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The use of enantiomerically pure *N*-sulfinimines in asymmetric Baylis–Hillman reactions

Varinder K. Aggarwal,* Ana M. Martin Castro, Andrea Mereu and Harry Adams

Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK

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Abstract—The electrophilic behaviour of enantiomerically pure *N*-*p*-toluenesulfinimines (**1a**–**d**) and *N*-*tert*-butanesulfinimine **2** has been tested in the asymmetric Baylis–Hillman reaction with methyl acrylate with and without Lewis acids. In the presence of $In(OTf)_3$ good yields and high diastereoselectivities have been achieved providing an effective route to β-amino-α-methylene esters.

The Baylis–Hillman reaction is commonly used for the coupling of Michael acceptors with aldehydes to give β-hydroxy-α-methylene esters/ketones/nitriles.[1] Imines have also occasionally been employed as electrophiles in place of aldehydes in this reaction providing a very useful and rapid entry to the corresponding β-amino products.[2] Even rarer, are attempts to render the latter process asymmetric. One example exists of a highly diastereoselective Baylis–Hillman reaction which employed an arylimine chromium tricarbonyl complex but such reagents limit the scope of the process to *o*-substituted aryl imines.[3] It would be more useful to place the chiral controller on the nitrogen of the imine as then both aromatic and aliphatic imines could be employed. At first sight, *N*-sulfinimines seemed to be ideal chiral auxiliaries[4] for use in the Baylis–Hillman reaction as (i) they can be readily prepared in enantiomerically pure form, (ii) there are numerous examples of highly diastereoselective nucleophilic additions to such imines, and (iii) further tuning of reactivity/selectivity is possible through variation of the sulfinyl substituent. However, we also recognised that the few cases describing the use of imines in the Baylis–Hillman reaction all employed the strongly electron withdrawing tosyl group on nitrogen.[2] It was not clear whether the much less electrophilic *N*-sulfinimines would even participate in the Baylis–Hillman reaction, as this reaction only works with highly reactive electrophiles. Nevertheless, we embarked on the study of *N*-sulfinimines as electrophiles as, even if they were unreactive under standard conditions, we and others have described methods for accelerating/improving the process.[5]

We report herein the results of the asymmetric Baylis–Hillman reaction of *N*-sulfinimines with methyl acrylate in the presence of different bases and metal catalysts.

Results and discussion

We decided to study both *N*-*p*-toluenesulfinimines **1** and *N*-*tert*-butanesulfinimine **2** (Fig. 1) as these imines offered considerable variation in both steric and electronic properties.

The synthesis of *N*-sulfinimines **1a**–**d** was performed following the procedure described by Davis,[6] consisting of the 'one-pot' reaction of commercially available (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate with lithium bis(trimethylsilyl)amide and an excess of aldehyde. *N*-*tert*-Butanesulfinimine **2** was prepared following the three-step procedure reported by Ellman.[7] Catalytic asymmetric oxidation of *tert*-butyl disulfide,

(*S*)-1a, R = Ph
(*S*)-1b, R = C_6H_4-*p*-NO_2
(*S*)-1c, R = C_6H_4-*p*-OCH_3
(*S*)-1d, R = *n*-Pr

(*R*)-2

Figure 1. Imine substrates to be tested in the Baylis–Hillman reaction.

* Corresponding author. Present address: Professor Varinder K. Aggarwal, School of Chemistry, University of Bristol, Bristol BS8 1TS, UK.

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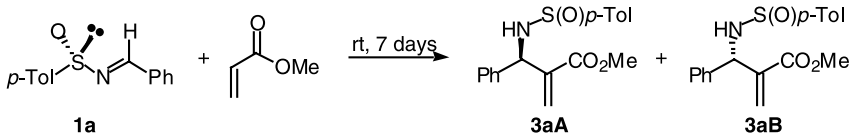
Table 1. Baylis–Hillman reactions of *N*-sulfinimine **1a**[a]



1a **3aA** **3aB**

Entry	Base	Lewis acid	Additive	Diastereomeric ratio **A**:**B**[b] (Yield (%))[c]
1	3-HQD	–	–	12:88 (23)
2	3-HQD	–	Formamide[d]	38:62 (12)
3	3-HQD	$La(OTf)_3$	–	14:86 (54)
4	3-HQD	$La(OTf)_3$	$N(CH_2CH_2OH)_3$[e]	23:77 (60)
5	DABCO	$La(OTf)_3$	$N(CH_2CH_2OH)_3$[e]	21:79 (46)
6	3-HQD	$Al(O\textit{i}\text{-}Pr)_3$	–	14:86 (30)
7	3-HQD	$Zn(OTf)_2$	–	25:75 (65)
8	3-HQD	$Zr(O\textit{i}\text{-}Pr)_4$	–	17:83 (65)
9	3-HQD	$Sc(OTf)_3$	–	23:77 (78)
10	3-HQD	$Yb(OTf)_3$	–	20:80 (74)
11	3-HQD	$In(OTf)_3$	–	18:82 (89)
12	(*S*)-3-HQD	–	–	9:91 (21)[f]
13	(*R*)-3-HQD	–	–	16:84 (34)[f]

[a] All reactions were performed under neat conditions using 5 equiv. of methyl acrylate in the presence of 1 equiv. of catalyst and 0.05 equiv. of Lewis acid.
[b] Determined by ^{1}H NMR.
[c] Yield of isolated **3a** (**A+B**). The isomers can be separated by chromatography.
[d] 5 equiv.
[e] 0.5 equiv.
[f] 10 equiv. of methyl acrylate were used.

followed by addition of lithium amide to the resulting thiosulfoxide and further condensation of the intermediate *tert*-butanesulfinamide with benzaldehyde gave the required imine.

We initially embarked on the reaction of *N*-*p*-toluenesulfinimines **1a** (which we expected to be more reactive than *N*-*tert*-butanesulfinimine **2**) with methyl acrylate in the presence of one of the most reactive amine catalysts, 3-hydroxyquinuclidine (3-HQD). However, not unexpectedly, only a low yield of the Baylis–Hillman adduct was obtained after 7 days (Table 1, entry 1). We therefore sought to use some of our improved reaction conditions to increase the rate of the process and thereby improve the yield of the adduct. We recently reported that small amounts of formamide show a marked increase in rate of the standard Baylis–Hillman reaction employing aldehydes,[8] but in this case no rate increase was observed when *N*-*p*-toluenesulfinimine **1a** was used (entry 2). We have also described the use of Lewis acids (e.g. $La(OTf)_3$) together with triethanolamine as co-catalysts to accelerate the Baylis–Hillman reaction[5a] and a significant improvement in yield was observed employing these conditions with *N*-*p*-toluenesulfinimine **1a** (entry 4). Further screening of Lewis acids (entries 6–11) revealed that $In(OTf)_3$ was the optimum Lewis acid providing 89% yield of the adduct after 7 days (entry 11). Shorter reaction times led to lower yields.

The diastereoselectivity of the process was not substantially affected by the reaction conditions but we were concerned that some erosion of selectivity and possibly even reactivity could result from using racemic 3-hydroxyquinuclidine where perhaps the matched and mismatched diastereomeric transition states would contribute different diastereoselectivity. Thus, 3-hydroxyquinuclidine was resolved[9] and tested under the standard reaction conditions (entries 12 and 13) but only a small variation in both yield and diastereoselectivity was observed, indicating that the stereochemistry of the sulfinimine dominates control in the selectivity of the process.

The absolute configuration of the major adduct **3aB** was unequivocally determined as *S* at the new stereogenic centre by X-ray crystallography (Fig. 2).[10]

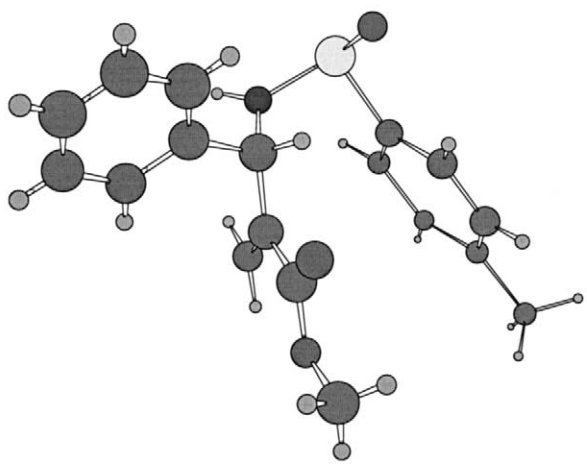
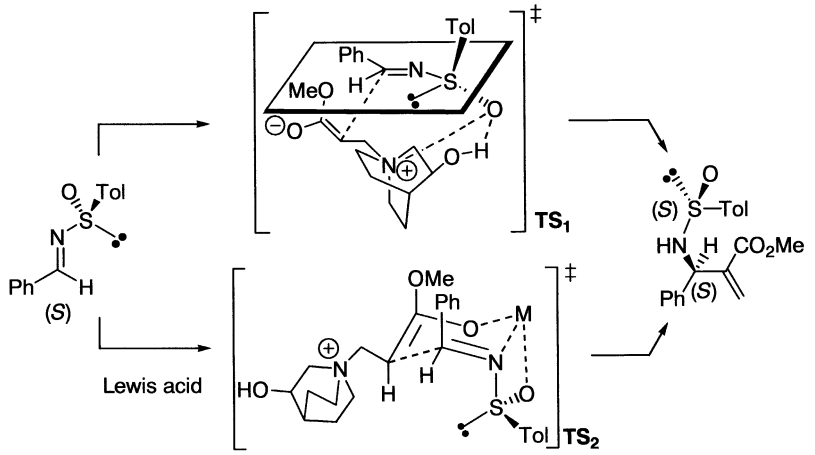
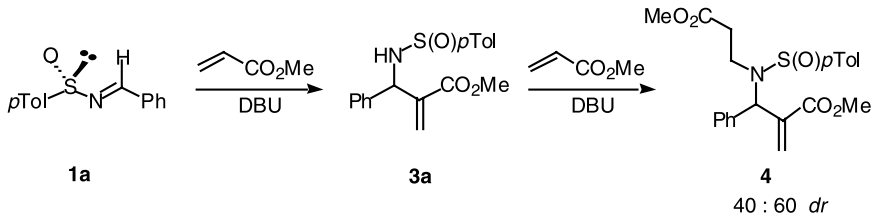


Figure 2. X-Ray structure of **3aB**.



Scheme 1.



Scheme 2.

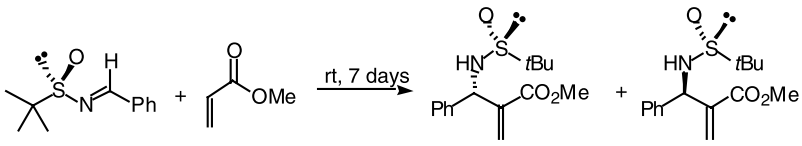
The diastereoselectivity can be explained in terms of the preferred conformation of the imine (Scheme 1), whereby $A^{(1,3)}$-strain is minimised by placing the bulky substituents at sulfur out of the plane of the double bond.[11] The nucleophile then preferentially approaches *anti* to the large *p*-tolyl substituent giving rise to the observed stereochemistry. Additionally, this approach is favoured by Coulombic attraction between the sulfinyl oxygen and the quaternary ammonium moiety in $\mathbf{TS}_1$ and perhaps by hydrogen bonding as well. In the presence of a Lewis acid catalyst, a chairlike transition state ($\mathbf{TS}_2$) based on the model proposed by Davis to explain the attack of ester enolates to sulfinimines[12] and applied by other authors[13] could also account for the formation of the major diastereomer. In this **TS** the metal coordinates with the imine nitrogen, the sulfinyl oxygen, and the oxygen of the acrylate, so that the C–C bond formation takes place intramolecularly from a rigid coordinated intermediate. Thus, in the presence/absence of metal catalysts both transition states lead to the same major diastereomer as observed.

We have previously reported DBU to be the most active catalyst for the Baylis–Hillman reaction[14] but in the case of *N*-*p*-toluenesulfinimine, an unexpected reaction occurred. The Baylis–Hillman product **3** reacted a second time with the acrylate in the presence of the stronger base to give adduct **4** as ca. 40:60 mixture of the diastereomers in 68% isolated yield (Scheme 2).

In the few examples described in the literature where the synthetic properties of *N*-*p*-toluenesulfinimines were compared to their *N*-*tert*-butanesulfinyl counterparts, higher levels of diastereocontrol were attained using the latter, bulkier derivative.[15] We therefore tested the reaction of *N*-*tert*-butanesulfinimine **2** with methyl acrylate under the same reaction conditions studied for **1a** and the results are summarised in Table 2.

Higher diastereoselectivity was indeed observed especially in the presence of Lewis acids but the yields were much poorer. The low yields are presumably due to the increased bulk and lower electron withdrawing power of the *tert*-butanesulfinyl moiety rendering the imine much less electrophilic than the *N*-*p*-toluenesulfinimine. Thus, the optimum group on nitrogen was the *p*-toluenesulfinyl group. We therefore tested other *N*-*p*-toluenesulfinimines derived from both aromatic and aliphatic aldehydes. Thus, the reactions of (*S*)-(+)-*N*-(*p*-nitrobenzylidene)-*p*-toluenesulfinamide (**1b**), (*S*)-(+)-*N*-(*p*-methoxybenzylidene)-*p*-toluenesulfinamide (**1c**), and (*S*)-(+)-*N*-*n*-butylidene-*p*-toluenesulfinamide (**1d**) with methyl acrylate in the presence of 3-hydroxyquinuclidine and the Lewis acid catalysts (indium, scandium and ytterbium triflate) that had afforded the best yields and diastereoselectivities for **1a**, were studied (Table 3). The *p*-nitrophenyl derivative **1b** reacted faster than substrate **1a**, giving high diastereoselectivities in moderate yields in only two days (entry 1). The much less activated sulfinimine, (*p*-methoxyphenyl)-*p*-toluenesulfinamide **1c**, failed to react even after long reaction times under all the tested conditions (entry 2). The aliphatic imine **1d** reacted in moderate yield and again with a good diastereoselectivity (entry 3).[16]

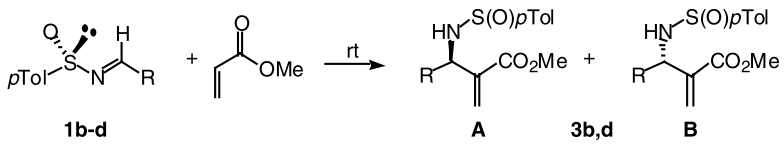
Table 2. Baylis–Hillman reactions of (*R*)-(−)-*N*-(benzylidene)-2-methylpropanesulfinamide **2**[a]



Entry	Base	Lewis acid	Diastereomeric ratio **A**:**B**[b] (Yield (%))[c]
1	3-HQD	–	12:88 (8)
2	DBU	–	45:55 (34)
3	3-HQD	$La(OTf)_3$	4:96 (12)
4	3-HQD	$Al(O\textit{i}\text{-}Pr)_3$	10:90 (4)
5	3-HQD	$Zn(OTf)_2$	11:89 (27)
6	3-HQD	$Zr(O\textit{i}\text{-}Pr)_4$	9:91 (9)
7	3-HQD	$Sc(OTf)_3$	8:92 (10)
8	3-HQD	$Yb(OTf)_3$	9:91 (10)
9	3-HQD	$In(OTf)_3$	18:82 (17)

[a] All reactions were performed under neat conditions using 5 equiv. of methyl acrylate in the presence of 1 equiv. of catalyst and 0.05 equiv. of Lewis acid.
[b] Determined by ^{1}H NMR.
[c] Yield of isolated **5B**.

Table 3. Baylis–Hillman reactions of *N*-sulfinimines **1b–d**[a]



Entry	R	Time (days)	Diastereomeric ratio **A**:**B**[b] (Yield (%))[c]		
			$Sc(OTf)_3$	$Yb(OTf)_3$	$In(OTf)_3$
1	*p*-NO_2-Ar (**1b**)	2	9:91 (50)	6:94 (52)	14:86 (48)
2	*p*-MeO-Ar (**1c**)	7	–	–	–
3	*n*-Pr (**1d**)	7	14:86 (46)	15:85 (45)	13:87 (47)

[a] All reactions were performed under neat conditions using 5 equiv. of methyl acrylate in the presence of 1 equiv. of catalyst and 0.05 equiv. of Lewis acid.
[b] Determined by ^{1}H NMR.
[c] Yield of isolated major diastereomern **B**.

In conclusion, we have described new methodology that affords a short synthesis of enantiomerically pure α-methylene-β-amino esters through a diastereoselective Baylis–Hillman reaction of weakly activated imines. The densely functionalised products will undoubtedly find applications in the synthesis of β-amino acids and other biologically important molecules. The use of lanthanide-based Lewis acids to increase the electrophilicity of the imines was critical to the success of the process.

Acknowledgements

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16. *General procedure for Baylis–Hillman reactions of N-sulfinimines with methyl acrylate catalysed by Lewis acids*. A mixture of sulfinimime (1 equiv.), methyl acrylate (10 equiv.), 3-hydroxyquinuclidine (1 equiv.), and Lewis acid catalyst (5 mol%) was stirred at room temperature for the indicated time. The reaction mixture was diluted with dichloromethane, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography.
(*S,S*)-*Methyl 2-[phenyl(p-toluenesulfinylamino)methyl]-acrylate* (**3aB**). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.20–7.40 (m, 7H), 6.40 (s, 1H), 5.80 (s, 1H), 5.45 (d, $J=7$ Hz, 1H), 4.95 (d, $J=7$ Hz, 1H), 3.69 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.5, 141.6, 141.3, 140.7, 139.9, 129.6, 128.6, 127.7, 127.6, 127.0, 125.8, 57.8, 51.9, 21.4. Anal. calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.82; N, 4.25; S, 9.74. Found: C, 65.46; H, 5.89; N, 4.10; S, 9.87. HRMS (EI): $C_{18}H_{19}NO_3S$ requires 329.1085. Found: 329.1079. $[\alpha]_D=+24$ (*c* 0.1, CH_2Cl_2).
(*R,R*)-*Methyl 2-[2-methylpropane-2-sulfinylamino)phenylmethyl]acrylate* (**5aB**). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.20–7.30 (m, 5H), 6.41 (s, 1H), 5.96 (s, 1H), 5.35 (d, $J=7$ Hz, 1H), 4.43 (d, $J=7$ Hz, 1H), 3.70 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 141.3, 139.6, 128.5, 127.8, 127.5, 127.3, 61.0, 56.2, 52.1, 22.7. $[\alpha]_D=-8.3$ (*c* 0.04, CH_2Cl_2).
(S,S)-Methyl 2-[(4-nitrophenyl(p-toluenesulfinylamino)-methyl]acrylate (**3bB**). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.20 (m, 2H), 7.60–7.30 (m, 6H), 6.37 (s, 1H), 5.78 (s, 1H), 5.35 (d, $J=7$ Hz, 1H), 5.15 (d, $J=7$ Hz, 1H), 3.63 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.5, 147.4, 141.9, 140.7, 139.6, 129.7, 128.1, 125.7, 123.8, 58.2, 52.2, 21.4.
(S,S)-Methyl 2-[1-(p-toluenesulfinylamino)butyl]acrylate (**3dB**). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.2 (m, 2H), 6.01 (s, 1H), 5.42 (s, 1H), 5.15 (d, $J=9$ Hz, 1H), 4.80 (m, 1H), 3.68 (s, 3H), 2.36 (s, 3H), 180–1.50 (m, 2H), 1.40–1.10 (m, 2H), 0.85 (t, $J=7$ Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.3, 141.9, 141.1, 141.0, 129.3, 126.3, 125.9, 57.4, 51.8, 38.3, 21.3, 19.6, 13.6.