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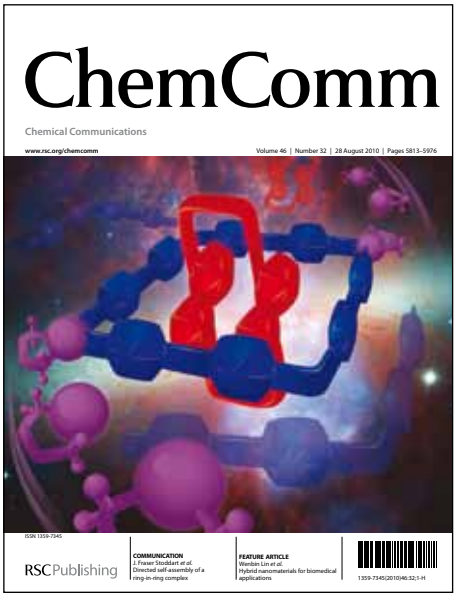

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Graphical Abstract

Zn-Mediated Asymmetric Allylation of *N*-*tert*-Butanesulfinyl Ketimines: An Efficient and Practical Access to Chiral Quaternary 3-Aminooxindoles

Diao Chen and Ming-Hua Xu*

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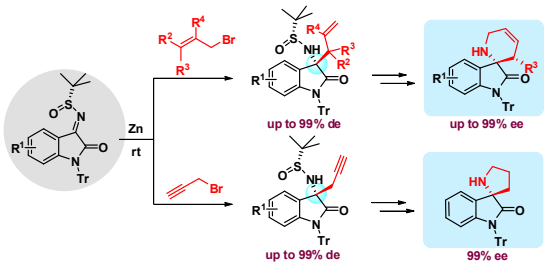

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Zn-Mediated Asymmetric Allylation of *N*-*tert*-Butanesulfinyl Ketimines: An Efficient and Practical Access to Chiral Quaternary 3-Aminooxindoles†

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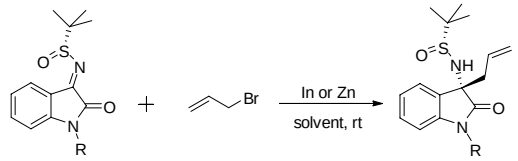
Room temperature zinc-mediated diastereoselective allylation or propargylation of isatin-derived *N*-*tert*-butanesulfinyl ketimines for synthesis of highly enantiomerically enriched tetrasubstituted 3-aminooxindoles is described.

3-Aminooxindoles construct the core skeletons of a large family of biologically active natural products and a series of pharmaceutically important compounds.[1] Consequently, the development of efficient methods to synthesize these valuable frameworks has been a topic of considerable interest in recent years.[1d,e] Among them, intensive research efforts have focused on the assembly of tetrasubstituted 3-aminooxindoles.[2-6] Catalytic asymmetric amination of 3-substitued oxindoles with azodicarboxylates using chiral metal catalyst[4] and organocatalyst[5] for the highly stereoselective construction of these structures has been successfully developed. However, these transformations still suffer from some drawbacks, such as the facts that they generally require a long reaction time (1–7 days), the starting 3-substitued oxindoles are not readily available, and the final cleavage of product N-N bond can not be easily accomplished. On the other hand, asymmetric addition of carbon nucleophiles to isatin-derived ketimines represents another straightforward route to chiral quaternary 3-aminooxindoles, but only limited success has been achieved due to often unsatisfactory results.[6] Therefore, a simple new method that provides efficient and direct access to enantiopure quaternary 3-aminooxindoles with useful functional groups remains highly desirable.

We have recently disclosed our success on α-allylation of various unprotected racemic amino acid esters to afford nonnatural α,α-disubstituted α-amino acids with great stereocontrol through an efficient stereospecfic [2,3]-sigmatropic rearrangement process.[7] In considering tetrasubstituted 3-aminooxindoles (cyclic α,α-disubstituted α-amino acid derivatives), we also became interested in stereoselectively installing an allyl functional group to the quaternary carbon center to form chiral 3-allyl 3-aminooxindoles. In our earlier work, efficient methods for the highly diastereoselective synthesis of chiral homoallylic amines by using *N*-*tert*-butanesulfinyl imine chemistry have been developed,[8] however, successful asymmetric allyl addition to ketimines is far less explored[8a,d] and remains a significant challenge.[9] In 2009, Silvani described allylmagnesium bromide addition to isatin-derived *tert*-butanesulfinyl ketimines to synthesize 3-allyl 3-aminooxindoles, but both the yields (25-46%) and diastereoselectivities (up to 78% de) were not ideal.[6a] Other known examples of effective allylation of isatin ketimines, however, led to racemic 3-allyl 3-aminooxindoles.[2b,c] Herein, we report a highly practical approach that allows convenient formation of a wide range of stereochemically defined 3-allyl 3-aminooxindoles via Zn-mediated asymmetric allylation of isatin-derived *N*-sulfinyl ketimines.

Table 1. Screening of reaction conditions for diastereoselective allylation of isatin *N*-sulfinyl ketimines[a]



1a, R = Me; **1b**, R = PMB; **1c**, R = Tr — **3a-c**

entry	R	M	solvent	additive[b]	yield[c] (%)	de[d] (%)
1	Me	In	sat. aq NaBr		78	28
2	Me	Zn	THF		80	39
3	Me	Zn	THF	$In(OTf)_3$	89	-7
4	Me	Zn	HMPA		85	74
5	PMB	In	sat. aq NaBr		80	54
6	PMB	Zn	THF		80	37
7	PMB	Zn	THF	$In(OTf)_3$	88	-10
8	PMB	Zn	HMPA		90	72
9	Tr	In	sat. aq NaBr		62	52
10	Tr	Zn	THF		58	53
11	Tr	Zn	THF	$In(OTf)_3$	62	-16
12	Tr	Zn	DMF		92	83
13	Tr	Zn	DMSO		90	89
14	Tr	Zn	HMPA		73	97
15[e]	Tr	Zn	THF	HMPA	56	90
16	Tr	Zn	THF	HMPA	80	97
17[f]	Tr	Zn	THF	HMPA	48	94
18[g]	Tr	Zn	THF	HMPA	80	97

[a]The reaction were performed with isatin *N*-sulfinyl ketimine **1** (0.06 mmol), Zn or In powder (3 equiv), allyl bromide (4 equiv) in 2 mL of dry solvent at room temperature, unless otherwise noted. [b]1.3 equiv of $In(OTf)_3$ or 0.2 mL of HMPA was employed, if indicated. [c]Isolated yield. [d]Determined by LC-MS analysis. [e]0.1 mL of HMPA was employed. [f]2 equiv of Zn was employed. [g]4 equiv of Zn was employed.

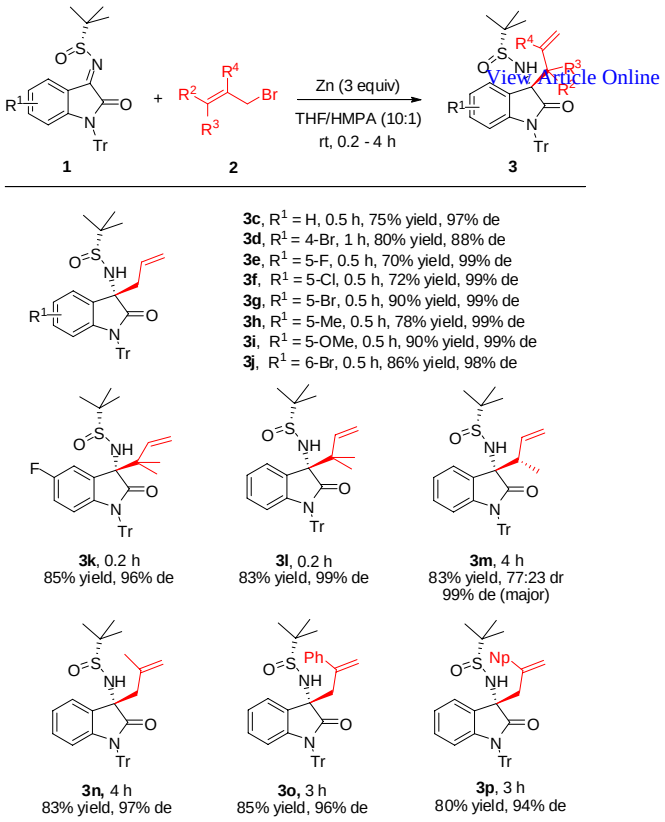
Initially, the reactions of simple allyl bromide (**2**) with a series of *N*-protected isatin-derived *N*-sulfinyl ketimines under previously

described mild conditions were carried out (Table 1). To our delight, all the reactions proceeded smoothly at room temperature, giving the desired product 3-allyl 3-aminooxindoles in goods yields, albeit with low to moderate diastereoselectivities in most cases (entries 1-14). It was found that Zn-mediated reactions showed much better stereocontrol than In-mediated ones. Surprisingly, unlike in the known cases of *N*-sulfinyl imines,[8a] the addition of Lewis acid $In(OTf)_3$ in THF led to sharp declines in diastereoselectivities (entries 3, 7 and 11). In contrast, we were delighted to observe significant increases in the diastereoselectivities of the reactions in polar aprotic solvents such as DMF, DMSO and HMPA in the presence of Zn powder (entries 4, 8 and 12-14). Among isatin substrates bearing different *N*-protecting groups, the reaction with *N*-Tr derivative (**1c**) in HMPA afforded the best result of diastereoselectivity (97% ee) (entry 14). In consideration of the carcinogenic potential of HMPA, we attempted to reduce the amounts of HMPA. Fortunately, the use of mixed solvent of THF and HMPA was found also effective. Moreover, the two solvents in a 10:1 volume ratio were essential to achieve the reaction with both high yield and excellent diasteroselectivity (80% yield, 97% de) (entry 16). In addition, the use of 3 equiv of zinc was determined to be the best in terms of atom economy and efficiency (entries 16-18).

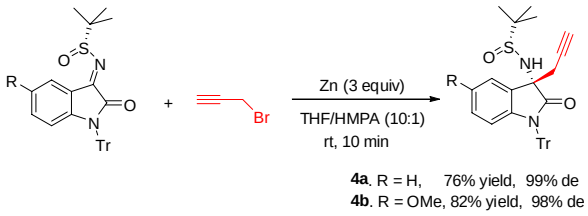
With the optimal reaction conditions identified, we then turned our attention to the evaluation of substrate generality. A wide range of *N*-trityl isatin ketimines bearing different substituents were investigated. Gratifyingly, the reaction was found to be general and efficient (Table 2). In all cases, it proceeded smoothly to completion in 0.2-4 hours. Isatin imines containing either electron-donating or electron-withdrawing groups at the C5 or C6 position could be successfully applied, affording quaternary 3-allyl 3-aminooxindole products **3e-j** in good yields and with excellent diastereoselectivities (typically 99% de) at room temperature. 4-Substituted substrate gave a slightly lower diastereselectivity (**3d**, 88% de), probably due to the conformational influence of the *N*-sulfinyl imine group by steric interaction. Notably, the scope of the reaction was substantially expanded with its compatibility with various substituted allyl bromides. For example, treatment of *N*-sulfinyl imine **1c** with 3,3-dimethylallyl bromide at room temperature resulted in exceptionally fast formation of **3k** and **3l** in good yields with 96-99% de. When a variety of 2- substituted ally bromides were employed, again, the reactions occurred readily to furnish the corresponding adducts **3n-p** in equal high yields and diastereoselectivities. More challenging (*E*)-1-bromo-2-butene was also found an applicable substrate.[10] Interestingly, two stereoisomers (**3m**) were produced with a diastereomeric ratio of 77:23 in favor of (*S*, *S*) isomer with 99% ee.

Encouraged by the above success on allylation, we reasoned that the same isatin ketimines might undergo asymmetric propargylation in a highly diastereoselective fashion to provide equally valuable 3-propargyl 3-aminooxindoles if 3-bromo-1-propyne instead of allyl bromide was employed under similar conditions. In literature, asymmetric method to such compounds is unprecedented.[11] As expected, the propargylation proceeded to completion very rapidly (within 10 min); accordingly, products **4a** and **4b** were formed in high yields with excellent diastereoselectivities (98-99% de) (Scheme 1).

Table 2. Diastereoselective allylation of isatin ketimines.[a,b,c,d]



[a]Reactions were performed in 0.06 mmol scale, with 3 equiv of Zn, 4 equiv of allyl bromide in 2 mL of dry THF and 0.2 mL of dry HMPA at room temperature, unless otherwise noted. [b]Isolated yields. [c]de was measured as enantiomeric excess for the oxidate derivative of product **3**; determined by chiral HPLC analysis. [d]For **3o** and **3p**, the reactions were carried out at 50°C.



Scheme 1 Diastereoselective propargylation of isatin ketimines

Conversion of the allylation/propargylation product to the corresponding free amine could be easily accomplished under acidic conditions. For example, upon treatment of TFA and HCl/MeOH, both the trityl and sulfinyl groups of **3c** were readily removed to afford clean 3-allyl 3-aminooxindole (**5**).[12] The absolute configuration at C3-stereogenic center was determined to be *S* by comparison of its optical rotation with that of the known compound.[12] Assuming an analogous reaction mechanism, the same stereochemistry of the obtained 3-aminooxindoles **3** and **4** were assigned. For the product **3m** with two stereogenic centers, the absolute structure was determined by single-crystal X-ray analysis[13] (See Supplementary Information).

To rationalize the observed diastereofacial selectivity, an acyclic transition state model is proposed (Figure 1). Because of the strong metal cation coordination ability of HMPA, the allylzinc

chelation to imine nitrogen or carbonyl oxygen is much less favored in solution. As the uncoordinated *N*-sulfinyl group adopts an approximate synperiplanar configuration, the bulky *tert*-butyl group is positioned at the *si*-face of ketimine molecule (TS-1). Thus, the allylzinc reagent attacks preferentially from the sterically unblocked *re*-face of the imine C=N bond, facilitating (*S*)-amine formation.

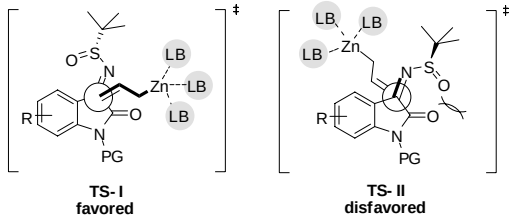
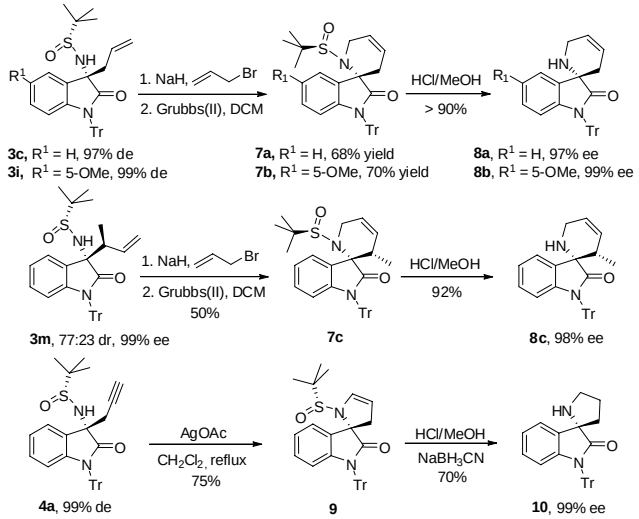


Figure 1. Mechanistic proposals for stereocontrol



Scheme 2 Facile synthesis of chiral spirocyclic oxindoles

Finally, the synthetic utility of this chemistry is demonstrated by facile access to a series of enantiopure spirocyclic aminooxindoles (Scheme 2). A sequential treatment of the addition products **3c**, **3i** with NaH/allyl bromide, followed by Grubbs' catalyzed ring-closing metathesis, gave chiral spirocyclic products **7a**, **7b** in good yields. After removal of the sulfinyl group, the corresponding spirocyclic aminooxindoles were obtained with no racemization detected. Similarly, by using **3m** as the substrate, spirocyclic product **8c** bearing two contiguous stereocenters on the 1,2,3,6-tetrahydropyridine ring was conveniently produced. Remarkably, we found that the propargyl adduct can also be applied to prepare specific spiro oxindoles through intramolecular hydroamination strategy. Upon exposure of **4a** to AgOAc (15 mol%) in CH_2Cl_2, the cyclized product **9** was generated in 75% yield. Under acidic conditions in the presence of $NaBH_3CN$, the stereochemically defined spiro-indolinone-pyrrolidine ring system was successfully constructed. It is noteworthy that these chiral spirocyclic oxindole compounds are valuable pharmacological components but usually difficult to access.[1e]

In summary, a highly practical asymmetric approach for the efficient preparation of chiral tetrasubstituted 3-aminooxindoles has been developed based on a simple Zn-mediated diastereoselective allylation/propargylation process at room temperature. The method provides easy access to a wide range of highly enantiomerically enriched 3-allyl or 3-propargyl substituted 3-aminooxindoles under exceptionally mild conditions. By taking advantage of the functional group transformations, the rapid asymmetric construction of two important classes of spirocyclic aminooxindoles has been established.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and spectral data for new compounds. See DOI: 10.1039/b000000x/

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12 See the Supplementary Information for details.

13 CCDC 916093 (**3m**) contains the supplementary crystallographic data.