastereomers **4b** could not be separated via flash chromatography resulting in **4b** (32%, dr 78:22 and 48%, dr 57:43). [f] The major diastereomer (R_s,*R*)-**4d** was isolated in 49% yield, and additionally, a mixture of diastereomers **4d** (dr 36:64) was isolated in 28% yield. [g] The diastereomers **4b** could not be separated via flash chromatography, resulting in **4b** (80%, dr 76:24). [h] The major diastereomer (R_s,*S*)-**4d** was isolated in 34% yield, and additionally, a mixture of diastereomers **4d** (dr 73:27) was isolated in 46% yield.

98:2), giving access to (R_s,*R*)-imidate **4h** in 84% yield after chromatography.

Analogously, a variety of new chiral α-alkylated *N*-sulfinyl imidates **4** were prepared in good-to-excellent diastereomeric ratios (dr 70:30 to >99:1) and yields (75−90%) using the optimized reaction conditions (Table 2). When the reaction was performed using iodoethane or 1-iodopropane as the electrophile, no reaction occurred at −78 °C, and therefore, the reaction was performed at higher temperatures (−78 °C to rt) to achieve full conversion (entries 2, 4, 8, and 10). It is noteworthy that the α-alkylation of *N*-sulfinyl imidates **3** with benzyl bromide and allyl bromide resulted in high diastereoselectivity (dr 96:4 to >99:1; entries 1, 3, 5, 7, 9, and 11), while in all the other cases where the *N*-*tert*-butanesulfinyl imidate **4** contained an α-methyl group a lower diastereoselectivity was observed (dr 70:30 to 79:21; entries 2, 4, 6, and 12), which resulted in a difficult separation by flash chromatography. The enantiomeric excess of *N*-*tert*-butanesulfinyl imidates **4** was determined by comparing ^{1}H NMR data obtained from the addition of *R*-Pirkle's alcohol as a chiral shift reagent[23] to racemic mixtures of *N*-*tert*-butanesulfinyl imidates **4**, prepared with *rac*-*tert*-butanesulfinamide **1** as starting material, and from the addition of *R*-Pirkle's alcohol to the chiral prepared *N*-(*tert*-butanesulfinyl)imidates **4** (see Supporting Information). These experiments allowed to conclude an enantiomeric excess of >98% for imidates **4**. The *Z*-stereochemistry of the *N*-*tert*-butanesulfinyl imidates **4**, that is, with the sulfinyl group and the methoxy function at the same side of the carbon−nitrogen double bond, was ascertained by executing several aromatic solvent-induced shift (ASIS) ^{1}H NMR experiments on imidates **3a** and **4a**.[24]

In the next step, the chiral *N*-*tert*-butanesulfinyl imidates **4** were N-deprotected by simple treatment with a saturated solution of anhydrous HCl (20 equiv of HCl) in dioxane for 1 h at rt.

TABLE 3. N-Deprotection of α-Alkylated *N*-Sulfinyl Imidates 4 to the Corresponding Imidate Hydrochlorides 5



entry	R^1	R^2	product **5**	yield[a] (%)
1	Me	Bn	*R*-**5a**	80
2	Me	allyl	*R*-**5c**	92
3	Me	Pr	*R*-**5d**	96
4	Et	Bn	*R*-**5e**	88
5	Et	allyl	*R*-**5f**	94
6	Et	Pr	*R*-**5g**	87
7	Pr	Bn	*R*-**5h**	77[b]
8	Pr	Et	*S*-**5g**	90
9	Pr	allyl	*R*-**5i**	85
10	Pr	Me	*S*-**5d**	87

[a] Yield after precipitation from Et_2O. [b] Reaction conditions: 5 equiv of HCl, dioxane, 0 °C, 5 min.

This afforded the imidate hydrochlorides **5** in high yield (80−96%) after precipitation from diethyl ether (Table 3, entries 1−6 and 8−10). Imidate hydrochloride *R*-**5h** was prepared by treatment of *N*-*tert*-butanesulfinyl imidate (R_s,*R*)-**4h** with 5 equiv of HCl in dioxane for 5 min at 0 °C (Table 3, entry 7). The use of more equivalents of HCl, higher temperature, and/or longer reaction time led to the formation of the corresponding amide. Imidate hydrochloride *R*-**5c** is a known compound in the literature, prepared by the Pinner method starting from the corresponding chiral nitrile, which is synthesized from the corresponding chiral ester, prepared using the Evans α-alkylation method.[8a] Comparing the optical rotations of the newly prepared imidate *R*-**5c** ($[\alpha]_D$ + 35.9 (*c* 1.0, $CHCl_3$) vs + 35.8 in lit.[8a]) afforded a first proof on the stereochemical outcome of the alkylation reaction. All efforts to determine the enantiomeric excess of imidate hydrochlorides **5** by chiral HPLC failed because of partial conversion to esters **6** on column.

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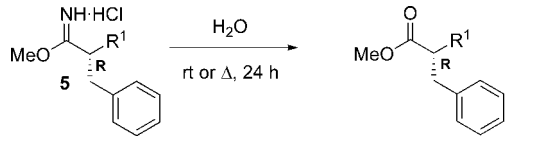
SCHEME 2. Synthesis of Chiral Esters 6 from Imidate Hydrochlorides 5



6a R^1 = Me (73%), > 99% ee
6e R^1 = Et (74%), > 95% ee

The α-benzylated imidate hydrochlorides *R*-**5a** and *R*-**5e** were treated with water to achieve the formation of chiral esters **6** (Scheme 2). Stirring imidate hydrochloride *R*-**5a** in water for 24 h at room temperature gave access to ester *R*-**6a** in 73% yield after flash chromatography. However, treating imidate hydrochloride **5e** with water for 24 h at room temperature afforded only 44% conversion to ester *R*-**6e**. Therefore, imidate hydrochloride *R*-**5e** was heated in water for 24 h at reflux temperature, giving full conversion to ester *R*-**6e** which was isolated in 74% yield (Scheme 2). All attempts to convert the other α-alkylated imidate hydrochlorides **5** to the corresponding esters failed, leading to incomplete conversions, amide formation, or complex reaction mixtures. Stirring imidate hydrochloride *R*-**5g** in water for 20 h at room temperature gave access to a mixture of the corresponding ester (36%) and amide (64%). Surprisingly, upon heating imidate hydrochloride *R*-**5g** in water for 24 h at reflux temperature, no formation of the corresponding ester was observed, but instead the formation of the corresponding amide was observed in the ^{1}H NMR spectrum of the crude reaction mixture. An analogous treatment of imidate hydrochloride *R*-**5d** afforded a complex mixture without ester formation.

Furthermore, *N*-sulfinyl imidates **3a** and **4d** could be easily oxidized with *m*-CPBA to the corresponding *N*-sulfonyl imidates **7** in excellent yields (Scheme 3). According to a literature procedure,[25] *N*-sulfonyl imidate **7d** was treated with a catalytic amount of DBU in DMF/H_2O (95:5) at room temperature to achieve the formation of the corresponding ester **6d**. Unfortunately, only a very low yield of the corresponding N-unsubstituted imidate was formed.

Ester *R*-**6a** is a known compound in the literature, prepared by the Evans methodology,[26] thus allowed a comparison of the optical rotations ($[\alpha]_D$ − 35.3 (*c* 0.5, $CHCl_3$) vs − 33.7 in lit.[26]), and confirmed the assigned stereochemistry of ester *R*-**6a**. Also, ester *R*-**6e** is a known compound in the literature, but no optical rotation was reported.[27] The enantiomeric excess of esters **6** was determined by chiral HPLC (see Supporting Information).

In the final part, chiral amides **8** were prepared starting from imidate hydrochlorides **5** (Table 4). In a first attempt, imidate hydrochloride *R*-**5a** was treated with saturated $NaHCO_3$(aq) for 30 min at room temperature, forming the corresponding free imidate, followed by flash chromatography on silica gel leading to amide *R*-**8a** in 87% yield (entry 1). Via an analogous treatment, imidate hydrochloride *S*-**5g** was converted to the corresponding free imidate, but chromatography led only to a 35% conversion of the free imidate to amide *S*-**8g** (entry 2). Therefore, the free imidate of salt *S*-**5g** was stirred with silica gel in diethyl ether for 20 h at room temperature, affording full conversion to amide *S*-**8g** which was isolated in 85% yield (entry 3). However, performing the latter method with imidate hydrochloride *R*-**5c** and *R*-**5e** gave an incomplete conversion to amides *R*-**8c** and *R*-**8e** of 86 and 87%, respectively (entries 4 and 5). Furthermore, when treating the free imidate of *R*-**5c** with several acids like *p*-TsOH and HCl, no reaction occurred. Heating of imidate hydrochloride *R*-**5c** at reflux temperature in chloroform for 16 h finally afforded chiral amide *R*-**8c** in 72% after recrystallization from diethyl ether (entry 6). Repeating the latter method on imidate hydrochlorides *R*-**5a**, *R*-**5e**, *R*-**5f**, *R*-**5i**, and *S*-**5d** gave access to optically pure amides *R*-**8a**, *R*-**8e**, *R*-**8f**, *R*-**8i**, and *S*-**8d** in a 74−99% yield after recrystallization from diethyl ether (entries 7−11).

Amide *R*-**8c** and the *S*-enantiomer of amide **8a** are known compounds in the literature,[8a,28] both prepared by the Evans methodology. Comparison of the optical rotations ($[\alpha]_D$ *R*-**8a** − 48.1 (*c* 0.5, EtOH) vs *S*-**8a** + 53.1 in lit.,[28] $[\alpha]_D$ *R*-**8c** − 15.7 (*c* 1.1, $CHCl_3$) vs − 22.9 in lit.[8a]) further confirmed the assigned stereochemistry of the obtained compounds. The overall transformation of imidates **3** to chiral amides **8** is clearly competitive with the methodology to prepare chiral amides via aminolysis of Evans's chiral oxazolidinones in terms of yields and simplicity.[8a,28,29]

The enantiomeric excess of amides **8** was determined by comparing ^{1}H NMR data obtained from the addition of *R*-Pirkle's alcohol to racemic mixtures of amides **8**, prepared with *rac*-*tert*-butanesulfinamide **1** as starting material, and from the addition of *R*-Pirkle's alcohol to the enantiomerically pure prepared amides **8**. These experiments, in addition to chiral HPLC or chiral GC analysis, allowed to conclude >95% ee for amides **8** (see Supporting Information).

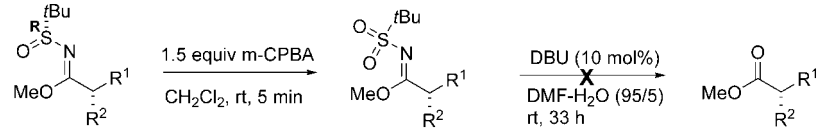
In analogy with a model proposed in a report on the asymmetric synthesis of 1,3-amino alcohols from *N*-sulfinyl imines,[30] the stereoselectivity of the alkylation reaction to imidates **4** can be explained with a model in which the reaction proceeds via transition state A instead of B (Figure 1).

Upon deprotonation of *N*-sulfinyl imidate **3**, the *E*-enolate will be preferentially formed with the R^1 group and the NSO*t*Bu group at opposite sides of the C−C double bond.[25] The stereoselectivity can be explained by the fact that the steric repulsion between the *tert*-butyl group and the approaching alkyl halides (R^2−X) in transition state B is a determining factor to drive the reaction via transition state A.

Conclusions

It was demonstrated that chiral α-substituted *N*-sulfinyl imidates are formed as new chiral building blocks in high yields with good-to-excellent diastereomeric ratios via α-alkylation of *N*-sulfinyl imidates. N-Deprotection of the alkylated *N*-sulfinyl

SCHEME 3. Synthesis of *N*-Sulfonyl Imidates 7 and Attempted DBU-Catalyzed Hydrolysis to the Corresponding Esters 6

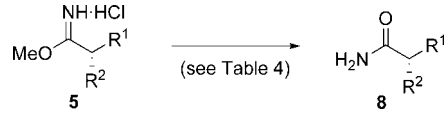


3a R^1 = Me, R^2 = H
4d R^1 = Pr, R^2 = Me (dr 73:27)

7a R^1 = Me, R^2 = H (86%)
7d R^1 = Pr, R^2 = Me (94%)

6d R^1 = Pr, R^2 = Me

TABLE 4. Synthesis of Chiral Amides 8 from Imidate Hydrochlorides 5



entry	R^1	R^2	reaction conditions	product **8**	yield[b] (%)
1	Me	Bn	(1) sat. $NaHCO_3$(aq), 30 min, rt (2) SiO_2 (chromatography)	*R*-**8a**	87
2	Pr	Et	(1) sat. $NaHCO_3$(aq), 30 min, rt (2) SiO_2 (chromatography)	*S*-**8g**	*c*
3	Pr	Et	(1) sat. $NaHCO_3$(aq), 30 min, rt (2) SiO_2, Et_2O, rt, 20 h	*S*-**8g**	85
4	Me	allyl	(1) sat. $NaHCO_3$(aq), 30 min, rt (2) SiO_2, Et_2O, rt, 20 h	*R*-**8c**	*d*
5	Et	Bn	(1) sat. $NaHCO_3$(aq), 30 min, rt (2) SiO_2, Et_2O, rt, 20 h	*R*-**8e**	*e*
6	Me	allyl	$CHCl_3$, Δ, 16 h	*R*-**8c**	72
7	Me	Bn	$CHCl_3$, Δ, 16 h	*R*-**8a**	75
8	Et	Bn	$CHCl_3$, Δ, 16 h	*R*-**8e**	99
9	Et	allyl	$CHCl_3$, Δ, 16 h	*R*-**8f**	74
10	Pr	allyl	$CHCl_3$, Δ, 16 h	*R*-**8i**	92
11	Pr	Me	$CHCl_3$, Δ, 16 h	*S*-**8d**	79

[a] Determined by ^{1}H NMR with Pirkle's alcohol (*R*-**8a**, *R*-**8c**, and *R*-**8e**) by chiral HPLC (*R*-**8a** and *R*-**8e**) and by chiral GC (*R*-**8c**). [b] Yield after chromatography or recrystallization from Et_2O. [c] 35% conversion to *S*-**8g**. [d] 86% conversion to *R*-**8c**. [e] 87% conversion to *R*-**8e**.

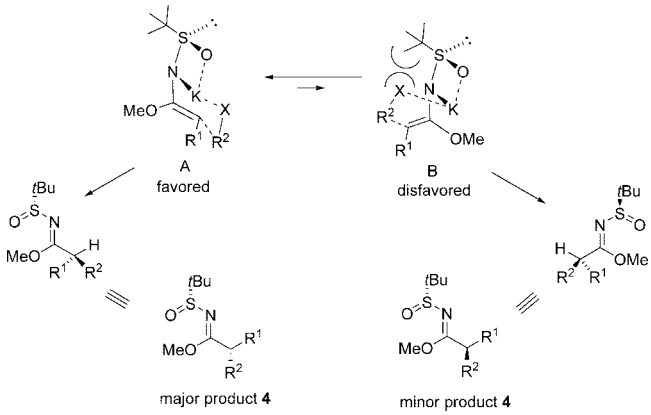


FIGURE 1. Proposed stereochemical model for the α-alkylation of *N*-sulfinyl imidates **3**.

imidates gave access to enantiopure imidate hydrochlorides in excellent yields, as useful intermediates for an easy transformation to chiral amides upon simple heating in chloroform. Hydrolysis of the α-benzylated imidate hydrochlorides afforded the corresponding chiral esters with >95% ee. By comparing the optical rotations of the synthesized imidates, esters, and amides with literature data from known compounds, evidence was obtained about the stereochemical outcome of the alkylation reaction.

Experimental Section

Synthesis of *N-tert*-Butanesulfinyl Imidates 3. The synthesis of R_s-methyl *N-tert*-butanesulfinyl propanimidate **3a** is representative. To a round-bottomed flask charged with R_s-*tert*-butanesulfinamide **1** (3.00 g, 24.79 mmol) were added trimethyl orthopropionate **2** (3 equiv, 9.98 g, 74.37 mmol) and *p*-toluenesulfonic acid monohydrate (0.005 equiv, 0.02 g, 0.12 mmol). The reaction mixture was stirred for 3 h at 100 °C, and the volatile materials were removed in vacuo. The crude oil was purified by vacuum distillation (57 °C, 0.1 mmHg) to yield 4.40 g (23.04 mmol) of pure R_s-methyl *N-tert*-butanesulfinyl propanimidate **3a**. Yield: 93%. $[\alpha]_D$ − 120.3 (*c* 2.9, $CHCl_3$). IR (cm^{-1}): ν_{max} 1073, 1607, 2948. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, d × d, *J* = 7.6, 7.6 Hz), 1.22 (9H, s), 2.68 (1H, d × q, *J* = 14.6, 7.6 Hz), 2.71 (1H, d × q, *J* = 14.6, 7.6 Hz), 3.77 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8, 21.9, 26.3, 54.2, 55.7, 178.0. MS (ES, pos. mode) *m*/*z* (%): 192 (M + H$^+$, 100). HRMS: calcd for $C_8H_{17}NO_2S$, 192.1053 [M + H]$^+$; found, 192.1048 [M + H]$^+$.

Synthesis of α-Alkylated *N-tert*-Butanesulfinyl Imidates 4. The synthesis of (R_s,*R*)-methyl *N-tert*-butanesulfinyl-2-methyl-3-phenylpropanimidate **4a** is representative. To a 0.5 M solution of KHMDS (1.2 equiv, 10.06 mL, 5.03 mmol) in toluene was added THF (7 mL) (2:3 THF/0.5 M solution KHMDS in toluene (v/v)), and the solution was cooled to −78 °C. R_s-Methyl *N-tert*-butanesulfinyl propanimidate **3a** (1 equiv, 0.80 g, 4.19 mmol) in THF (8 mL) was slowly added, and the resulting solution was stirred for 45 min at −78 °C. Benzyl bromide (1.3 equiv, 0.65 mL, 5.45 mmol) was then added, and the reaction mixture was stirred at −78 °C for 1.5 h. To the reaction mixture was added 2 N AcOH/THF (10 mL), which was cooled to the same temperature as the reaction vessel before the addition. A saturated aqueous solution of $NaHCO_3$ (10 mL) was then added to the mixture upon stirring. The aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography to yield 0.91 g (3.23 mmol) of pure (R_s,*R*)-methyl *N-tert*-butanesulfinyl-2-methyl-3-phenylpropanimidate **4a**. R_f = 0.16 (7:3 petroleum ether/Et_2O). Yield: 77%. $[\alpha]_D$ − 118.0 (*c* 2.6, $CHCl_3$). Ee >98%. IR (cm^{-1}): ν_{max} 1075, 1603, 2946. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (3H, d, *J* = 6.6 Hz), 1.18 (9H, s), 2.64 (1H, d × d, *J* = 13.2, 9.1 Hz), 3.07 (1H, d × d, *J* = 13.2, 5.8 Hz), 3.57−3.66 (1H, m), 3.72 (3H, s), 7.14−7.33 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3, 21.7, 38.8, 39.8, 53.8, 55.5, 126.1, 128.1, 128.9, 138.7, 178.2. MS (ES, pos. mode) *m*/*z* (%): 282 (M + H$^+$, 100). HRMS: calcd for $C_{15}H_{23}NO_2S$, 282.1522 [M + H]$^+$; found, 282.1504 [M + H]$^+$.

Synthesis of Imidate Hydrochlorides 5. The synthesis of imidate hydrochloride **5a** is representative. To a solution of (R_s,*R*)-methyl *N-tert*-butanesulfinyl-2-methyl-3-phenylpropanimidate **4a** (0.40 g, 1.42 mmol) in dioxane (10 mL) was added dropwise freshly prepared saturated dioxane/HCl (15 mL, ∼20 equiv HCl). The mixture was allowed to stir for 1 h. Then the reaction mixture was concentrated in vacuo. Precipitation in diethyl ether afforded 0.24 g (1.14 mmol) of pure *R*-methyl 2-methyl-3-phenylpropanimidate hydrochloride **5a**. Yield: 80%. $[\alpha]_D$ − 21.2 (*c* 1.3, $CHCl_3$). Mp

119.3−119.5 °C. IR (cm^{-1}): ν_{max} 1644, 2870. ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, d, $J = 6.9$ Hz), 2.84 (1H, d × d, $J = 13.5$, 8.0 Hz), 3.06 (1H, d × d, $J = 13.5$, 7.4 Hz), 3.43−3.55 (1H, m), 4.22 (3H, s), 7.22−7.33 (5H, m), 11.55 (1H, br s), 12.52 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7, 39.7, 40.3, 60.8, 127.2, 128.9, 129.1, 136.9, 182.8. MS (ES, pos. mode) *m*/*z* (%): 178 ($M + H^+ - HCl$, 100). Anal. Calcd for $C_{11}H_{16}ClNO$: C, 61.82; H, 7.55; N, 6.55. Found: C, 62.08; H, 7.72; N, 6.70.

Synthesis of *R*-Methyl 2-Methyl-3-phenylpropanoate 6a. *R*-Methyl 2-methyl-3-phenylpropanimidate hydrochloride **5a** (0.18 g, 0.84 mmol) was dissolved in H_2O (10 mL). The reaction mixture was stirred for 24 h at room temperature, subsequently poured in a saturated aqueous solution of $NaHCO_3$ (15 mL), and extracted with diethyl ether (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography to yield 0.11 g of pure *R*-methyl 2-methyl-3-phenylpropanoate **6a**. $R_f = 0.60$ (6:4 petroleum ether/Et_2O). Yield: 73%. $[\alpha]_D$ − 35.3 (*c* 0.5, $CHCl_3$) vs − 33.7 in lit.[26] Ee = 99.4%, HPLC Daicel Chiralcel OJ-RH column: MeOH (75%)/20 mM NH_4HCO_3 + 0.1% diethylamine in water (v/v) (25%), 0.5 mL min^{-1}, 20 °C, t_R (*R*-**6a**) = 26.53 min, t_R (*S*-**6a**) = 29.00 min (see Supporting Information). ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (3H, d, $J = 6.6$ Hz), 2.62−2.79 (2H, m), 2.97−3.05 (1H, m), 3.62 (3H, s), 7.10−7.36 (5H, m). All spectroscopic data were in good agreement with reported data.[26,27]

Synthesis of *N-tert*-Butanesulfonyl Imidates 7. The synthesis of methyl *N-tert*-butanesulfonyl propanimidate **7a** is representative. R_s-Methyl *N-tert*-butanesulfinyl propanimidate **3a** (0.15 g, 0.79 mmol) was dissolved in CH_2Cl_2 (4 mL). *m*-CPBA (1.5 equiv, 0.20 g, 1.18 mmol) was then added in one portion. The reaction mixture was stirred for 5 min at room temperature, subsequently poured in a saturated aqueous solution of $NaHCO_3$ (10 mL), and extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with 2 M NaOH (3 × 10 mL), and the mixture was subsequently dried ($MgSO_4$), filtered, and evaporated in vacuo to yield 0.11 g of pure methyl *N-tert*-butanesulfonyl propanimidate **7a**. Yield: 86%. IR (cm^{-1}): ν_{max} 1122, 1290, 1613, 2925. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (3H, t, $J = 7.2$ Hz), 1.47 (9H, s), 2.89 (2H, q, $J = 7.2$ Hz), 3.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.1, 24.1, 27.6, 55.1, 58.7, 178.2. MS (ES, pos. mode) *m*/*z* (%): 208 ($M + H^+$, 100).

Synthesis of *R*-2-Methyl-3-phenylpropanamide 8a. The synthesis of amide **8a** is representative for the synthesis of amides **8c**, **8d**, **8e**, **8f**, and **8i**. *R*-Methyl 2-methyl-3-phenylpropanimidate hydrochloride **5a** (0.14 g, 0.66 mmol) was dissolved in chloroform (10 mL). The reaction mixture was stirred for 16 h at reflux temperature and subsequently evaporated in vacuo. Recrystallization from diethyl ether afforded 0.08 g of pure *R*-2-methyl-3-phenylpropanamide **8a**. Yield: 75% (yield is 87% according to an alternative procedure; see Supporting Information). $[\alpha]_D$ − 48.1 (*c* 0.5, EtOH) vs + 53.1 in lit. for *S*-**8a**.[28] Mp 113.3−113.6 °C vs 113−114 °C in lit.[28] Ee = 99.8%. HPLC Daicel Chiralcel OD-RH column: MeOH (50%)/20 mM NH_4HCO_3 + 0.1% diethylamine in water (v/v) (50%), 0.5 mL min^{-1}, 25 °C, t_R (*S*-**8a**) = 13.44 min, t_R (*R*-**8a**) = 18.64 min (see Supporting Information). ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, d, $J = 6.9$ Hz), 2.47−2.59 (1H, m), 2.64−2.71 (1H, m), 2.92−3.02 (1H, m), 5.36 (1H, br s), 5.69 (1H, br s), 7.12−7.31 (5H, m). All spectroscopic data were in good agreement with reported data.[28,31]

Synthesis of *S*-2-Ethylpentanamide 8g. To *S*-methyl 2-ethylpentanimidate hydrochloride **5g** (0.13 g, 0.72 mmol) was added a saturated aqueous solution of $NaHCO_3$ (10 mL). The reaction mixture was stirred for 30 min at room temperature and subsequently extracted with diethyl ether (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated in vacuo. The resulting free imidate was dissolved in diethyl ether (5 mL), and silica gel (1.00 g) was added. The reaction mixture was stirred for 20 h at room temperature, subsequently filtered, and evaporated in vacuo. Recrystallization from diethyl ether afforded 0.09 g of pure *S*-2-ethylpentanamide **8g**. Yield: 85%. $[\alpha]_D$ − 1.4 (*c* 1.0, $CHCl_3$). Mp 121.6−121.9 °C. IR (cm^{-1}): ν_{max} 1653, 3370. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89−0.96 (6H, m), 1.22−1.66 (6H, m), 2.01−2.10 (1H, m), 5.54 (1H, br s), 5.95 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.1, 14.2, 20.9, 26.1, 35.0, 48.8, 178.4. MS (ES, pos. mode) *m*/*z* (%): 130 ($M + H^+$, 100). Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.93; H, 11.60; N, 10.80.

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Supporting Information Available: General experimental conditions and spectroscopic data for *N*-sulfinyl imidates **3**, α-alkylated *N*-sulfinyl imidates **4**, imidate hydrochlorides **5**, chiral esters **6**, *N*-sulfonyl imidates **7**, and chiral amides **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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