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Stereoselective α-Aminoallylation of Aldehydes with Chiral *tert*-Butanesulfinamides and Allyl Bromides†

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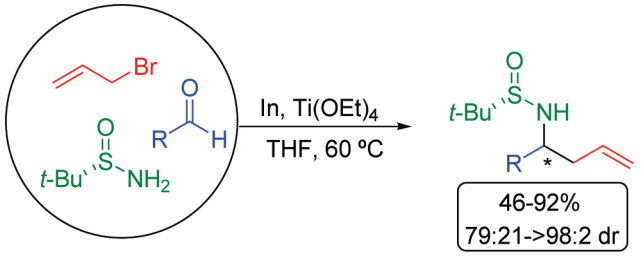

The combination of an aldehyde, an allylic bromide, and *tert*-butanesulfinamide in the presence of indium metal and titanium tetraethoxide allows straightforward access to homoallylamine derivatives in high yields and stereoselectivities. Moreover, the synthetic utility of the enantioenriched homoallylamine derived from *n*-decanal was illustrated in a concise synthesis of (+)-isosolenopsin. In this context, similar homoallylamines has been recently used by other groups in the synthesis of naturally occurring alkaloids.

Chiral homoallylic amines are of great value as building blocks in organic synthesis because the carbon−carbon double bond can be readily converted to a variety of functional groups and the free amine moiety can be diversely functionalized. The importance of these versatile intermediates is emphasized by the prevalence of chiral α-branched amines in natural products, biologically active molecules, and ligands.[1] The addition of allylmetals to C=N double bonds is a useful synthetic method for the formation of homoallylic amine derivatives.[2] However, chiral homoallylic amines are still very commonly prepared by enantioselective allylation of carbonyl compounds and subsequent transformation of the resulting alcohol into the corresponding amine derivative, a process that typically requires about four synthetic operations.[3] In this context, three-component reactions involving carbonyl compounds, nitrogen nucleophiles, and allylic nucleophiles are particularly attractive in assembling both nitrogen−carbon and carbon−carbon bonds around the carbonyl carbon. These reactions are referred to as α-aminoallylations of carbonyl compounds,[4] and several variations have been reported for different nucleophiles.[5] However, only a few methods have been reported for the efficient preparation of enantiomerically enriched homoallylic amines.[6]

Additions of nucleophiles to the C=N bond of enantiomerically pure *N*-*tert*-butanesulfinyl imines are among the most widely used approaches for the asymmetric synthesis of amines.[7] The ready availability of both enantiomers of *tert*-butanesulfinamide in large-scale processes,[8] the easy deprotection of the amine under acidic conditions, and a practical procedure for recycling the chiral auxiliary have undoubtedly contributed to the widespread use of this approach.[9] In this context, the additions of allylmagnesium,[10] allylzinc,[11] and allylindium[12] species to enantiopure *N*-*tert*-butanesulfinylimines have also been exploited. We have been particularly interested in the indium-mediated allylation reaction[12b] due to the low toxicity of the metal and the high tolerance to a wide range of functional groups, aqueous solvents, and exposure to air.[13] Continuing our interest in this topic, we describe here the first one-pot α-aminoallylation of aldehydes with chiral *tert*-butanesulfinamide, allyl bromides, and indium to provide homoallylic amines with high chemo- and stereoselectivities (Scheme 1).

† Dedicated to Professor Carmen Nájera on occasion of her 60th birthday.

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SCHEME 1. α-Aminoallylation Using Chiral *tert*-Butanesulfinamide

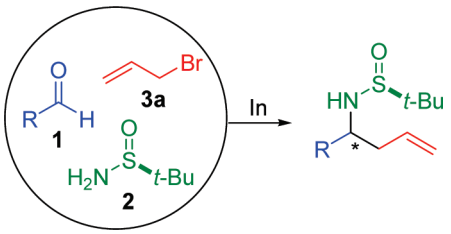
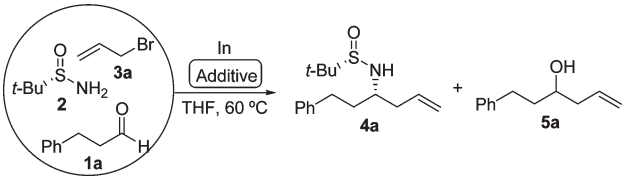


TABLE 1. Screening Conditions for α-Aminoallylation



entry	additive (mol %)	**4a**[a] (%)	**5a**[a] (%)
1	none	27	69
2[b]	CF_3CO_2H (600)	0[c]	100[c]
3	$In(OTf)_3$ (10)	51	40
4	$In(OTf)_3$ (20)	24	60
5	$Ti(OEt)_4$ (200)	91[d]	0
6	$Ti(OEt)_4$ (100)	70[c]	30[c]

[a]Isolated yield of analytically pure compounds. [b]The reaction was run at 23 °C. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]91:9 dr relative to sulfur was determined by ^{1}H NMR.

Since the formation of homoallyl alcohols from the reaction of aldehydes or ketones with allylindium species is well precedented,[14] chemoselectivity was the first issue to address in order to develop the α-aminoallylation. An important limitation for the chemoselectivity was imposed by the fact that only 1 equiv of chiral *tert*-butanesulfinamide should be used for practical reasons, and it was not obvious how to minimize the concentration of aldehyde in the equilibrium.[15] In a preliminary experiment, a mixture of 3-phenylpropanal (**1a**, 0.55 mmol), (*S*)-*N*-*tert*-butanesulfinamide (**2**, 0.50 mmol), allyl bromide (**3a**, 0.60 mmol), and indium metal (0.50 mmol) was heated in THF (1 mL) at 60 °C over 5 h. To our surprise, apart from homoallyl alcohol **5a**, homoallylsulfinylamine derivative **4a** was isolated in 27% yield (Table 1, entry 1). Following this lead, we examined different additives in an effort to improve the chemoselectivity in favor of compound **4a**. The addition of TFA[16] afforded exclusively homoallyl alcohol **5a** and $In(OTf)_3$ led to an almost 1:1 mixture of compounds **4a** and **5a** (Table 1, entry 3).[17] It was found that 2 equiv of $Ti(OEt)_4$ promoted the reaction to afford homoallylamine **4a** with excellent chemoselectivity (>95:5, entry 5).[18] In an additional control experiment, the use of zinc instead of indium, under otherwise identical optimized conditions, gave less than 20% conversion of **2** into compound **4a**.

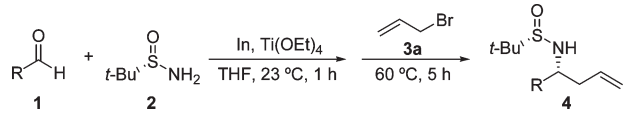
Since the reaction was conducted in the presence of indium and titanium, both species that could act as Lewis acids, as well as water and/or ethanol, which can act as Lewis bases, the stereoselectivity of the reaction was a major concern at the outset.[19] Given these precedents, we were pleased to find the same diastereoselectivity (91:9) was obtained as previously observed for the indium-mediated allylation of the preformed *N*-sulfinylimine.[12b] The generality of the substrate was screened, and some problems were encountered in obtaining good chemoselectivity for different substrates. The results were more consistent in all cases when all reactants except allyl bromide (**3a**) were stirred for 1 h at room temperature, and after the addition of **3a**, the reaction mixture was heated at 60 °C for a further 5 h. Notably, full conversion of the aldehyde into the *N*-sulfinimine was not necessary. Different aldehydes were examined in conjunction with this minor modification (Table 2).

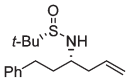
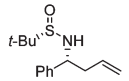
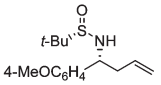
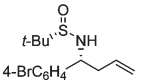
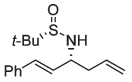
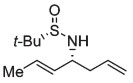
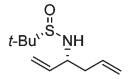
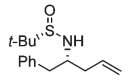
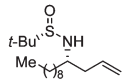
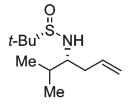
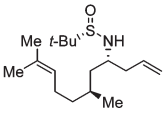
Notably, aromatic aldehydes gave lower stereoselectivities and isolated yields than 3-phenylpropanal regardless of whether the substituent was electron-withdrawing or -donating (**4b**−**4d**, Table 2, entries 2−4). Interestingly, α,β-conjugated aldehydes gave exclusive 1,2-addition in synthetically useful isolated yields and diastereoselectivities (**4e**−**g**, Table 2, entries 5−7). More importantly, aliphatic aldehydes that commonly complicate the reaction with organometallic reagents due to enamine formation perform cleanly in the α-aminoallylation reaction (**4h**−**k**, Table 2, entries 8−11). Unfortunately, homoallylamine formation was not observed for the more sterically hindered pivalaldehyde or for acetophenone under the conditions studied. The stereochemical outcome of the α-aminoallylation reaction was determined by comparison of spectroscopic data with those of previously characterized diastereomers of amines **4a**,**b**,**i**,**j**.[20]

The reaction of 3-phenylpropanal was also investigated with methallyl bromide (**3b**), prenyl bromide (**3c**), and cyclohexenyl bromide **3d**, with very good chemo- and stereoselectivities obtained in all cases (Figure 1). Importantly, high γ-addition selectivity was also observed for **3c**, and excellent anti addition selectivity was observed for cyclohexenyl bromide. The absolute stereochemistry of **4n** was confirmed by X-ray analysis[22] and is in accordance with the addition of the allylindium reagent over the Re face of the C=N in the (S_S)-sulfinyl imine. This stereochemical outcome can be explained in terms of a chairlike transition-state model, where the indium atom is coordinated to both the nitrogen and

(14) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.
(15) It is worth noting that in the α-aminoallylation with ammonia, a large excess of ammonia was crucial to obtain high chemoselectivity. See: (a) Reference 5c. (b) Kobayashi, S.; Hirano, K.; Sugiura, M. *Chem. Commun.* **2005**, 104.
(16) Very recently, it has been shown that TFA promotes efficiently the intramolecular indium-mediated allylation of chiral hydrazones. See: Samanta, D.; Kargbo, R. B.; Cook, G. R. *J. Org. Chem.* **2009**, *74*, 7183.
(17) It is known that $In(OTf)_3$ increases both the stereoselectivity and the rate of the indium-mediated allylation of chiral hydrazones. See: Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741.
(18) (a) $Ti(OEt)_4$ it is an excellent water scavenger and catalyst for the formation of *N*-*tert*-butanesulfinylimines, see: Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278. (b) $Ti(OEt)_4$ has also been successfully used in a one-pot protocol for the formation and reduction of *N*-*tert*-butanesulfinylketoimines, see: Tanuwidjaja, J.; Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2007**, *72*, 626.
(19) It is known that the stereochemical outcome of the Zn/In-mediated allylation of *N*-*tert*-butanesulfinyl imines can be highly dependent on the presence of Lewis acids or bases. See: Lin, G.-Q.; Xu, M.-H.; Zhong, Y. W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831.
(20) (a) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979. (b) Medjahdi, M.; González-Gómez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 7859.
(21) NMR analysis by comparison to diastereomer mixture standards prepared according to: Brak, K.; Barret, K. T.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 3606.
(22) Crystal data (excluding structure factors) deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 779151.

TABLE 2. α-Aminoallylation of Aldehydes 1

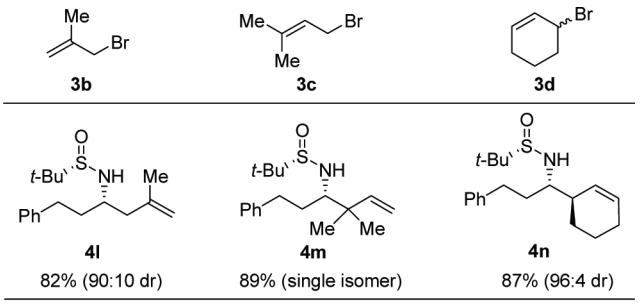


Entry	Homoallylamine derivative 4 No.	Structure	Yield (%)[a]	dr[a]
1	**4a**		92	91:9
2	**4b**		77	89:11
3	**4c**		46	92:8
4	**4d**		56[b]	92:8
5	**4e**		82[c]	98:2
6	**4f**		76	79:21
7	**4g**		65	97:3
8	**4h**		81	98:2
9[d]	**4i**		81	95:5
10	**4j**		85	>98:2
11	**4k**		85	>98:2

[a]Yields and diastereoselectivities (^{1}H NMR analysis)[21] were determined for isolated pure compounds after column chromatography. [b]The corresponding imine was isolated in 40% yield. [c]The C-4 epimer was isolated pure in 8% yield; see the Supporting Information. [d]Similar results were obtained on a 5 mmol scale.

the oxygen of the sulfinyl imine moiety in the *s-trans* conformation. Interestingly, this latter example complements the recently reported addition of racemic cyclohexenyl zinc chloride to (S_S)-*N*-*tert*-butanesulfinyl imines, where the opposite configuration was observed for the two newly created stereocenters.[23]

In an attempt to understand the scope of the reaction, even without the necessity of full conversion of the aldehyde into the sulfinyl imine, we considered several alternatives. In a competition experiment, we observed that allylation of 3-phenylpropanal and the corresponding sulfinyl imine have



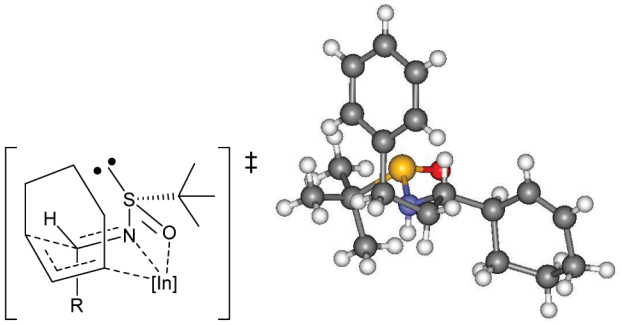


FIGURE 1. Reaction with allylic bromides **3b**−**d** and model approach of cyclohexenylindium intermediate to the aldimine and X-ray structure of **4n**.

similar rates under the conditions studied. Treatment of homoallyl alcohol **5a** in the absence of allyl bromide, under otherwise optimized conditions, did not afford any homoallylamine derivative **4a**, thus ruling out interconversion between these two products.[24] With the present data, we speculate that indium(III) salts formed in situ should accelerate both the formation of the *N*-sulfinylimine and its allylation, a situation that would account for the good chemoselectivity observed (Table 1, entry 3).

Following our previously reported route, amine **4i** was used in a concise synthesis of the natural (+)-isosolenopsin (**7**).[25] Cross-metathesis of amine **4i** with methyl vinyl ketone afforded intermediate **6**, which after conjugate reduction, amine deprotection, and iminium reduction afforded the expected (+)-isosolenopsin (**7**) in very good overall yield and diastereoselectivity (Scheme 2). Notably, only four synthetic operations and three purification steps were required to prepare efficiently this natural piperidine from *n*-decanal. To further illustrate the synthetic utility of homoallylamine **4i** in the field of alkaloid natural products, Wolfe and coworkers have developed a seven-step synthesis from *ent*-**4i** of (+)-preussin and several analogs.[26] Moreover, Rao and coworkers recently used the *N*-Cbz analogue of amine **4i** in a four-step synthesis of the alkaloid (+)-241D.[3b]

In summary, one-pot reactions of commercially available aldehydes, allyl bromides, indium, and chiral *tert*-butanesulfinamide were found to afford enantioenriched homoallylic amines in high yields and with high chemo- and stereoselectivities. The reaction performs better when aliphatic

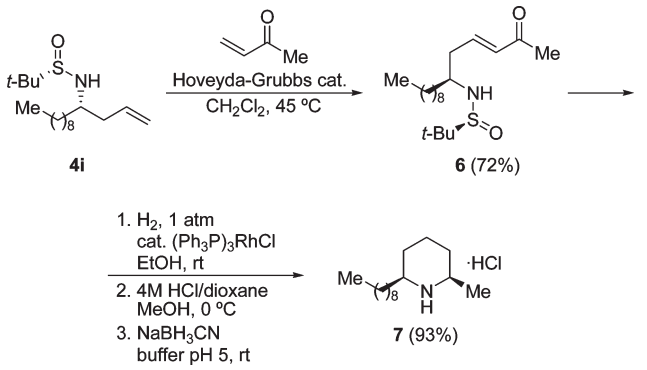
(23) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Org. Lett.* **2008**, *10*, 3109.

(24) Although formation of an allyltitanium species can not be excluded at present, we believe that allylindium is the actual nucleophile because the same stereoinduction is achieved when the allylation of the preformed imine is conducted in the absence of $Ti(OEt)_4$.

(25) González-Gómez, J. C.; Foubelo, F.; Yus, M. *Synlett* **2008**, 2777.

(26) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353.

SCHEME 2. Synthesis of (+)-Isosolenopsin (7)



aldehydes are used and is well-suited for allyl-, methalyl-, prenyl-, and cyclohexenyl bromides.

Experimental Section

Representative Procedure for the α-Aminoallylation of Aldehydes: (3*R*,1′*S*,*S*s)-*N*-(*tert*-Butanesulfinyl)-3-(1-amino-3-phenylpropyl)cyclohexene (4n). A mixture of indium powder (173 mg, 1.50 mmol), (S_S)-*N*-*tert*-butanesulfinamide (**2**, 121 mg, 1.00 mmol), phenylpropanal (**1a**, 150 μL, 1.15 mmol), and $Ti(OEt)_4$ (450 μL, 2.00 mmol) in THF (2 mL) was stirred under argon for 1 h at 23 °C. At this time, allylic bromide **3d** (254 mg, 1.50 mmol) was added and the reaction mixture heated for 5 h at 60 °C. The mixture was allowed to cool to room temperature, quenched with brine (2 mL), and diluted with EtOAc. The resulting suspension was filtered through a short pad of Celite and concentrated in vacuo (15 Torr). The residue was purified by column chromatography (silica gel), eluting with hexane/EtOAc (4:1, then 3:1) to afford 277 mg (87%, 96:4 dr) of compound **4n** as a colorless solid: mp 72−73 °C; $[\alpha]^{20}_D$ +44 (*c* 0.86, CH_2Cl_2); R_f 0.25 (hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (m, 2H), 7.19 (m, 3H), 5.84 (ddd, *J* = 9.9, 6.4, 3.2, 1H), 5.52 (d, *J* = 10.1, 1H), 3.31 (d, *J* = 7.6, 1H), 3.21 (ddd, *J* = 11.8, 7.9, 4.0, 1H), 2.78 (m, 1H), 2.58 (m, 2H), 1.98 (m, 2H), 1.89 − 1.69 (m, 4H), 1.51 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0 (C), 130.9 (CH), 128.53 (CH), 128.46 (CH), 127.0 (CH), 126.0 (CH), 60.1 (CH), 56.3 (C), 40.8 (CH), 35.7 (CH_2), 32.9 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 23.0 (CH_3), 22.0 (CH_2); IR (neat, cm^{-1}) 3300, 2935, 2863, 1452, 1047; HRMS (EI) calcd for $C_{15}H_{21}NOS$ ($M - C_4H_8$) 263,1344, found 263.1352. Crystallization from hexane/CH_2Cl_2 afforded crystals of a single isomer suitable for X-ray analysis.

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Supporting Information Available: Experimental procedures, full characterization, and copies of ^{1}H and ^{13}C NMR spectra of all compounds and X-ray crystal data for compound **4n**. This material is available free of charge via the Internet at http://pubs.acs.org.