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Asymmetric Aza-Henry Reactions from *N*-*p*-Tolylsulfinylimines

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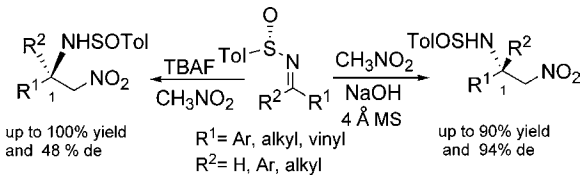
ABSTRACT



***N*-Sulfinylimines derived from aromatic or aliphatic aldehydes and ketones react with nitromethane and NaOH in a highly diastereoselective manner under mild conditions. In the presence of TBAF, the reaction rates are strongly increased and the stereoselectivity is inverted. This method provides enantiomerically pure *β*-nitroamines derived from enolizable aldimines and ketimines, which so far are hardly accessible by aza-Henry reactions.**

Optically pure *β*-nitroamines, obtained by aza-Henry (or nitro-Mannich) reactions, are attractive targets in asymmetric synthesis, mainly due to their easy conversion into vicinal diamines. They have remarkable structural motifs, not only because of their occurrence in biologically active compounds, including natural products, but also as valuable building blocks, chiral auxiliaries, and metal ligands.[1]

Diastereoselective aza-Henry reactions have been described by Anderson[2] and Bernardi[3] using different conditions for aromatic aldimines. In the first of these papers, the authors comment on the difficulties associated with the use of aliphatic imines as starting materials. However, these reactions have been studied on racemic substrates, and to our knowledge, there are no general studies involving diastereoselective aza-Henry reactions yielding optically pure compounds.[4]

The catalytic enantioselective aza-Henry reaction was first reported by Shibasaki using *N*-phosphinoylimines and a heterobimetallic catalyst.[5] Jørgensen described the addition of different nitronates to α-iminoesters, catalyzed by chiral copper complexes to provide precursors of α,*β*-diamino carboxylic acids in high diastereo- and enantioselectivity.[6] In addition to these strategies, based on metal Lewis acid activation of the imine and Brønsted base activation of the nucleophile, several organocatalytic approaches have recently been published. Johnston[7] has reported the proton-catalyzed reaction of *N*-Boc aromatic aldimines with nitroethane in the presence of a chiral bisamidine ligand providing *β*-nitroamines in a highly diastereo- and enantioselective manner. The bifunctional thiourea-based chiral organocatalysts, de-

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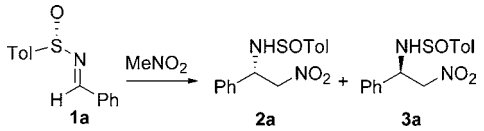
signed by Takemoto[8] and Jacobsen,[9] have also been shown to be efficient for catalyzed reactions of *N*-phosphinoylimines and *N*-Boc-imines. Recently Jørgensen has reported high ee's for the reaction of tertiary nitro compounds with α-iminoesters using a combination of chiral Lewis acids and chiral organocatalysts.[10]

The main drawback for all of these conceptually brilliant enantioselective aza-Henry reactions is the restricted scope of the starting substrates, using only aromatic aldimines, which seriously limits their synthetic usefulness.[11] As this limitation could be due to the difficulties associated in the synthesis of the enolizable activated imines so far used in these reactions, we reasoned that it would be overcome by using other activating groups of the C═N bonds lacking this synthetic restriction.

N-Sulfinylimines have shown to be one of the most efficient imine derivatives in asymmetric processes involving reactions with nucleophiles. As a consequence, they have been successfully applied, mainly by Davis[12] and Ellman,[13] in the synthesis of a broad variety of structurally diverse nitrogen-containing molecules. However, to our knowledge, they have never been used as activated imines in the aza-Henry processes. Despite the presumably lower activation induced by the sulfinyl group at the C═N bond, with respect to that of the usually employed in these reactions, the use of the *N*-sulfinylimines as substrate of the aza-Henry reactions would have the advantage of the few structural restrictions found in their synthesis in optically pure form, even when they have enolizable protons. These features prompted us to evaluate their behavior as substrates in aza-Henry reactions. We report herein the initial study of conditions concerning the use of *N*-sulfinylimines as starting products in the asymmetric aza-Henry reactions with nitromethane. It has allowed us the synthesis of a wide variety of *β*-nitroamines derived from *N*-sulfinylaldimines and ketimines, with or without an enolizable proton, in a highly stereoselective manner. This strategy provides some advantages in terms of handling and substrate variety.

N-Sulfinylimines **1a**−**i** were obtained by condensation of the corresponding aldehydes and ketones with (*S*)-*N*-*p*-tolylsulfinylamide following the $Ti(OEt)_4$ Davis protocol[12] with slight modifications in the workup.[14] Optimization of their reactions with nitromethane were examined on the aromatic *p*-tolylsulfinylaldimine **1a** by exploring several solvents (THF, CH_2Cl_2, toluene, nitromethane), bases,[15] and Lewis acids [CuF_2, $Yb(O^iPr)_3$, $Yb(Cl)_3$, $Yb(OTf)_3$].

Table 1. Optimization of the Reaction Conditions



1a **2a** **3a**

entry	conditions	*t* (h)	*T* (°C)	conv[a] (%)	de[a] (%) **2a/3a**	yield[b] (%)
1	NaOH (5 equiv) 4 Å MS	120	rt	95	94:6	85 (62)[c]
2	NaOH (5 equiv) 4 Å MS	24	40	98	94:6	90 (65)[c]
3	NaOH (5 equiv) 4 Å MS[d]	96	40	91	83:17	59
4	$Yb(O^iPr)_3$ (1 equiv)[d]	200	rt	20	77:23	14
5	$Yb(O^iPr)_3$ (1 equiv)	144	rt	16	83:17	*e*
6	$Yb(O^iPr)_3$ (1 equiv) NaOH (5 equiv)	24	rt	95	93:7	75
7	TBAF (1 equiv)	0.1	rt	100	36:64	99
8	TBAF (1 equiv)	0.3	0	100	36:64	99
9	TBAF (0.2 equiv)	0.3	rt	100	37:63	95
10	TBAF (1 equiv) NaOH (5 equiv)	1	rt	100	38:62	95

[a] Determined by ^1H NMR. [b] After silica gel chromatography. [c] Isolated yield of **2a** after crystallization in ether. [d] Solvent: THF, $MeNO_2$ (20 equiv). [e] Not determined.

As shown in Table 1, the best results were obtained with NaOH (5 equiv) in the presence of powdered 4 Å molecular sieves using nitromethane as solvent. After 120 h at room temperature (entry 1), a 94:6 mixture of nitroamines **2a** and **3a** was obtained in 85% yield (95% conversion). The mixture can be purified by chromatography, which indicate the isomers are stable to the retro-aza-Henry reaction, and the major isomer could be isolated in 62% yield after crystallization in ether. By increasing the temperature to 40 °C, the reaction times are shortened (24 h) with slightly improving yields without affecting the selectivity (entry 2). Lowering the temperature did not improve the stereoselectivity but dramatically increased the reaction times. Slower reactions and very low stereoselectivity are the result of using THF as solvent (entry 3).

The use of lanthanide Lewis acids such as $Yb(O^iPr)_3$, which have proven to be excellent catalysts for the activation of *N*-sulfonylimines in their aza-Henry reactions in THF,[16] had no positive influence in THF (entry 4) or nitromethane (entry 5) as the solvent. Nevertheless, when it was used in combination with NaOH a small decrease in reaction time was observed at room temperature (entry 6). The highest increase of the reaction rate was promoted by the addition of TBAF which reduced the reaction time to 20 min at 0 °C

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(11) During the preparation of the present manuscript, a case of enantioselective nitro-Manich addition of nitroethane into two alkyl-derived aldimines was published: Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson C. *J. Org. Chem.* **2005**, *70*, 5565. Nevertheless, the authors state the moderate stability of these two prepared aldimines.
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(15) Bases of lithium (LiO^tBu, LiH, $LiNH_2$, LiHMDS, Li_2CO_3, LiOH), sodium (NaO^tBu, NaHMDS, NaOH), and potassium (KOH, KO^tBu) have been explored.
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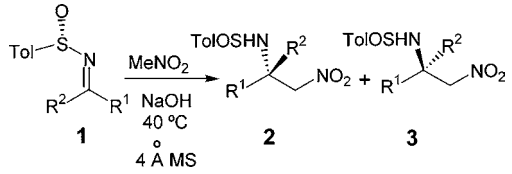
(entry 7). With this catalyst the selectivity is inverted, with **3a** obtained as the major isomer, but the de observed was low and changing the temperature had little effect (entry 8). The use of substoichiometric amounts of TBAF does not substantially modify the results (compare entries 7 and 9), which reveals the catalytic role of this additive, whereas the addition of NaOH to the reactions catalyzed by TBAF does not improve the results (entry 10). Reaction of *N*-*tert*-butylsulfinylbenzylidenimine under the conditions of entry 7 was slower than that of **1a** (16 h) but evolved with similar stereoselectivity.

With the optimized conditions in hand, we examined the scope and limitations of the reaction of a wide variety of *N*-sulfinylimines with nitromethane by using NaOH (Table 2) and TBAF (Table 3) as reagents. As expected, reactions

Table 2. Aza-Henry Reaction of Nitromethane and (*S*)-*N*-Sulfinylimines **1b**−**i** with NaOH

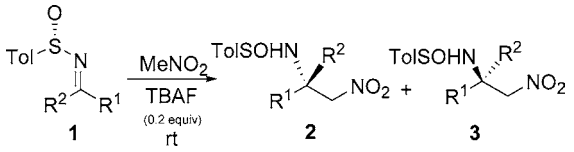


entry	R^1	R^2	s.m./prod	t (h)	conv[a] (%)	**2/3**[a]	yield (%)
1	C_6H_5	H	**a**	24	98	94:6	90
2	*p*-CNC_6H_4	H	**b**	12[b]	95	94:6	75
3	*p*-$MeOC_6H_4$	H	**c**	48	80	92:8	76[c]
4	PhCH=CH	H	**d**	12[b]	77	89:11[h]	69[d]
5	Me	H	**e**	12[b]	95	94:6	79 (66)[d]
6	*i*-Pr	H	**f**	21	84	97:3[h]	69[e]
7	*t*-Bu	H	**g**	160	68	97:3	46[f] (36)[d]
8	*t*-Bu	H[g]	**g**	160	46	95:5	*j*
9	Ph	Me[g]	**h**	72	100	85:15	60
10	*i*-Pr	Me	**i**	96	100[i]	94:6	25
11	*i*-Pr	Me[g]	**i**	48	100[i]	93:7	32

[a] Determined by ^{1}H NMR. [b] rt. [c] 19% of **1c** was recovered. [d] Isolated yield of **2a** after crystallization in ether. [e] 11% of **1f** was recovered. [f] 19% of **1g** was recovered. [g] In the presence of 1 equiv of $Yb(O^iPr)_3$ at rt. [h] Determined by HPLC after chromatography. [i] 30−38% of *p*-tolylsulfinamide was detected in the crude by HPLC. [j] Not determined.

of **1b** and **1c** catalyzed by NaOH are, respectively, faster and slower than that of **1a** (compare entries 2 and 3 with 1, Table 2) but the stereoselectivity is very similar. The α,β-unsaturated imine **1d** also provided the β-nitroamine **2d** with no traces of 1,4-conjugate addition product (entry 4, Table 2). More interestingly, the enolizable aliphatic *N*-sulfinylaldimines **1e** and **1f** also evolve into the aza-Henry products in similar yields and stereoselectivities than those observed for the aromatic aldimines (entries 5 and 6, Table 2). The bulky *N*-sulfinylimine **1g** requires longer reaction times (entry 7, Table 2), and the addition of $Yb(O^iPr)_3$ did not improve the reactivity (entry 8). *N*-Sulfinylketimines **1h**−**i** exhibit lower reactivity (entries 9−11), thus requiring Yb-$(OiPr)_3$ catalysis and longer reaction times to get their complete evolution under conditions similar to those used

Table 3. Aza-Henry Reaction of Nitromethane and *N*-Sulfinylimines with TBAF



entry	R^1	R^2	s.m./prod	t (h)	conv[a] (%)	**2/3**[a]	yield (%)
1	C_6H_5	H	**a**	0.3	98	36:64	99
2	*p*-CNC_6H_4	H	**b**	23	60	30:70	56
3	*p*-CNC_6H_4[b]	H	**b**	0.1	90	30:70	*c*
4	*p*-$MeOC_6H_4$	H	**c**	0.25	99	38:62	90
5	*p*-$MeOC_6H_4$[b]	H	**c**	0.1	99	38:62	*c*
6	Me	H	**e**	0.3	99	34:66	97
7	*t*-Bu	H	**g**	19	83	26:74	62
8	Ph	Me	**h**	2.5	100	36:64	79
9	*i*-Pr	Me	**i**	4	100	38:62	76

[a] Determined by ^{1}H NMR. [b] 1 equiv of TBAF was used. [c] Not determined.

for aldimines. It is noteworthy that **2h**, bearing a quaternary stereogenic center (entry 9), is formed in notable yield and stereoselectivity. The instability of **1i** under NaOH during the long times required for reaction with nitromethane (entries 10 and 11) must be responsible for the low yield of **2i**. It would also explain the formation of 30−38% of the sulfinamide resulting in the hydrolysis of ketimine **1i**.

Reactions catalyzed by substoichiometric amounts of TBAF (Table 3) show a dramatic increase in the reactivity as well as an inversion of the stereoselectivity. The few minutes required for aromatic *N*-sulfinylaldimines **1a** and **1c** (entries 1 and 4, Table 3) and the aliphatic *N*-sulfinylaldimine **1e** (entry 6) contrast with the much longer times of their reactions with NaOH (Table 2), with isolated yields higher than 90% in all cases. Despite the expected lower reactivity of bulky **1g** under TBAF (after 19 h only 83% conversion was observed, entry 7), it is much higher than under NaOH (compare entry 7, Table 3 ,with entry 7, Table 2). Remarkable are the results obtained from **1h** and **1i**, which complete their evolution in less than 4 h affording **2h** and **2i** in very good yields (entries 8 and 9, Table 3), revealing that both starting imines are stable enough under these reaction conditions. The most intriguing result is that obtained for **1b** which reacts more slowly under TBAF (0.2 equiv) than under NaOH (compare entry 2 in Tables 2 and 3). Nevertheless, this inversion of reactivity is not observed when 1 equiv of TBAF was used. Thus, reactions of **1b** and **1c** are both instantaneous (entries 3 and 5, Table 3). This observation could suggest that the effect of TBAF was partially inhibited by the presence of the CN substituent (entries 2 and 3, Table 3). All reactions provide mixtures of diastereoisomers with **3** being the major ones. The stereoselectivity is only moderate (30−48% de), and it is not significantly improved by decreasing the temperature (reactions performed at 0 °C afford mixtures of composition similar to that indicated in Table 3). The electronic density

at the aromatic ring does not have significant influence on the stereoselectivity. Thus, imines **1a**−**c** afford quite similar de (entries 1−5).

The configuration of compound **2a** was established by X-ray crystallography of a racemic sample (see the Supporting Information). As the conditions used in these reactions do not affect the configuration of the sulfinyl sulfur, we can unequivocally assign the (S_S,*S*) configuration to **2a** as well as to the major diastereoisomers obtained in all reactions performed with NaOH, because it is expected that similar stereochemical evolution takes place for all the imines. The β-nitroamines **3** are therefore assigned as (*S*s, *R*).

The high selectivity of the addition of nitromethane in the presence of NaOH could be attributed to the formation of a rigid transition state involving both reacting partners coordinated to the metal (Figure 1). The important role of the

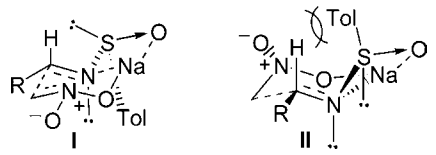


Figure 1. Transition states involved in the aza-Henry reactions carried out in the presence of NaOH.

metal in the stereoselectivity has been proven by performing the reaction of **1a** with nitromethane in the presence of 5 equiv of 15-crown-5. Under these conditions, a complex reaction mixture was obtained in which **2a** and **3a** were detected in a 1:1 ratio. The *S* configuration of the imine favors the transition state **I** leading to the (S_S,*S*) isomer since the transition state **II** affording the (S_S,*R*) one would be destabilized by the steric interactions of the bulky *p*-tolyl group (Figure 1).

Concerning the role of the TBAF, a simultaneous and double activation of the nucleophile (nitromethane) and the electrophile (*N*-sulfinylimine) would explain its strong increase in reactivity. Initially, we thought that the F^- was responsible for the double activation. It would form the conjugate base of the nitromethane and the resulting HF would provoke the protonation and, therefore, activation of the imine. However, the fact that the increase of the reaction rate is also evident in the presence of 5 equiv of NaOH (entry 10, Table 1), which immediately would capture the proton from HF, suggests other possibilities. The basic strength of the F^- ($pK_a = 3.17$) is enough to activate the nucleophile by conversion of a significant part of the nitromethane into its conjugated base. Although this activation is a necessary condition (tetrabutylammonium hydroxide shows the same accelerating influence as TBAF, whereas the reaction does not work in the presence of tetrabutylammonium bromide) the activation of the *N*-sulfinylimine by the ammonium cation seems much more important. This activation has been reported, among others, for aldehydes[17] in their condensation with nitroalkanes (Henry reaction) and for enolates[18] in their alkylation reactions, which is attributed to the formation of a contact ion pair $O^-\cdots N^+$ between the reagent and the catalyst. The same explanation could be used for explaining the strong increase of the reactivity observed for *N*-sulfinylimines, with the sulfinyl oxygen involved in the interaction. The formation of this contact ion pair precludes the formation of the transition states postulated in Figure 1, thus justifying the observed changes in the stereoselectivity.

In summary, we have proved that stable and easily available *N*-sulfinylimines react with nitromethane anion in a highly diastereselective manner under mild conditions providing enantiomerically pure versatile β-nitroamines derived from aromatic or aliphatic aldehydes and ketones which had not been accessible by other previously described methods. These reactions are strongly catalyzed by ammonium ions, which can afford the opposite diastereomer as the major in moderate selectivity.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2a**−**i** and **3a**−**i** and X-ray ORTEP diagram of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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