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Racemization Free Protocol for the Synthesis of *N*-*tert*-Butanesulfinyl Ketimines

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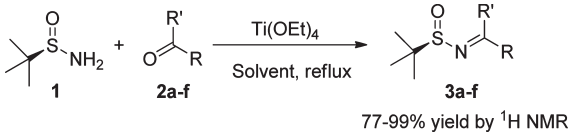
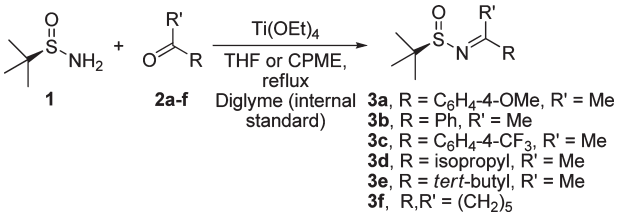


A general and robust racemization-free protocol for the synthesis of a variety of *N*-*tert*-butanesulfinyl ketimines is reported. Reaction progress was monitored by ^{1}H NMR using the nonperturbing internal standard diglyme, and ketimines were formed in good to high yields in either THF or CPME (cyclopentyl methyl ether) as solvent with heating to reflux.

N-*tert*-Butanesulfinyl imines are now among the most extensively used compounds in asymmetric synthesis.[1] The popularity of *N*-*tert*-butanesulfinyl imines derives not only from the chiral directing ability of the sulfinyl group but also the fact that they are stable to hydrolysis and tautomerization and consequently are easily manipulated, stored, and purified while at the same time showing high reactivity for the addition of a wide range of nucleophiles in excellent yields. A further desirable feature of *N*-*tert*-butanesulfinyl imines is their high-yielding one-step synthesis by direct condensation of *tert*-butanesulfinamide (**1**) with carbonyl compounds. Indeed, a number of mild and general methods have been reported for the condensation of **1** with aldehydes.[1a,2] In contrast, for the condensation of the comparatively less electrophilic and more sterically encumbered ketones, heating is required and only the use of titanium alkoxides, which serve as both Lewis acids and water scavengers,

SCHEME 1. Synthesis of *N*-*tert*-Butanesulfinyl Ketimines



has proven to be generally effective.[2b,3] Recently, a personal communication alerted us to the susceptibility of the sulfinyl stereocenter to racemization upon $Ti(OR)_4$-mediated condensation of a proprietary ketone under particularly harsh conditions.[4] This observation prompted us to reinvestigate $Ti(OR)_4$-mediated ketone condensations under different conditions, including extended reaction times and elevated temperatures. Herein, we report the racemization-free condensation of *tert*-butanesulfinamide (**1**) with a variety of ketones even under forcing conditions. Moreover, by monitoring the rate of condensation, optimal conditions for the preparation of *N*-sulfinyl ketimines for different substrate classes were also established. Finally, for challenging substrates that require prolonged reaction times, the importance of performing reactions under an inert atmosphere is documented.

Our investigation began with a model condensation reaction with enantiomerically pure **1** and the electron-rich and therefore unreactive aromatic ketone 4-methoxyacetophenone (**2a**) (Scheme 1). All condensation reactions were carefully monitored by ^{1}H NMR using the nonperturbing internal standard diglyme, and yields were quantitated on the basis of the production of ketimine **3a** at 3, 6, 12, 24, and 48 h time points (Table 1). Under previously reported conditions, 0.5 M **1**, ketone (1.1 equiv), and $Ti(OEt)_4$ (2.0 equiv) in THF at reflux the reaction was slow and required 48 h for imine **3a** to be obtained in 84% yield (entry 1). Interestingly, performing the reaction at double the concentration resulted in only modest acceleration in the rate of reaction (entry 2). The effect of reversing the stoichiometry of **1** and **2a** was next evaluated by using 1.1 equiv of **1** rather than a slight excess of ketone (entry 3). Under these conditions, the initial reaction rate was modestly faster, and based upon the limiting ketone starting material also resulted in a comparable overall yield (86%). For each of the reaction conditions, the enantiomeric purity of the imine product was determined by HPLC analysis, and in all cases no racemization to the limits of detection (< 0.5% ee) was observed even at the longest reaction times. To enable convenient reaction conditions that enabled higher conversion at shorter reaction times, the reaction was also performed by replacing THF (bp = 66 °C) with the higher boiling solvent cyclopentyl methyl ether (bp = 106 °C), which has become increasingly popular in process research because of its higher chemical stability and lower flammability relative to that of other

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TABLE 1. Optimization of Reaction Parameters for Ketimine 3a[a]

						NMR yields (%)[b] at specified times				
entry	ketone	solvent	conc (M)	**1** (equiv)	**2** (equiv)	3 h	6 h	12 h	24 h	48 h
1	**2a**	THF	0.5	1.0	1.1	38	51	65	72	84
2	**2a**	THF	1.0	1.0	1.1	37	58	68	76	84
3	**2a**	THF	1.0	1.1	1.0	46	57	67	78	86
4	**2a**	CPME	1.0	1.0	1.1	84	90	79	79[c]	79[d]

[a]All condensation reactions were performed under nitrogen atmosphere using 2.0 equiv of $Ti(OEt)_4$. No racemization of the ketimine product **3a** was observed (>99.5% ee) unless otherwise indicated, as determined by HPLC analysis with use of the racemic imine as standard for comparison (see Supporting Information). [b]NMR spectra recorded using a single scan. [c]98% ee. [d]91% ee.

TABLE 2. Results for Condensation Reactions to form Ketimines 3[a]

						NMR yields (%)[b] of ketimines **3** at specified time						
entry	ketone	solvent	conc (M)	**1** (equiv)	**2** (equiv)	1.5 h	3 h	6 h	12 h	24 h	48 h	ee (%) (at 48 h)
1	**2b**	THF	1.0	1.0	1.1		63	83	94	97	99	>99.5
2	**2b**	THF	1.0	1.1	1.0		58	65	76	81	85	>99.5
3	**2c**	THF	1.0	1.0	1.1	66	75	79	87	90	90	>99.5
4	**2c**	THF	1.0	1.1	1.0	71	77	81	83	81	82	>99.5
5	**2d**	THF	1.0	1.0	1.1	52	61	71	81	87	93	>99.5
6	**2d**	THF	1.0	1.1	1.0	65	77	85	95	95	97	>99.5
7	**2e**	THF	1.0	1.0	1.1				57	67	78	>99.5
8	**2e**	CPME	1.0	1.0	1.1	41	47	58	73	77	77	>99.5
9	**2e**	CPME	1.0	1.1	1.0	74	85	95	90	86	80	>99.5
10	**2f**	THF	1.0	1.0	1.1	84	86	88	97	97	99	>99.5
11	**2f**	THF	1.0	1.1	1.0	80	92	76	74	67	56	>99.5

[a]All condensation reactions were performed under nitrogen atmosphere using 2.0 equiv of $Ti(OEt)_4$. No racemization of the ketimine products **3** was observed even at the longest time point (>99.5% ee) as determined by HPLC analysis with use of the racemic imine as standard for comparison (see Supporting Information). [b]NMR spectra recorded using a single scan.

common ethers such as diethyl and *tert*-butyl methyl ethers.[5] Under these conditions, an 84% yield of imine **3a** was observed within 3 h (entry 4). Notably, the product yield increased to 90% after a 6 h reaction time and thereafter gradually decreased to 79% over 48 h. The enantiomeric purity of the product was also determined at each time point, and through 12 h, which is well past reaction completion, no racemization was observed (>99.5% ee). However, at longer times racemization did occur, and at 48 h, the product enantiomeric purity was only 91% ee. This result suggests that at least for aromatic ketone substrates, racemization of ketimine products should be monitored if elevated temperatures and prolonged reaction times are employed.

The rate of condensation was next explored with a variety of ketone substrates **2**, with either **1** or ketone **2** each being evaluated as the limiting reagent (Table 2). As expected, the rate of condensation of acetophenone (**2b**) was faster than for electron-rich ketone **2a**, and high yields were observed for both substrate stoichiometries (entries 1 and 2). The electron-deficient 4-trifluoromethylacetophenone (**2c**) was correspondingly converted to imine **3c** at an even faster rate, and again high yields were observed (entries 3 and 4). Because of the rapid rate of condensation for ketones **2b** and **2c** with THF as solvent, reactions in the higher boiling CPME were not performed for these substrates. Aliphatic ketones were also investigated. The condensation of isopropyl methyl ketone (**2d**) proceeded rapidly and in high yields (entries 5 and 6). Not surprisingly, condensation of the more hindered *tert*-butyl methyl ketone (**2e**) proceeded considerably more slowly (entry 7). The condensation of ketone **2e** was therefore also performed at refluxing temperatures with the higher boiling CPME as solvent, with a good 73% yield of **3e** obtained within 12 h followed by a modest increase in yield after a 48 h reaction time (entry 8). Using a slight excess of **1**, a high yield was observed within 6 h with subsequent gradual reduction in yield over longer reaction times (entry 9). Notably, under all of the listed reaction conditions (Table 2, entries 1−9), no racemization to the limits of detection (<0.5% ee) was observed for imines **3b**−**3e** even at the longest reaction times. Cyclohexanone (**2f**) was also investigated due to the numerous reports of synthetic and drug discovery applications of imines prepared from cyclohexanone derivatives. As expected for this unhindered ketone substrate, high conversion was observed within a short time period (entries 10 and 11).

TABLE 3. Configurational Stability of Enantiomerically Pure Imines 3 in THF for 20 h at 100 °C

		enantiomeric purity (%)[a]	
entry	imine	N_2 atmosphere[b]	in air[c]
1	**3a**	>99.5[d]	96.8[d]
2	**3b**	>99.5	80.6
3	**3c**	>99.5	>99.5
4	**3d**	>99.5	>99.5

[a]Enantiomeric purity of ketinimine determined by HPLC analysis with use of racemic standard for comparison (see Supporting Information). [b]The reaction solution was prepared and placed in a sealed tube in an inert atmosphere glovebox. [c]The reaction solution was prepared and placed in a sealed tube in air prior to heating. [d]Significant decomposition of **3a** was also observed.

To gain a better understanding of the configurational stability of *N*-*tert*-butanesulfinyl ketimines **3** at elevated temperatures and under prolonged reaction times, the extent of racemization of analytically and enantiomerically pure ketimines **3a**, **3b**, **3c**, and **3d** was evaluated after heating at 100 °C for 20 h as 1.0 M solutions in THF in sealed tubes (Table 3). No racemization was detected for the electron-deficient

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aromatic imine **3c** or aliphatic imine **3d** (entries 3 and 4). In contrast, whereas imines **3a** and **3b** did not racemize when set up under an inert atmosphere, significant racemization was observed when set up in air (entries 1 and 2). The mechanism of racemization is not clear, although the oxygen dependence on the rate of racemization is consistent with seminal work by Cram,[6] who proposed homolytic S−N bond cleavage followed by radical chain mechanisms for the racemization of enantioenriched *N*-aryl benzenesulfinamide derivatives. In his study, Cram observed that the presence of oxygen resulted in a significantly shorter induction period prior to the onset of racemization.

In conclusion, we have demonstrated the racemization free synthesis of *N*-*tert*-butanesulfinyl ketimines **3** in high yields by condensation of **1** with a variety of ketones. For most ketones THF is an appropriate reaction solvent, but for electronically deactivated or sterically hindered ketones use of CPME is preferred because higher reaction temperatures can readily be achieved. Finally, for challenging substrates that require prolonged reaction times, the importance of performing reactions under an inert atmosphere is documented.

Experimental Section

Representative Procedure for Monitoring Rate and Yield for Imine Formation by ^{1}H NMR Analysis. Preparation of (R_S)-*N*-(1-(4-Methoxyphenyl)ethylidene)-2-methylpropane-2-sulfinamide (3a) [entry 2, Table 1]. $Ti(OEt)_4$ in 5−15% isopropyl alcohol (4.31 g, 18.0 mmol, 2.0 equiv), ketone **2a** (1.49 g, 9.90 mmol, 1.1 equiv), diglyme (603 mg, 4.5 mmol, 0.5 equiv), and 9 mL of THF were added to a three-neck round-bottom flask equipped with magnetic stirrer, reflux condenser, and rubber septum under a nitrogen atmosphere. (**R**)-**1** (1.09 g, 1.0 equiv, 9.00 mmol) was thereafter added, and the solution was heated to reflux under a nitrogen atmosphere. The rate of formation, yield, and enantiomeric purity of ketimine **3a** were determined at different time points by taking aliquots followed by ^{1}H NMR and chiral HPLC analysis. To determine the NMR yields, all ^{1}H NMR spectra were recorded with a single scan. NMR peak listing of reaction mixture at 48 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.26 (m, $Ti(OEt)_4$), 1.3 (s, 9H, *tert*-butyl group from **3a**), 1.81−1.87 (m, THF), 2.6 (s, methyl group of **2a**), 2.8 (s, 3H, methyl group of **3a**), 3.4 (s, methoxy group of diglyme used as standard for integration), 3.53−3.55 (m, diglyme and $Ti(OEt)_4$), 3.62−3.63 (m, diglyme and $Ti(OEt)_4$), 3.71−3.84 (m, THF and $Ti(OEt)_4$), 4.36 and 4.38 (s, methoxy group in **2a** and **3a**), 6.90−6.94 (m, Ar−H, **2a** and **3a**), 7.87−7.94 (m, Ar−H, **2a** and **3a**). Imine **3a** was previously prepared and fully characterized by Anderson and co-workers at Amgen.[7]

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Supporting Information Available: Full experimental details, spectral data, and characterization for all relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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