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Highly efficient synthesis of chiral quaternary 3-aminooxindoles promoted by zinc(II) chloride *via* Et_2Zn-catalysed addition of Grignard reagents to isaltin-derived *N-tert*-butanesulfinyl ketimines†

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A highly efficient and practical approach to chiral quaternary 3-aminooxindoles was developed *via* Et_2Zn catalyzed diastereoselective addition of Grignard reagents to isaltin-derived *N-tert*-butanesulfinyl ketimines giving good to excellent yields and diastereoselectivities with broad substrates and reagent scopes promoted by zinc(II) chloride.

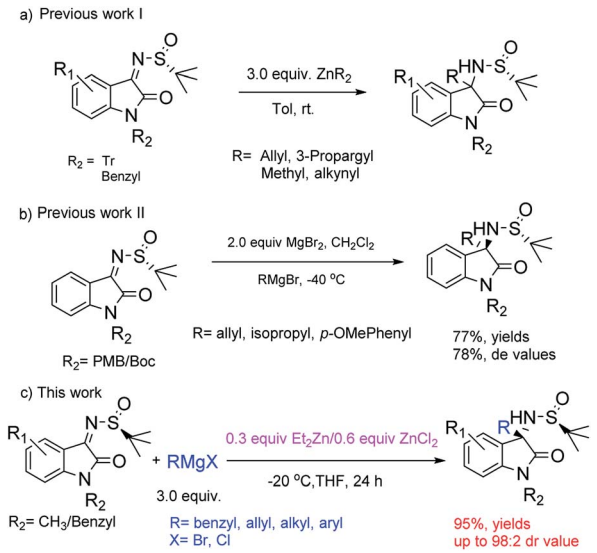
Introduction

As a widely used chiral auxiliary due to its excellent stereoselectivity, facile preparation and low cost, the application of chiral *tert*-butanesulfinamide to build a chiral C–N center has been well documented.[1] Although constructing chiral quaternary C–N centers is still a challenging task in asymmetric synthesis,[2] using chiral *tert*-butanesulfinamide as a chiral auxiliary to construct tertiary chiral C–N centers *via* the addition of organometallic reagents to *N-tert*-butanesulfinyl aldimines has been reported.[1a,3] The use of chiral *tert*-butanesulfinamide and organometallic reagents such as Grignard reagents provided a practical strategy to synthesize chiral quaternary carbon C–N bonds. For example, using isaltin-derived *N-tert*-butanesulfinyl ketimines to build quaternary C–N centers has been becoming a hot research topic in recent years.[4] The core skeleton of chiral quaternary 3-aminooxindoles can be found in VIb receptor antagonist SSR-149415 (ref. 5) and the antimalarial drug candidate NITD609.[6]

To synthesize chiral quaternary 3-aminooxindoles, several methodologies *via* metal-mediated diastereoselective addition of isaltin-derived *N-tert*-butanesulfinyl ketimines have been developed. Among them, methylation/terminal alkynylation and allylation/propargylation *via* alkyl zinc reagent were carried out by Wang[4g] and Xu[4h] (Scheme 1a); and $MgBr_2$ mediated addition of the ketimines with Grignard reagents was first reported by Alessandra Silvani's group[4i] (Scheme 1b). Excessive $ZnMe_2$, zinc powder and $MgBr_2$ were needed for these methodologies accordingly. Herein, we report an effective Et_2Zn catalyzed approach to chiral quaternary 3-aminooxindoles *via* diastereoselective addition of diverse Grignard reagents to a variety of *N-tert*-butanesulfinyl ketimines derived from isatin in mild conditions, giving satisfactory yields and diastereoisomeric ratios promoted by zinc(II) chloride (yields up to 95% and dr up to 98 : 2) (Scheme 1c).

Results and discussion

Ishihara[7] showed that $ZnCl_2$ could catalyze the addition of Grignard reagents to varied imines efficiently. And Yu[8] also



Scheme 1 Synthetic approaches to chiral quaternary 3-aminooxindoles.

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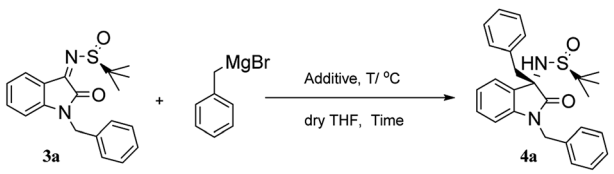
reported that stoichiometric amount of Et_2Zn could promote the addition of RMgBr to *N-tert*-butanesulfinyl aldimines, but few to ketimines. Surprisingly, we found that $ZnCl_2$ and Et_2Zn could have synergistic effect in the synthesis of chiral quaternary 3-aminooxindoles *via* the addition of Grignard reagents to isaltin-derived *N-tert*-butanesulfinyl ketimines.

Initially, we conducted the reaction in −78 °C without any additives. After the mixture was stirred for 3 days, good diastereoselectivity but low yield was obtained (Table 1, entry 1). When the temperature was increased to −55 °C, the product yield was enhanced a lot with decrease of the dr value. Surprisingly, when $ZnCl_2$ was added the diastereoselectivity of the reaction was improved obviously (Table 1, entry 3). When catalytic amount Et_2Zn was used respectively, the rate of reaction was greatly increased and 65% isolated yields after 48 hours (Table 1, entry 4). We then examined the efficiency of $ZnCl_2$ and Et_2Zn in the addition reaction between *N-tert*-butanesulfinyl ketimine **3a** and benzylmagnesium bromide separately in −40 °C (Table 1, entries 5 and 6). In the presence of 0.3 equiv. of $ZnCl_2$ only, although the reactivity was unsatisfied, the diastereoselectivity of the reaction was very high (>98 : 2 dr) at −40 °C for 24 h. Meanwhile, 0.3 equiv. of Et_2Zn gave the desired product with 80% yields and 98 : 2 dr value under the same conditions. As we expected, when combining Et_2Zn and $ZnCl_2$, the product yield was increased to 86% without reduction in diastereoselectivity (Table 1, entry 7). Elevating the reaction temperature to −20 °C, the corresponding yield of the product was improved to 90%, but its dr value was decreased to 96 : 4 (Table 1, entry 8). Further increasing the loading amount of $ZnCl_2$ enhanced the de value of the product with lower yield (Table 1, entries 9 and 10). The loading amount of Et_2Zn was critical and 0.3 equiv. of Et_2Zn was shown to be the best (Table 1, entries 5, 11 and 12). Replacing $ZnCl_2$ by $ZnBr_2$, the product yields dropped a lot with slightly decreasing of the dr value (Table 1, entries 9 and 13). Using $PhCH_2MgCl$ instead of $PhCH_2MgBr$ in the presence of 0.3 equiv. of Et_2Zn and 0.6 equiv. of $ZnCl_2$ at −20 °C improved the yield to 92% and the dr value to 98.5 : 1.5 (Table 1, entries 9 and 14). Further elevating the reaction temperature to 0 °C resulted in the decrease of the dr value to 94.5 : 5.5 (Table 1, entry 15).

With the optimized conditions in hand, we then investigated the substrate scope of the reaction system. As shown in Table 2, this system worked very well for a variety of substrates with H-, CH_3-, OCH_3-, Cl-, Br-substitution on 3-, 4-, 5-position of the aromatic ring and Bn-, CH_3-substitution on the nitrogen center

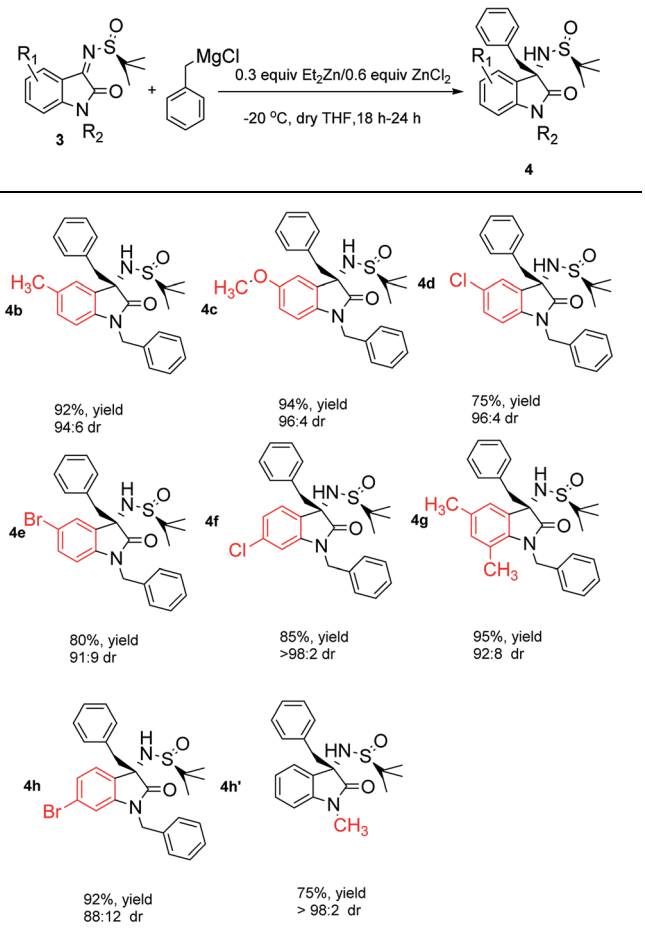
Table 1 Optimization of experimental conditions[10a]



Entry	T/°C	Additive/equiv. Et_2Zn	Additive/equiv. $ZnCl_2$	Time/h	Yield[b] %	Dr[c]
1	−78	—	—	72[d]	19	>98 : 2
2	−55	—	—	72[d]	35	95.5 : 4.5
3	−55	—	0.3	72[d]	42	98.5 : 1.5
4	−55	0.3	—	48[d]	65	97.5 : 2.5
5	−40	—	0.3	24[d]	39	>98 : 2
6	−40	0.3	—	24	80	98 : 2
7	−40	0.3	0.3	24	86	>98 : 2
8	−20	0.3	0.3	24	90	96 : 4
9	**−20**	**0.3**	**0.6**	**24**	**88**	**97.5 : 2.5**
10	−20	0.3	1.0	24	70	>98 : 2
11	−20	0.4	0.6	24	61	>98 : 2
12	−20	0.2	0.6	24[d]	63	98.5 : 1.5
13[e]	−20	0.3	0.6	24	79	96 : 4
14[f]	**−20**	**0.3**	**0.6**	**18**	**92**	**98.5 : 1.5**
15[f]	0	0.3	0.6	24	93	94.5 : 5.5

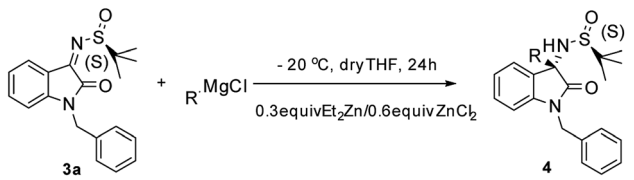
[a] Reaction conditions: **3a** (0.2937 mmol), the Grigard reagents (0.8811 mmol), dried THF, N_2. [b] Isolated yields. [c] Analyzed by NMR and HPLC. [d] SM did not react completely detected by TLC. [e] $ZnBr_2$ was used instead of $ZnCl_2$. [f] Benzylmagnesium chloride was used instead of benzylmagnesium bromide.

Table 2 Scope of ketimines derived from isatin[a]



[a] Reaction conditions: the corresponding substrates **3** (0.2937 mmol), benzylmagnesium chloride (0.8811 mmol), Et_2Zn (0.08811 mmol), $ZnCl_2$ (0.1762 mmol), dried THF, N_2, −20 °C, 18–24 h. Yield is for isolated yields and dr is analyzed by NMR.

Table 3 Scope of the Grignard reagents[a]



Entry	No.	R-	Time/h	Yield[b]/%	Dr[c]
1	**4i**	Isopropyl-	24	84	>98 : 2
2	**4j**	Allyl-	24	92	>98 : 2
3	**4k**	Phenyl-	24	85	88 : 12
4	**4l**	*p*-Methylphenyl-	24	88	94 : 6
5	**4m**	Ethyl-	24	95	>98 : 2
6[d]	**4n**	Methyl-	24	94	>98 : 2

[a] Reaction conditions: **3a** (0.2937 mmol), the Grignard reagents (0.8811 mmol), Et_2Zn (0.08811 mmol), $ZnCl_2$ (0.1762 mmol), dried THF, N_2, −20 °C, 24 h. [b] Isolated yields. [c] Analyzed by NMR. [d] Only methyl addition product was isolated. The reason might be that Et_2Zn was the catalytic amount and no or less ethyl addition product could be isolated.

of **3** giving 75–95% yields and up to 98 : 2 dr value of the desired products. Furthermore, our methodology was also applicable for diverse Grignard reagents, containing aryl, benzyl, alkyl and allyl Grignard reagents (Table 3).

The S configuration of the new generated stereocenters of **4** was assigned on the basis of **4n** and **4m**. The relative configuration of the quaternary C–N center of **4n** was confirmed by chemical transformation to a known compound **5** (ref. 4*g*) and the absolute configuration of **4m** was determined by X-ray crystal structure (Fig. 1).[11]

Based on our studies and previous published results by other groups,[4i,7–9] we proposed the possible catalytic mechanism as follows (Fig. 2): catalytic Et_2Zn reacted with $ZnCl_2$ and RMgCl to generate active triorganozincate $REt_2ZnMgCl$ and $MgCl_2$. The Lewis acid $MgCl_2$ activated *N-tert*-butanesulfinyl ketimine **3a** by

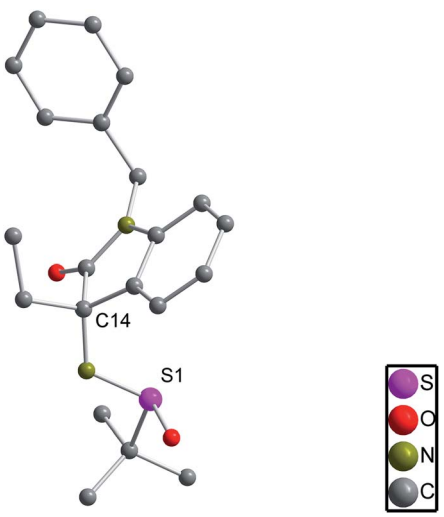


Fig. 1 X-ray structure of **4m**. Hydrogen was omitted for clarity.

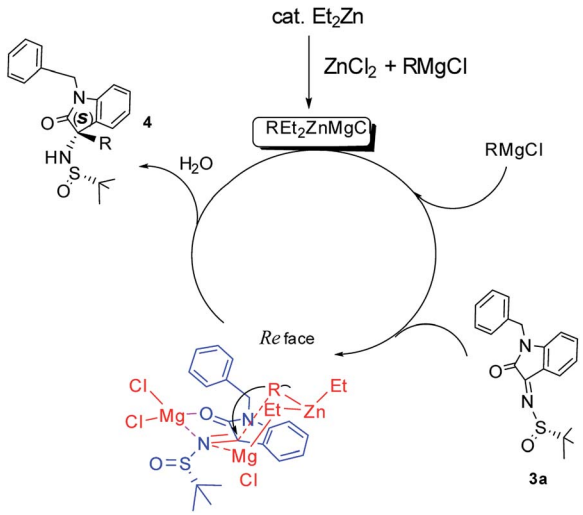


Fig. 2 Proposed the possible catalytic mechanism.

coordinating with the oxygen of C=O and the nitrogen of C=N in the ketimine. It facilitated the R-group transfer of REt_2MgCl and favored the equilibrium of E configuration of the imine which preferred the Re attack of R-group of REt_2MgCl to obtain the S configuration on the quaternary C–N center of the final product.

Conclusions

To summarize briefly, we developed a new and effective methodology for the diastereoselective addition of diverse Grignard reagents to a variety of *N-tert*-butanesulfinyl ketimines derived from isatin in good to excellent yields and diastereoselectivities. We provided a very practical synthetic approach to chiral quaternary 3-aminooxindoles. The rate of reaction and yield was greatly increased through the use of Et_2Zn. The dr values of products were promoted obviously by zinc(II) chloride. The *in situ* generated active triorganozincate and rigid transition state are the key factors for the high reactivity and diastereoselectivity of the reaction.

Acknowledgements

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10 The diastereoisomers **4a** and **4a′** was separable, see: ^{1}HNMR, ^{13}CNMR and HRMS in ESI.† The dr value of **4a** in optimization of experimental conditions was determined by NMR and HPLC.

11 The X-ray crystal structure of **4m** was confirmed by CCDC 1523303.†