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Asymmetric synthesis of α,α-diaryl and α-aryl-α-heteroaryl alkylamines by organometallic additions to *N*-*tert*-butanesulfinyl ketimines

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Abstract—Organometallic addition to *tert*-butanesufinyl ketimines derived from diaryl and aryl-heteroaryl ketones provided the corresponding α,α-diaryl and α-aryl-α-heteroaryl alkylamines in good yield with high diastereoselectivity. In many cases, imine facial selectivity is reversed on changing the organometallic counterion. © 2001 Published by Elsevier Science Ltd.

The amine functionality is an important component of many bioactive compounds. In pursuit of farnesyl protein transferase (FPTase) inhibitors possessing a diaryl ether moiety[1] we observed that the presence of a primary amine attached to a quaternary carbon in compound **1** enhanced cell activity without compromising intrinsic potency (Fig. 1).[2]

To aid in SAR studies we required intermediates which contained a chiral nitrogen-substituted quaternary carbon. Methods for the synthesis of α-branched chiral amines employing organometallic addition to sulfenimines have been described by Davis[3] and Ellman.[4] Most of the work has focussed on addition to aldimines. Limited studies have been carried out on ketimines[5] derived from unsymmetrical ketones. The diastereoselective 1,2-addition of organometallic reagents to the *N*-*tert*-butanesulfinyl ketimines of diaryl or aryl-heteroaryl ketones seemed an appropriate method for the preparation of **1**. In this paper we describe our preliminary findings on the asymmetric syntheses of chiral α,α-diaryl and α-aryl-α-heteroaryl alkylamines from *N*-*tert*-butanesulfinyl ketimines. Notably, reversal of diastereoselectivity was observed in most cases when the substrate was treated with either Grignard or organolithium reagents in THF. To carry out these studies, we required an efficient method for the large scale preparation of the key ketimine intermediate **6** (Scheme 1). Aldehyde **3** was prepared in four

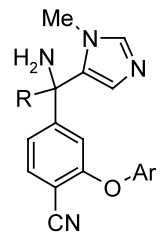

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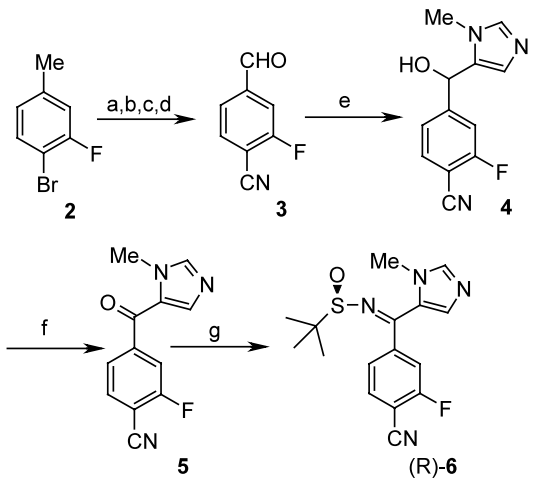
Figure 1.



Scheme 1. *Reagents and conditions*: (a) $KMnO_4$, pyridine, H_2O, reflux, 40 h, 94%; (b) BH_3–THF, 5°C to rt, 24 h, 92%; (c) $Zn(CN)_2$, $Pd(Ph_3P)_4$, DMF, 95°C, 18 h, 66%; (d) pyridine–SO_3, DMSO, Et_3N, 0°C, 2 h, 100%; (e) 1-methylimidazole, *n*-BuLi, Et_3SiCl, THF, −78°C to rt, 18 h; *sec*-BuLi, THF, −78°C to rt, 2 h; (f) MnO_2, CH_2Cl_2, CH_3CN, 3 h, 48%; (g) (*R*)-(+)-2-methyl-2-propanesulfinamide, $Ti(OEt)_4$, THF, reflux, 72 h, 76%.

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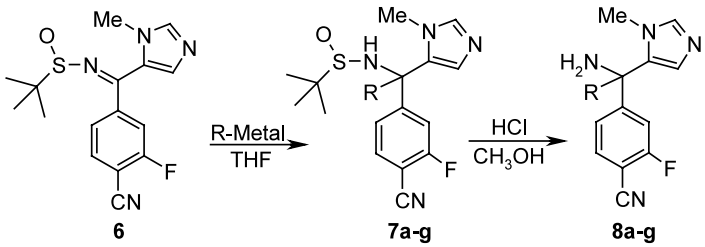
steps from commercially available **2**. Alkylation of aldehyde **3** was achieved with 5-lithio-1-methyl-2-triethylsilylimidazole[6] to give alcohol **4** which was oxidized to ketone **5**. The ketimine **6** was prepared by $Ti(OEt)_4$ mediated condensation of **5** with either commercially available *R*- or *S*-sulfinamide following Ellman's procedure.[7] Compound **6** was isolated in 76% yield after refluxing for 3 days in THF with the mass balance recovered as unreacted ketone **5**. Addition of more sulfinamide, $Ti(OEt)_4$, molecular sieves, and longer reaction times were unsuccessful in driving the reaction to completion. Variable temperature NMR studies of **6** at −40 to 25°C indicates the presence of both *E* and *Z* isomers which rapidly interconvert.[8] Attempts at further structural characterization using NOE experiments were unsuccessful due to rapid exchange.

The versatility of ketimine **6** was evidenced by the introduction of a wide variety of alkyl, alkynyl, and aryl substituents in good to excellent diastereoselectivity (Table 1). The chirality of the amine could be controlled by the choice of organometallic reagent or chiral sulfinamide. Treatment of **6** with a Grignard reagent or alkyllithium in THF, followed by cleavage of the *tert*-butanesulfinyl group with 4 M HCl in dioxane and CH_3OH, liberated the amines **8a**–**g**. THF was the solvent of choice due to the insolubility of the ketimine substrate in diethyl ether or CH_2Cl_2. Reactions were run for 5–15 min, then quenched with water. Grignard additions required many equivalents (~6 equiv.) at 0°C to consume all of the starting material, whereas alkyl lithium additions required only 1–1.5 equiv. at −78°C. The addition was selective for the ketimine over the nitrile when the organometallic was added to the substrate, but not under inverse conditions. Good to excellent yields were obtained in all cases except for **8f** and **8g** (entries 10–13), presumably due to the instability of the pyridyllithium reagents. Aryl organometallic addition was consistently more selective than aliphatic organometallic addition probably due to the steric bulk of the nucleophile (entries 4,5 versus 1,2). Grignard versus alkyllithium additions to the *R*-ketimine gave opposite stereoselectivity (entries 1 versus 2 and 4 versus 5). Thus, with the proper choice of organometallic reagent or chiral ketimine, either enantiomer of **8** could be synthesized.

To determine whether the facile and diastereoselective addition to the (*R*)-ketimine **6** was unique to this particular compound, a series of diaryl and aryl-heteroaryl ketimines were examined.[10] Examples were chosen (Table 2) to determine the role of the 4-cyano group as well as the imidazole moiety on reactivity and selectivity. As before, Grignard additions were generally performed at 0°C whereas organolithium additions were performed at −78°C.

With aryl-heteroaryl ketimines (entries 1–4), a reversal in selectivity is observed suggesting imidazole is not

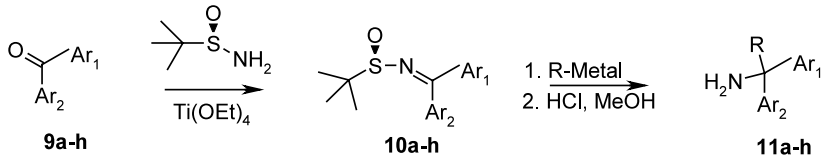
Table 1. 1,2-Addition of organometallic reagents to **6**[a]



Entry	Substrate	*R*-Metal	*T* (°C)	Product	Ratio (−):(+)[b]	Yield (%)[c]
1	*R*-**6**	CH_3MgBr	0	**8a**	(80:20)	74
2	*R*-**6**	CH_3Li	−78	**8a**	13:87	82
3	*S*-**6**	CH_3Li	−78	**8a**	(94:6)	65
4	*R*-**6**	$(C_6H_5)MgBr$	0	**8b**	6:94	78
5	*R*-**6**	$(C_6H_5)Li$	−78	**8b**	94:6	83
6	*S*-**6**	4-F-C_6H_4MgBr	0	**8c**	96:4	86
7	*R*-**6**	4-OCH_3-C_6H_5MgBr	0	**8d**	7:93	83
8	*R*-**6**	$(C_3H_5)C{\equiv}CMgBr$	0	**8e**	21:79	(100)
9	*S*-**6**	$(C_3H_5)C{\equiv}CMgBr$	0	**8e**	78:22	(100)
10	*R*-**6**	3-Pyr Li	−78	**8f**	3:97	35
11	*S*-**6**	3-Pyr Li	−78	**8f**	96:4	31
12	*R*-**6**	2-OCH_3-5-Pyr Li	−78	**8g**	5:95	57[d]
13	*S*-**6**	2-OCH_3-5-pyr Li	−78	**8g**	96:4	57[d]

[a] Reactions were performed by slow addition of organometallic solution to a solution of **6** in THF (see Ref. 9).
[b] Enantiomeric ratios of amine **8** (−):(+) determined by chiral HPLC (ratios in parenthesis are for diastereomeric ratios of precursor sulfinamides **7** determined by reverse-phase HPLC).
[c] Isolated yields (−/+ combined) of sulfinamide **7** (crude yields are in parenthesis) are based on ketimine **6**, and are not optimized.
[d] Isolated yields of amine **8**.

Table 2. 1,2-Addition of organometallic reagents to **10**[a]



Entry	Substrate	Ar_1	Ar_2	CH_3MgBr (−):(+)[b]	Yield **11** (%)[c]	CH_3Li (−):(+)[b]	Yield **11** (%)[c]
1	*R*-**6**	1-CH_3Im	3-F-4-CNPh	80:20	74	13:87	82
2	**10a**	1-CH_3Im	Ph	77:23	52	7:93	48
3	**10b**	3-py	3-F-4-CNPh	73:27	89	45:55	88
4	**10c**	3-py	Ph	60:40	100	36:64	100
5	**10d**	Ph	4-CNPh	73:27	100	30:70	88
6	**10e**	4-OCH_3Ph	4-CNPh	63:37	93	14:86	72
7	**10f**	4-OCH_3Ph	Ph	39:61	90	27:73	95
8	**10g**	2-CH_3Ph	Ph	100:0	76[d]	100:0	38[e]
9	**10h**	2-CH_3Ph	3-F-4-CNPh	95:5	92	85:15	64

[a] Reactions were performed by slow addition of organometallic solution to a solution of **10** in THF.
[b] Enantiomeric ratios of (−) and (+)-**11** were determined by using chiral HPLC.
[c] Isolated yields of (−) and (+)-**11** are based on ketimine **10** and are not optimized.
[d] No reaction at 0°C, allowed to warm to rt.
[e] No reaction at −78°C, allowed to warm to rt.

critical for this effect. Furthermore, selectivity is observed regardless of whether an electron withdrawing group is on the aryl ring or not. With diaryl ketimines, turnover is observed, but only if an electron withdrawing group is on one of the aryl rings (entries 5,6 versus 7). Replacement of the 4-methoxy group with an *o*-tolyl group (entries 8 versus 7), retains lack of turnover in selectivity even when an electron withdrawing group is present (entries 9 versus 6). A boost in selectivity is also observed (entries 8 versus 7). This phenomenon could be due, in part, to conformational effects analogous to observations by Corey in oxazaborolidine-catalyzed enantioselective carbonyl reductions[11]. The inability to accurately determine the structure of our ketimines by NOE experiments[8] makes mechanistic interpretation of these subtle trends difficult.

The addition of organometallic reagents to chiral diaryl sulfinimines is a useful tool for the asymmetric synthesis of α,α-diaryl and α-aryl-α-heteroaryl alkylamines. Reversal of chirality with change in counterion is observed with aryl-heteroaryl ketimines and with diaryl ketimines containing electron withdrawing groups, but not electron rich or neutral diaryl ketimines. *o*-Tolyl ketimines are highly selective, but chirality does not reverse with a change in counterion, possibly a result of a strong conformational bias. Elucidation of the mechanisms accounting for these reversals in diastereoselectivity will require additional studies.

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8. Ketimine **10e** was found to exist as a 85:15 mixture of isomers at −40°C using a Double Pulse Field Gradient NOE run on an INOVA 600 spectrometer. Ketimines *R*-**6, 10c, d, h** were found to be exchanging too fast at −40°C to see a mixture of isomers.
9. *General procedure:* Compound **6** (1.50 g, 4.51 mmol) was dissolved in anhydrous THF (30 mL) at 0°C to which a 3.0 M solution of MeMgBr (4.50 mL, 13.5 mmol) in Et_2O was added. The reaction was quenched with aq. NH_4Cl solution, diluted with saturated $NaHCO_3$ solution and

extracted with CH_2Cl_2 (3X). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give 1.57 g (99%) of an 80:20 mixture of **7**. To a solution of this crude product (0.880 g, 2.51 mmol) dissolved in MeOH (50 mL) was added a cold methanolic HCl solution (50 mL) with stirring for 1 h at rt. After concentration and purification 0.47 g (59%) of **8** was obtained.

10. Ketones **9b, c, d,** and **h** were obtained from commercial sources. The remaining ketones **9a, e, f,** and **g** were prepared by addition of the requisite Ar_1 Grignard reagent or aryl lithium and the appropriate Ar_2 aldehyde followed by oxidation.
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