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# Intermolecular Alkyl Radical Additions to Enantiopure *N*-*tert*-Butanesulfinyl Aldimines

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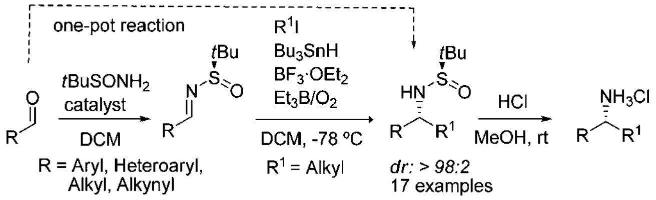
## ABSTRACT



**The sulfinyl group in (*R*)-*N*-*tert*-butanesulfinyl aldimines provides efficient control of the stereoselectivity in the intermolecular reactions with alkyl radicals. The methodology is applicable to aryl, heteroaryl, benzyl, and alkynyl imines, even those containing CN, CO$_2$Me, COR, and OH groups. The best results are attained with hindered radicals (tertiary and secondary ones) without C=N bond reduction. This reaction complements the well-established organometallic additions to *N*-sulfinyl aldimines to obtain enantiomerically pure functionalized α-branched primary amines.**

The nucleophilic addition of organometallic reagents to imine derivatives is one of the most important methods to prepare a broad range of α-branched amines,[1] which are present in biologically active compounds and are valuable synthetic building blocks. The main drawbacks limiting its scope are the aza-enolization,[2] the compatibility of the reagents with electrophilic functional groups, and the competitive formation of reduction products.[3] Moreover, hindered reagents, such as *t*-BuMgBr or *t*-BuLi, usually fail to give addition products.[4] *N*-Sulfinimines[5] have usually been the substrates of choice to synthesize α-branched amines mediated by carbon nucleophiles. The use of these sulfinyl derivatives, especially those carrying the bulky *tert*-butyl group, has solved the aza-enolization (it is slower than the nucleophilic addition), but most of the drawbacks associated with the nucleophilic addition to imines remain. Diastereoselective C=N reduction of *N*-sulfinyl ketimines[6] has been less used because of the added problem of the *E*/*Z* equilibration. Then, good results were only obtained for aryl/*n*-alkyl (Me, Et, *n*Pr, *n*Bu) *N*-*tert*-butanesulfinylketimines,[6a−c] whereas they are poorer for aryl/*t*-Bu (23%, 92% *de*) and aryl/*i*-Pr (82%, 70% *de*) ketimines.[6d]

The intermolecular radical addition to aldimine derivatives[7] offers some advantages as an alternative method. It takes place under mild and neutral conditions

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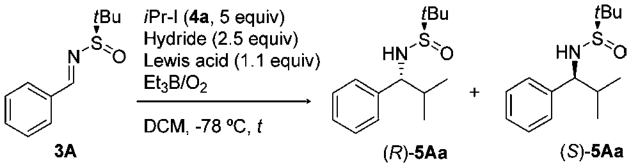
that avoid the aza-enolization, is tolerated by a wide range of functional groups, and does not produce C═N bond reduction. Diastereo-[8] and enantioselective[9] intermolecular radical additions to the C═N bond, including radical reductions,[10] have been developed in the past few years with the most efficient enantioselective process involving the use of chiral Lewis acids[9a−c] and organocatalysts[9d−g] on hydrazones or oxime ethers as radical acceptors. The stoichiometric amounts of the catalyst often required to obtain high enantioselectivity and the need for additional cleavage steps, using SmI$_2$ and HMPA, to attain the corresponding free amines are the main handicap of these reactions.

*N*-Sulfinylimines have been scarcely studied as radical acceptors in the diastereoselective process (to our knowledge, only their cross-coupling reactions with carbonyl compounds mediated by SmI$_2$,[11] and the radical additions of ethers and acetals[12] mediated by Me$_2$Zn-air, have been reported). Therefore, the stereoselective C−C bond formation based on the intermolecular carbon-centered radical addition to these imine derivatives remains as a challenging and promising task.

The usually accepted model to explain the stereoselectivity of the reactions of *N*-sulfinylimines with organometallics is based on the association of substrate and reagent with the metal[5e,13] as a previous step to the intramolecular nucleophilic addition. As the latter is not possible for radical additions, a presumably low stereoselectivity would be expected for these reactions, accounting for the lack of studies about this topic. However, the open transition states[14,15] invoked to explain the highly stereoselective behavior of organolithium compounds in coordinating solvents could be applicable to the radical additions to *N*-sulfinylimines. This observation prompted us to evaluate the utility of these radical reactions to prepare enantiomerically pure α-branched amines. The results obtained in this study are reported herein.

Initially, we examined the isopropyl radical addition to enantiopure (*R*)-*N*-*tert*-butanesulfinyl imine **3A** as a model substrate[16] to find the optimal reaction conditions (Table 1).

**Table 1.** Optimization of the Reaction Conditions for Imine (*R*)-**3A**



| entry | Lewis acid | hydride | *t* (h) | yield (%)[a] | dr[b] (*R*/*S*) |
|---|---|---|---|---|---|
| 1 | – | Bu$_3$SnH | 8 | –[c] | – |
| 2 | BF$_3$·OEt$_2$ | Bu$_3$SnH | 3 | (*R*)-**5Aa**(91) | >98:2 |
| 3 | BF$_3$·OEt$_2$[d] | Bu$_3$SnH | 1.1 | (*R*)-**5Aa**(91) | >98:2 |
| 4 | Yb(OTf)$_3$ | Bu$_3$SnH | 6.5 | –[c] | – |
| 5 | TMSOTf | Bu$_3$SnH | 1 | –[e] | – |
| 6 | BF$_3$·OEt$_2$ | – | 8 | –[c] | – |
| 7 | BF$_3$·OEt$_2$ | CySiH$_3$ | 6 | –[f] | – |
| 8 | TMSOTf | (TMS)$_3$SiH | 3 | (*R*)-**5Aa**(60) | >98:2 |

[a] Isolated yield. [b] Determined by $^1$H NMR of the crude materials. [c] Starting material was recovered. [d] 2.1 equiv of BF$_3$·OEt$_2$ and 10 equiv of *i*-PrI were used. [e] Reduction product PhCH$_2$NHSO*t*Bu was observed. [f] *i*-Pr adducts were not observed at the crude mixture.

Et$_3$B/O$_2$ was chosen as a radical initiator system since it allowed the reaction to start at a low temperature (−78 °C).[17] The radical addition, mediated by tributyltin hydride as a chain carrier, failed without Lewis acid activation (entry 1), and only in the presence of BF$_3$·OEt$_2$ did it proceed with excellent diastereoselectivity and good yield (compare entries 2, 4, and 5). As the amount of Lewis acid increased to 2.1 equiv,[18] a shorter reaction time was observed, though the yield and the diastereoselectivity remain unaltered (entry 3). All the attempts carried out to avoid the use of Bu$_3$SnH were not successful (entries 6 and 7). Only the combined treatment with TMSOTf and (TMS)$_3$SiH afforded the *i*-Pr adduct in moderate yield and high diastereoselectivity (compare entries 2 and 8, Table 1). Then, we choose as the optimal conditions those from entry 3, which provide a 91% yield and complete control of the stereoselectivity. This is a remarkable result, in contrast to the modest yield observed in most of the nucleophilic additions studied, due to the competence with the reduction processes.[13,19,20]

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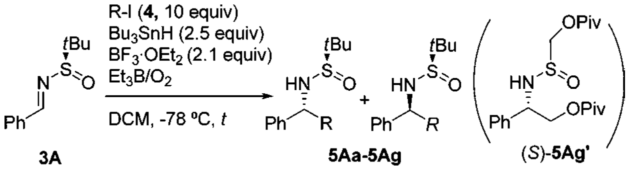
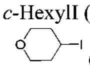
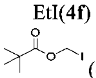
Then, we investigated the scope of the reaction toward a wide range of halides as a radical source. The results, depicted at Table 2, indicate that the stereoselectivity control is complete in all the studied reactions. The addition of secondary alkyl radicals give excellent yields (entries 1 and 2). The use of alkyl bromides instead of the iodides does not affect the stereoselectivity, but the yield is poorer. This is also the case with radicals containing heteroatoms (entry 3), which require an excess of the Lewis acid (presumably due to their mutual association).

The reaction of benzylidene imine **3A** with the *tert*-butyl radical (entry 4) produced the addition product (*R*)-**5Ad** in 75% yield and complete control of the stereoselectivity. This is a very interesting result because, to our knowledge, there are no reports describing the efficient incorporation of tertiary residues by nucleophilic additions to *N*-sulfinylimines. Other functionalized tertiary residues were also introduced in a completely stereoselective way (entry 5).

**Table 2.** Alkyl Radical Addition to Imine (*R*)-**3A**



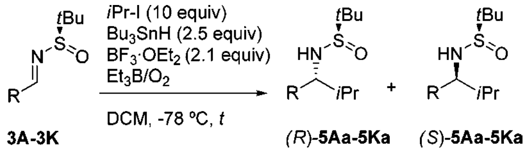
| entry | RX | *t* (h) | Yield (%)$^{a}$ | dr$^{b}$ |
|---|---|---|---|---|
| 1 | *i*-PrI (**4a**) | 1.1 | (*R*)-**5Aa** (91) | >98:2 |
| 2 | *c*-HexylI (**4b**)$^{c}$ | 3 | (*R*)-**5Ab** (90) | >98:2 |
| 3 |  (**4c**) | 7$^{d}$ | (*R*)-**5Ac** (65) | >98:2 |
| 4 | *t*-BuI(**4d**) | 8 | (*R*)-**5Ad** (75) | >98:2 |
| 5 | $Cl(CH_2)_3C(Me)_2$-I (**4e**)$^{e}$ | 5 | (*R*)-**5Ae** (50) | >98:2 |
| 6 | EtI(**4f**) | 5 | (*R*)-**5Af** (60) | >98:2 |
| 7 |  (**4g**) | 12+12$^{d}$ | (*S*)-**5Ag** (32)+<br>(*S*)-**5Ag′**(40)$^{f}$ | >98:2 |

$^{a}$ Isolated yield. $^{b}$ Determined by $^{1}$H NMR of the crude materials. $^{c}$ Starting from *c*-hexylbromide, a 50% conversion was attained yielding a mixture of **4Ab** (> 96% *de*) and the reduction product. $^{d}$ 6 equiv of $BF_3 \cdot OEt_2$ were used (see SI for experimental details). $^{e}$ 13 equiv of RI were used. $^{f}$ Compound (*S*)-**5Ag′** was isolated as pure diastereomer (sulfur configuration not determined).

The reaction of primary radicals mediated by the $Et_3B/O_2$ system usually results in complications because of the presence of ethyl radicals or of a competitive reduction.[21] We found no problems starting from ethyl iodide, and the reaction took place with excellent diastereoselectivity though moderate yield (entry 6). Interesting results were obtained in the addition of iodomethyl pivalate[22] to **3A** (entry 7). It afforded a mixture of the expected compound (*S*)-**5Ag** (32%) and (*S*)-**5Ag′** (40%), produced by a radical substitution at the S atom. The *N*-desulfinylation of the above mixture gave the corresponding amine in enantiomerically pure form (see Supporting Information (SI)), indicating complete control of the stereoselectivity at the initial radical addition.

To state the generality and scope of the reaction, a wide range of (*R*)-*N*-*tert*-butanesulfinyl aldimines were subjected to the above optimized conditions. The results are summarized in Table 3.

**Table 3.** Scope of the Isopropyl Radical Addition to Imines **3**



| entry | imine (R) | *t* (h) | yield (%)$^{a}$ | dr$^{b}$ |
|---|---|---|---|---|
| 1 | **3A** (Ph) | 1.1 | (*R*)-**5Aa** (91) | >98:2 |
| 2 | **3B** (*p*-$CNC_6H_4$) | 0.5 | (*R*)-**5Ba** (89) | >98:2 |
| 3 | **3C** (*p*-$BrC_6H_4$) | 0.7 | (*R*)-**5Ca** (90) | >98:2 |
| 4 | **3D** (*p*-$CO_2MeC_6H_4$) | 0.5 | (*R*)-**5 Da** (98) | >98:2 |
| 5 | **3E** (*p*-$COMeC_6H_4$) | 4 | (*R*)-**5Ea** (72)$^{c}$ | >98:2 |
| 6 | **3F** (*p*-$CHOC_6H_4$) | 1 | (*R*)-**5Fa** (80)$^{d,e}$ | >98:2 |
| 7 | **3G** (*p*-$OHC_6H_4$) | 3 | (*R*)-**5Ga** (70)$^{f}$ | >98:2 |
| 8 | **3H** (*p*-$OMeC_6H_4$) | 2 | (*R*)-**5Ha** (75) | >98:2 |
| 9 | **3I** (2-furyl) | 0.7 | (*R*)-**5Ia** (60) | >98:2 |
| 10 | **3J** (Bn) | 3 | (*R*)-**5Ja** (72)$^{g}$ | 95:5 |
| 11 | **3K** (C≡CPh) | 0.2 | (*R*)-**5Ka** (80) | >98:2 |

$^{a}$ Isolated yield. $^{b}$ Determined by $^{1}$H NMR of the crude materials. $^{c}$ The reaction was carried out at −98 °C. $^{d}$ 3.5 equiv of $Bu_3SnH$. $^{e}$ See text. $^{f}$ 2.5 equiv of $Et_3B/O_2$ were added each hour. $^{g}$ 1.1 equiv of $BF_3 \cdot OEt_2$.

First, we studied the addition with a large number of *p*-substituted aryl and heteroaryl aldimines.[23] Regardless of the electronic character of the substituent, the yields ranged from good to excellent (entries 2–9). The compatibility of the reaction conditions with the presence of groups such as CN, $CO_2Me$,[24] CO, and OH was remarkable, as this would have been affected by most of the organometallics. The use of $Bu_3SnH$ determined the reduction of the carbonyl group at **3E** and **3F** at −78 °C. The competitive reaction could be avoided for **3E** by a decrease in the reaction temperature. Thus, complete chemo- and

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[20] The reduction process was not observed using zincates (Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 3198), which provided a similar yield (90%) but lower stereoselectivity (94:6 dr) than those indicated in entry 3 in Table 1 (91%; > 98:2 dr).

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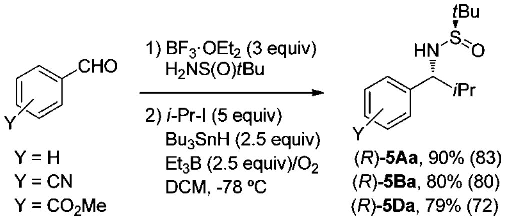
[23] Futher extension of the process to the less reactive *N*-sulfinyl ketimine derived from acetophenone was unsuccessful.

[24] It is remarkable that the acid resulting in the hydrolysis of **5Da** has been used for obtaining antidiabetic agents (See:Demong, D.; Miller, M. W.; Dai, X.; Stamford, A. PCT Int Appl. (2012) WO 2012/009226 A1) and substituted hydroxamic acids employed as inhibitors of HDCAC6 (histone deacetylase 6) (See: Blackburn, C.; Gigstad, K. M.; Harrison S. J.; Xu, H. PCT Int Appl. (2011) WO2011/106632 A1). In these patents, the addition of *i*-PrLi to an *N*-*tert*-butanesulfinylaldimine is the key step in the synthesis of the starting acid. It requires starting from a *t*-Bu ester (to avoid nucleophilic attack to the carbonyl group) and yields a mixture of diastereoisomers that, once separated, give a 46% yield of the appropriated one. By contrast, in our case, we perform the radical addition starting from the methyl ester (**3D**) with complete control of the stereoselectivity and quantitative yield (entry 4, Table 3).

diastereoselectivity for the radical addition were attained at −98 °C (entry 5). Starting from **3F** (entry 6), an aminoalcohol was obtained (as a result of the simultaneous addition of the isopropyl radical to the C=N bond and the reduction of the formyl group). The compound was oxidized with $MnO_2$ to afford **5Fa** in an 80% overall yield and > 98% *de*. Heteroarylimines (**3I**) and arylimines bearing EDG (**3G** and **3H**) also gave good results (entries 7−9). The alkylidene imine **3J** successfully afforded the expected product (entry 10).[25] Alkynyl imine **3K** (entry 11), with a potentially competitive triple bond, underwent the radical addition to the C=N bond with complete chemo- and diastereoselectivity.

**Scheme 1.** One-Pot Synthesis of Sulfinamides (between brackets, overall yield using the conventional two-step procedure)



The synthesis of the *N*-sulfinylamines **5** can be readily performed from the aldehydes, according to a two-step one-pot reaction involving the formation of the imines **3** under $BF_3{\cdot}OEt_2$ catalysis (instead of the usual $CuSO_4$[26]) and subsequent radical addition under our standard conditions (Scheme 1).

To understand the stereochemical results of these reactions, the stability of different conformers of the *N*-*tert*-butanesulfinyl benzaldimine **3A** was theoretically studied at the DFT level.[27] The conformational equilibrium is shifted toward the rotamer displaying the sulfinyl oxygen in the *s-cis* arrangement with respect to the C=N ($\Delta G$ = 4.0 kcal/mol, Figure 1), with the hydrogen bond O---HC being one of the most important factors in its stabilization.[28] According to these calculations, the approach of the radical to the less hindered *re*-face of imines in their more stable ***A*** conformation could easily account for the *R* configuration assigned to the obtained compounds **5** (Figure 1).

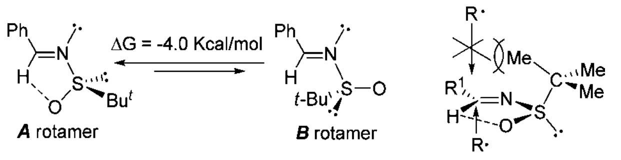
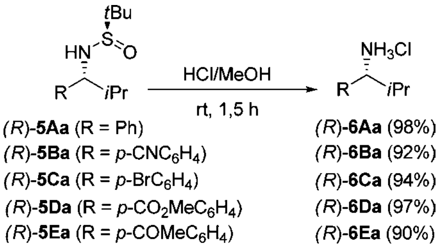


**Figure 1.** Relative conformational stability around the N−S bond at *N*-sulfinyl imines. Stereochemical prediction ($CPCM_{THF}$/mPW1PW91/6-311G(d,p)//6-31G(d)).

Finally, removal of the sulfinyl group with HCl/MeOH at rt produced amine hydrochlorides **6** in almost quantitative yields, without erosion of the enantiomeric purity (Scheme 2).[29]

**Scheme 2.** *tert*-Butanesulfinyl Group Removal[30]



In summary, we have demostrated the utility of a wide variety of *N*-*tert*-butanesulfinyl aldimines as acceptors in intermolecular radical additions of alkyl iodides mediated by $Et_3B/O_2$. The addition is highly diastereoselective and mainly applicable to secondary and tertiary radicals, although some primary radicals have been successfully added. An efficient one-pot approach to the α-branched sulfinamides, from the corresponding aldehydes, has been described. The tolerance of functional groups and the low restrictions to steric effects, allowing the efficient incorporation of hindered alkyl groups, suggest these radical additions as a synthetic alternative to the use of organometallic reagents to prepare enantiopure functionalized α-branched primary amines.

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**Supporting Information Available.** Experimental procedures, characterization data, and theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The addition of benzyl zinc to aliphatic *N*-*tert*-butanesulfinyl aldimines gave low *dr* (up to 77:23), in contrast to the high stereoselectivity attained with the aromatic counterparts. See ref 14b.

(26) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

(27) See SI for the details.

(28) Similar results, but lower $\Delta G$ values, had been obtained for the *N*-benzenesulfinyl benzaldimine: García Ruano, J. L.; Torrente, E.; Alonso, I.; Rodriguez, M.; Martín-Castro, A. M.; Degl'Innocenti, A.; Frateschi, L.; Capperucci, A. *J. Org. Chem.* **2012**, *77*, 1974. Also see ref 12b.

(29) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268.

(30) The absolute configuration of the new chiral center at the major diastereoisomer **5Aa** has been established as *R* by the coincidence in the specific rotation of amine hydrochloride **6Aa**, with that previously reported: Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19* (603), 2484. Tentatively, the absolute configurations of major sulfinamides **5** were assigned as *R* by analogy.

The authors declare no competing financial interest.