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Remarkable Salt Effect on In-Mediated Allylation of *N-tert*-Butanesulfinyl Imines in Aqueous Media: Highly Practical Asymmetric Synthesis of Chiral Homoallylic Amines and Isoindolinones

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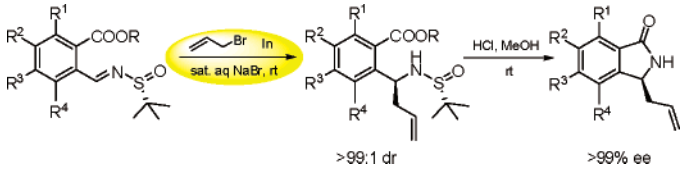
ABSTRACT



A highly practical and efficient asymmetric synthesis of chiral homoallylic amines by In-mediated allylation of chiral *N-tert*-butanesulfinyl imines in aqueous media at room temperature was developed. With 2-formylbenzoate imine substrates, the method allows the highly enantioselective achievement of a variety of pharmacologically important 3-allyl isoindolinone compounds.

In recent years, organic reactions that can be performed in aqueous media without using organic cosolvent have attracted great interest because of significant environmental and economical advantages over conventional reactions in organic solvents.[1] Among them, the indium-mediated reactions under aqueous conditions have been an important subject.[2] Since the first report of allylindium addition to aldehydes in water in 1991,[3a] considerable progress has been made in the allylation of carbonyl compounds in aqueous media.[3] However, the corresponding addition of the allylindium reagents to imine compounds to give homoallylic amines in aqueous media has been little explored.[4] One major and severe problem is that imines are often easily hydrolyzed in aqueous media and are less electrophilic. Thus far, only a few examples of using imine analogues such as sulfonimines,[5] hydrazones,[6] oxime ethers,[7] and glyoxylate imines[8] have shown some success in aqueous indium-mediated allylation. To the best of our knowledge, there has been no report on

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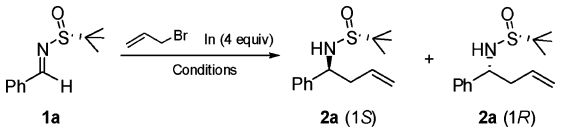
the asymmetric synthesis of optically active homoallylic amines in aqueous media by indium-mediated allylations. In this paper, we present our studies regarding a solution to this issue and disclose a highly practical, efficient, and stereospecific approach for the synthesis of chiral homoallylic amines and isoindolinones under environmentally friendly reaction conditions.

We previously documented the successful use of chiral *N*-*tert*-butanesulfinyl imines for room-temperature highly diastereoselective allylation in both THF and HMPA systems mediated by zinc.[9] Encouraged by these results, we considered the possibility of developing an aqueous chemical strategy toward a more practical synthesis of chiral homoallylic amines. In our effort to develop such a process, we discovered that the reaction of *N*-*tert*-butanesulfinyl imines with indium and allyl bromide in saturated aqueous NaBr[10] could proceed smoothly to give the desired allylation products in excellent dr's and yields at ambient temperature.

By using (*R*)-*N*-sulfinyl imine **1a** as a substrate, we first examined the potential of allylation mediated by zinc and indium in water (Table 1, entries 1−2). To our delight, the reaction with indium took place at room temperature and gave the desired homoallylic amine **2a** in 20% yield and 92:8 (1*S*:1*R*)[11] dr after 12 h. Although the yield was not ideal, we realized that the diastereoselectivity of the reaction remained as high under aqueous conditions as in organic solvents.[12] To achieve better results, the reaction conditions were carefully screened, and a series of saturated aqueous salt solutions were employed as the reaction media. The results were promising, as revealed in entries 3−12. An increase of the reaction yield was observed in all cases in electrolyte-rich aqueous solutions. When saturated aqueous NH_4Br was used as the solvent, the reaction produced a very good yield of 90%, along with a high diastereomeric ratio of 94:6 (1*S*:1*R*) (entry 5). With saturated aqueous NaBr, a significant improvement in diastereoselectivity (97:3 dr) was obtained (entry 6). Notably, the use of 4 equiv of In was found essential to achieve a higher yield (92%) than when 2 or 3 equiv was used (entry 6 vs entries 11 and 12). According to the observations, it appears that the reaction stereoselectivity is sensitive to the cation and anion in the solution. However, the exact reasons for this salt effect are not clear at this time.

After identifying the optimal reaction conditions, we set out to explore the substrate generality. A wide variety of *N*-sulfinyl imines were investigated, and the results are summarized in Table 2. Gratifyingly, aromatic, heteroaromatic, aliphatic, and olefinic imines were all found to be suitable substrates and produced the corresponding homo-

Table 1. Effect of Salt and Optimization of the Reaction Conditions

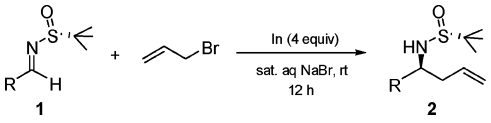


1a **2a** (1*S*) **2a** (1*R*)

entry[a]	M	solvent	time (h)	yield[b] (%)	dr[c] (1*S*:1*R*)
1	Zn	H_2O	24	trace	–
2	In	H_2O	12	20	92:8
3	In	sat. aq NH_4Cl	12	76	88:12
4	In	sat. aq NH_4I	12	67	93:7
5	In	sat. aq NH_4Br	12	90	94:6
6	In	sat. aq NaBr	12	92	97:3
7	In	sat. aq NaI	12	88	90:10
8	In	sat. aq NaCl	12	86	89:11
9	In	sat. aq KBr	12	92	94:6
10	In	sat. aq LiBr	12	92	94:6
11[d]	In	sat. aq NaBr	12	83	97:3
12[e]	In	sat. aq NaBr	12	75	97:3

[a] Reaction was performed with 0.25 mmol of imine **1a** in 5 mL of solvent at rt. [b] Isolated yield. [c] Determined by ^1H NMR of the crude materials. [d] 3 equiv of In. [e] 2 equiv of In.

Table 2. Scope of Diastereoselective Allylation in Aqueous Media



1 **2**

entry[a]	1	R	2	yield (%)[b]	dr[c]
1	**1b**	4-ClC_6H_4	**2b**	99	97:3
2	**1c**	4-MeC_6H_4	**2c**	97	98:2
3	**1d**	4-$CF_3C_6H_4$	**2d**	99	97:3
4	**1e**	4-$MeOC_6H_4$	**2e**	85	98:2
5	**1f**	4-PhC_6H_4	**2f**	93	99:1
6	**1g**	3-ClC_6H_4	**2g**	98	98:2
7	**1h**	3-$MeOC_6H_4$	**2h**	95	98:2
8	**1i**	2-$MeOC_6H_4$	**2i**	94	>99:1
9	**1j**	2-FC_6H_4	**2j**	92	>99:1
10	**1k**	2-BrC_6H_4	**2k**	99	>99:1
11	**1l**	2,4-$Cl_2C_6H_3$	**2l**	95	>99:1
12	**1m**	2,4-$(MeO)_2C_6H_3$	**2m**	84	>99:1
13	**1n**	3,4-$(MeO)_2C_6H_3$	**2n**	81	98:2
14	**1o**	α-naphthyl	**2o**	99	98:2
15	**1p**	β-naphthyl	**2p**	98	98:2
16	**1q**	2-thiophenyl	**2q**	98	94:6
17	**1r**	3-furanyl	**2r**	90	95:5
18	**1s**	2-pyridyl	**2s**	73	95:5
19	**1t**	ferrocenyl	**2t**	74	>99:1
20	**1u**	propyl	**2u**	84	92:8
21	**1v**	isopropyl	**2v**	82	96:4
22	**1w**	cyclohexyl	**2w**	87	96:4
23	**1x**	phenethenyl	**2x**	92	95:5

[a] Reactions were carried out with 0.25 mmol of imine **1**, 1 mmol of In/allyl bromide in 5 mL of sat. aq NaBr at rt. [b] Isolated yield. [c] Determined by ^1H NMR of the crude materials.

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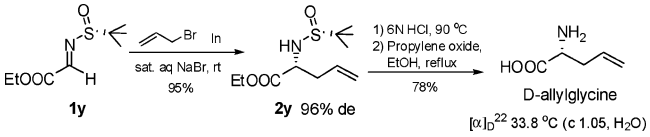
allylic amines in good to excellent yields as well as very high diastereoselectivities.[13] In the cases of aryl imines **1b**−**1n**, electron-donating or -withdrawing substituents did not seem to affect the reaction diastereoselectivity. Remarkably, substrates having an ortho substituent on the benzene ring afforded extremely high diastereoselectivities (99%) in all cases (entries 8−12), indicating an evident steric effect of R. With ferrocenyl imine, an equally high stereoselection (>99:1 dr) was observed (entry 19). For alkyl imines, it is similar that more bulky isopropyl and cyclohexyl gave better selectivity (entries 20−22). Further extension to a less reactive ketimine substrate was also studied. With the *N*-sulfinyl imine of 4′-bromoacetophenone, a diastereomeric ratio of 94:6 was observed, but the yield was low (30%). Assuming an analogous reaction mechanism, the absolute configurations of the amine products were considered as *S*.[14]

A demonstration of the synthetic utility of this aqueous allylation is presented in Scheme 1. *N*-Sulfinyl imino ester

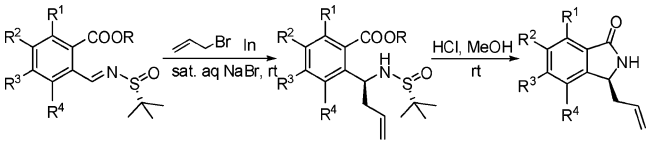
Scheme 1. Synthesis of D-Allylglycine



1y was subjected to the allylindium addition in saturated aqueous NaBr at room temperature on a gram scale, and *N*-sulfinyl-α-amino ester product **2y** was obtained in 95% yield with 96% de. Removal of the sulfinyl and ethyl groups using 6 N HCl followed by neutralization with propylene oxide yielded unnatural amino acid D-allylglycine.[15] To our knowledge, this approach represents one of the most convenient asymmetric syntheses of allylglycine reported to date.[16]

Inspired by the above findings that sterically encumbered ortho-substituted arylimines are fantastic reactants, we next turned our attention to more challenging 2-formylbenzoate imine substrates. Under similar reaction conditions, (*R*)-**3a**−**g** were treated with indium and allyl bromide in saturated aqueous NaBr. The reactions proceeded smoothly at room temperature and gave desired products **4a**−**g** with excellent diastereoselectivities (>99:1 dr)[13] (Scheme 2). The stereo-

Scheme 2. Synthesis of Chiral 3-Substituted Isoindolinones



3a: $R^1 = R^2 = R^3 = R^4 = H$, R = Me
3b: $R^1 = R^4 = H$, $R^2 = R^3 = Cl$, R = Me
3c: $R^1 = R^3 = H$, $R^2 = R^4 = OMe$, R = Me
3d: $R^1 = R^2 = R^4 = H$, $R^3 = F$, R = Me
3e: R^1-$R^2 = C_4H_4$, $R^3 = R^4 = H$, R = Me
3f: $R^1 = R^4 = H$, R^2-$R^3 = C_4H_4$, R = Me
3g: $R^1 = R^2 = R^4 = H$, $R^3 = Br$, R = Et

4a: 94% yield, >99:1 dr
4b: 98% yield, >99:1 dr
4c: 42% yield, >99:1 dr
4d: 95% yield, >99:1 dr
4e: 92% yield, >99:1 dr
4f: 98% yield, >99:1 dr
4g: 89% yield, >99:1 dr

5a-**g**
88-99% yields

chemistry of the newly formed carbon center was further confirmed as *S* by X-ray crystallography of homoallylic amine **4g** (Figure 1).[17] It is noteworthy that the reaction

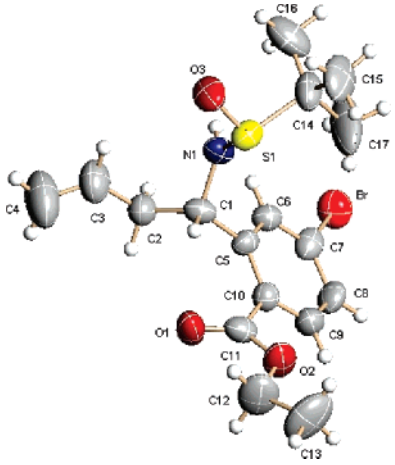


Figure 1. X-ray crystal structure of the allylation product **4g**.

stereoselectivity is not influenced by the aromatic substitution. For imine **3c** that contains two ortho substituents, a relatively low yield was observed due to the understandable addition difficulty. Furthermore, *N*-sulfinyl cleavage of the obtained allyl adducts **4a**−**g** with HCl in MeOH resulted in the subsequent lactamization to a series of highly enantiomerically enriched 3-allyl-isoindolinones **5a**−**g** in excellent yields (88−99%). The optical purity of **5a** was proved to be

(10) For a report of In-mediated addition of allyl bromide to *N-tert*-butanesulfinyl imines in THF, see: Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823.

(11) The configuration was assigned by comparison with the results in ref 9.

(12) A 90:10 dr was observed in Zn-mediated allylation in THF. See ref 9.

(13) The dr's were determined by ^{1}H NMR of the crude materials. For comparsion, the minor diastereomers were assigned independently by our previously reported Zn-mediated approach in the HMPA system. See ref 9 for reaction details.

(14) The allylation with 2-pyridyl imine (**1s**) may exhibit reversal of stereoselectivity to give the (*R*)-product. See: Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641.

(15) 95% ee by HPLC. The opposite stereochemical outcome in this case may be rationalized by considering the transition state change because of the chelation of the indium atom with the ester carbonyl.

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(17) Crystallographic data for **4g** ($C_{17}H_{24}BrNO_3S$): $T = 293$ (2) K; wavelength: 0.71073 Å; crystal system: orthorhombic; space group: $P2_12_12_1$; unit cell dimensions: $a = 8.9648(10)$ Å, $b = 9.3633(11)$ Å, $c = 24.021(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; $V = 2016.3(4)$ Å^3; $Z = 4$; $\rho_{calcd} = 1.325$ Mg/m^3; $F(000) = 832$; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0600$, $wR_2 = 0.1180$; R indices (all data), $R_1 = 0.1008$, $wR_2 = 0.1370$; 11004 reflections measured, 3953 were unique ($R_{(int)} = 0.1437$);. CCDC 671400 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request /cif.

>99% ee by chiral HPLC analysis on a Chiralpak OJ−H column.[18] Chiral 3-substituted isoindolinones are valuable pharmacological compounds and important synthetic building blocks; however, methods for their stereoselective synthesis remain few.[19] Notably, our current strategy of chiral 3-allyl-isoindolinone synthesis provides alternative access to a broad range of 3-alkyl-isoindolinones[20] as the 3-allyl function group offers a particularly useful reaction site for further elaborations.

In summary, we have developed a simple, mild system for highly diastereoselective indium-mediated allylation of *N*-sulfinyl imines. The reactions can be accomplished with ease in aqueous media without any organic cosolvents at room temperature. This practical method not only allows access to a wide range of enantiomerically enriched homoallylic amines but also enables the further synthesis of a variety of chiral 3-allyl-isoindolinone derivatives in good yields.

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

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(18) See Supporting Information for details.

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(20) For a catalytic asymmetric strategy to 3-aryl-isoindolinones by us: Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336.