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Copper(I)-Catalyzed Kinetic Resolution of *N*-Sulfonylaziridines with Indoles: Efficient Construction of Pyrroloindolines

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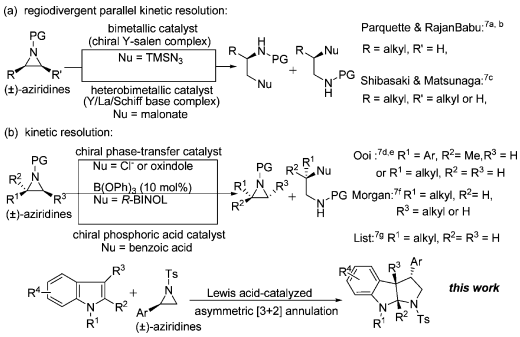
Supporting Information

ABSTRACT: The first Lewis acid catalyzed [3 + 2] annulation of indoles and 2-aryl-*N*-tosylaziridines was realized by using copper(I)/chiral diphosphine complexes as a catalyst. With this method, a variety of uniquely substituted chiral pyrroloindolines bearing multiple contiguous stereogenic centers were facilely accessed in a straightforward, high-yielding, and highly stereoselective way under mild conditions.

Enantioselective annulation reactions utilizing readily available three-membered ring compounds as masked 1,3-dipoles have recently emerged as a powerful approach to various chiral cyclic structures. The well-developed Lewis acid catalyzed asymmetric [3 + *x*] annulation of D−A cyclopropanes with various dipolarophiles providing facile access to carbocycles and heterocycles in highly stereoselective ways is an outstanding example.[1] As another important member of the three-membered ring system, aziridines are versatile building blocks for the expedient construction of various useful nitrogen-containing structures.[2] To date, great advances have been achieved in the catalytic asymmetric desymmetrization of *meso*-aziridines with a variety of nucleophiles by both chiral metal- and organo-catalysts.[3−5] However, except for 2-vinyl aziridines, with which highly enantioselective transformations could be achieved by chiral Pd(0) catalysts via π-allyl palladium intermediates,[6] examples of highly stereoselective asymmetric catalytic ring opening of other racemic aziridines via C−N bond cleavages are still very limited (Scheme 1).[7] Indeed, the Lewis acid catalyzed asymmetric [3 + *x*] annulation of racemic aziridines remains a formidable challenge, despite many known racemic examples.[8]

Chiral pyrroloindolines are an important structural motif present in a number of biologically active molecules such as (−)-physostigmine with acetylcholinesterase (AChE) inhibiting activities,[9a] P-glycoprotein inhibitor (+)-nocardioazine A,[9b] and antiarrhythmic agent ajimaline.[9c] Consequently, numerous innovative methods have been developed for constructing this important type of structures.[10] The recently developed asymmetric [3 + 2] annulation of an indole with a dipolarophile represents one of the most straightforward and convergent ways from simple precursors. However, successful examples with this strategy have been rather limited, including Reisman's work using 2-amidoacrylates as a dipolarophile and a combination of

Scheme 1. Catalytic Asymmetric Nucleophilic Ring-openings of Racemic Aziridines



catalytic (*R*)-BINOL and stoichiometric $SnCl_4$ as a catalyst,[11a−c] Davies' work with 4-aryl-1-sulfonyltriazoles using chiral Rh(II) catalysts,[11d] and Wang's work with *meso*-aziridines under the catalysis of a chiral organomagnesium complex.[4b] To date, the viability of racemic aziridines as dipolarophiles in such an annulation, which would provide pyrroloindoline products with a substitution type unreadily accessible from other methods, is unknown, and so are the catalytic asymmetric versions.[12] Here, we disclose *the first Lewis acid catalyzed asymmetric [3 + 2] annulations of indoles with 2-arylaziridines*, providing chiral pyrroloindolines bearing multiple contiguous stereogenic centers with excellent regio-, diastereo-, and enantioselectivity.

Initially, the reaction between 1,3-dimethylindole **1a** and 2-phenyl-*N*-tosyl aziridine **2a** was chosen as a model reaction to optimize the reaction conditions (Table 1),[13] and 2.2 equiv of the aziridine were used in case a kinetic resolution process occurs. Notably, while most previous relevant works on the activation of 2-aryl-*N*-tosylaziridines via Lewis acid catalysis for ring openings by neutral carbon-atom-based nucleophiles required the use of relatively stronger Lewis acids such as $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, and $Zn(OTf)_2$,[8] we found that less Lewis acidic Cu(I) salts were efficient catalysts for this annulation (see Table S1 in Supporting Information (SI) for a screen of different Lewis acids). In the absence of a ligand, 5 mol % of $[(CH_3CN)_4Cu]BF_4$ provided the desired product **3a** in moderate yield with good diastereose-

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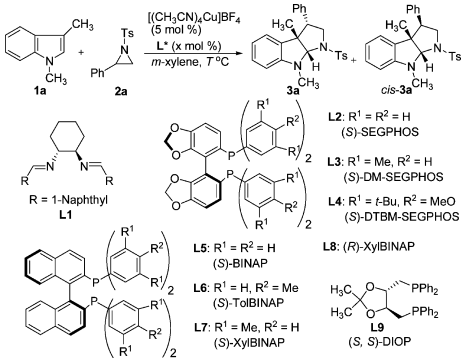
Table 1. Screen of Reaction Conditions[a]

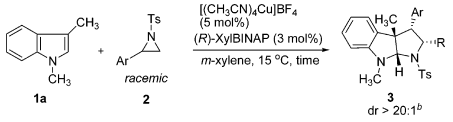


entry	L* (*x* mol %)	*T* (°C)	yield (%)[b]	d.r.[c]	ee (%)[d]
1[e]	–	23	63	11:1	N/A
2	**L1** (6)	45	57	20:1	−44
3	**L2** (6)	45	88	>20:1	−88
4	**L3** (6)	45	83	>20:1	−92
5	**L4** (6)	45	68	8:1	−4
6	**L5** (6)	45	76	>20:1	−90
7	**L6** (6)	45	94	>20:1	−92
8	**L7** (6)	45	95	>20:1	−91
9	**L8** (6)	45	95	>20:1	92
10	**L9** (6)	45	67	8:1	−6
11[f]	**L8** (6)	23	95	>20:1	93
12[f,g]	**L8** (6)	23	40	14:1	86
13[f,h]	**L8** (6)	23	97	>20:1	90
14	**L8** (3)	23	97	>20:1	93
15	**L8** (3)	15	97	>20:1	95
16[i]	**L8** (3)	0	90	>20:1	95
17[j]	**L8** (1.5)	15	90	>20:1	95

[a]Unless otherwise noted, reactions were performed with **1a** (0.1 mmol), **2a** (0.22 mmol) in 1.0 mL of solvent for 12 h. [b]Isolated yields of a mixture of **3a** and *cis*-**3a**. [c]dr values (**3a**/*cis*-**3a**) were estimated by ^{1}H NMR analysis of the crude mixture. [d]Determined by chiral HPLC. [e]Run with 0.1 mmol of each **1a** and **2a** for 24 h. [f]Reaction time: 24 h. [g]Run with 5 mol % of $[(CH_3CN)_4Cu]OTf$, and recovered starting materials account for the material balance. [h]Run with 5 mol % of $[(CH_3CN)_4Cu]PF_6$. [i]Reaction time: 48 h. [j]Run with 2.5 mol % of $[(CH_3CN)_4Cu]BF_4$.

lectivity (entry 1). Given the relevant successful work of Jacobsen and Evans on the enantioselective synthesis of aziridines,[14] our initial attempts to achieve stereocontrol were focused on chiral bisoxazoline and diamine ligands, with which an elevated reaction temperature was required to provide satisfactory conversions and yields (see Table S2 in the SI for details). The use of the optimal ligand **L1** of such types gave an excellent diastereoselectivity but with a moderate yield and enantioselectivity (entry 2). Pleasingly, excellent results were obtained when we turned to a series of commercially available chiral diphosphine ligands (entries 3−10), and the ligand **L8** (*R*)-XylBINAP was identified as optimal (entry 9). With this ligand, other reaction parameters such as reaction temperature, Cu(I) salts, and the metal/ligand ratios were examined. Lowering the reaction temperature to 23 °C led to a sluggish reaction with slightly better enantioselectivity (entry 11), while decreasing the amount of the ligand by half significantly accelerated the reaction so that it could complete within 12 h at 15 °C with an improved enantioselectivity. Performing the reaction at 0 °C or with half the catalyst loading led to a relatively lower yield due to incomplete conversion (entries 16−17). Thus, the optimal

Table 2. Scope of Aziridine Substrate 2[a]



entry	**2** (Ar)	time	**3**	yield (%)[c]	ee (%)[d]
1	**2a** (Ph)	12 h	**3a**	97	95
2	**2b** (4-FC_6H_4)	18 h	**3b**	98	94
3	**2c** (4-ClC_6H_4)	32 h	**3c**	98	97
4	**2d** (3-ClC_6H_4)	18 h	**3d**	95	97
5	**2e** (2-ClC_6H_4)	18 h	**3e**	97	97
6	**2f** (4-BrC_6H_4)	36 h	**3f**	96	96
7	**2g** (4-$O_2NC_6H_4$)	72 h	**3g**	50	97
8	**2h** (4-MeC_6H_4)	10 h	**3h**	98	96
9	**2i** (4-*t*-BuC_6H_4)	12 h	**3i**	98	97
10	**2j** (4-$MeOC_6H_4$)	1 h	**3j**	98	96
11[e]	**2k** (2-Naphthyl)	24 h	**3k**	95	93

[a]Unless otherwise noted, reactions were performed with **1a** (0.05 mmol), **2** (0.11 mmol) in 0.5 mL of *m*-xylene. [b]dr values were estimated by ^{1}H NMR analysis of the crude mixture. [c]Isolated yields. [d]Determined by chiral HPLC. [e]Run with 2.0 equiv of **2k**, 49% recovery of **2k** (93% ee), $s = 60$, $S = \mathrm{Ln}[(1 - C/100)(1 - \mathrm{ee}/100)]/\mathrm{Ln}[(1 - C/100)(1 + \mathrm{ee}/100)]$.

reaction conditions were determined as 5 mol % of $[(CH_3CN)_4Cu]BF_4$, 3 mol % of (*R*)-XylBINAP in *m*-xylene at 15 °C (entry 15).

With the optimal conditions in hand, we then examined the reaction scope with regard to different 2-arylaziridines (Table 2). In general, excellent diastereo- and enantioselectivity could be obtained irrespective of the electronic nature or positions of the substituents on the benzene ring (Ar). For aziridines **2b**−**2j** derived from substituted styrenes, those bearing electron-donating substituents reacted much faster than those with electron-withdrawing ones (entries 8−10). Particularly, the aziridine **2g** bearing a strongly electron-withdrawing group (NO_2) was very sluggish in the reaction with low conversion even after a prolonged reaction time (entry 7), while **2j** bearing a methoxyl group was exceptionally reactive (entry 10).[15] In both cases, excellent diastereo- and enantioselectivity were obtained. Such results suggest significant development of positive charge at the 2-carbon center of the aziridine ring. The 2-naphthyl aziridine **2k** also underwent the reaction smoothly, and the high ee value of the recovered aziridine indicated the involvement of a highly efficient simple kinetic resolution process of the aziridine in this reaction ($s = 60$, entry 11). It is worth mentioning that, in most previous successful catalytic asymmetric transformations with racemic aziridines (Scheme 1),[7] 2-alkylaziridines have been the suitable substrates while simple 2-arylziridines have been rarely studied. In contrast, 2-alkylaziridines hardly underwent the reaction under the optimized conditions, which is a limitation of the current reaction system.

Subsequently, we probed the reaction scope with regard to different indoles (Table 3). In general, high diastereo- and enantioselectivity were obtainable regardless of the changes of the substituents on the benzene ring, nitrogen atom, or 3-position of the examined indoles. For indoles bearing different substituents on the benzene ring, those with electron-withdrawing ones were generally more sluggish in the reaction (**3m**−**3q**), probably due to reduced nucleophilicity. *N*-Allyl and *N*-benzyl indoles were also suitable substrates for the reaction (**3p**−**3r**).[16] Various alkyl substituents at the 3-position of the indole

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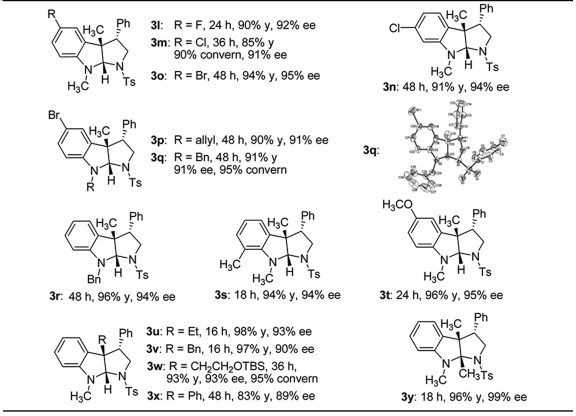
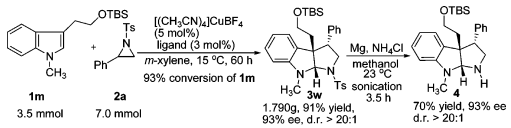
Table 3. Scope of Indole Substrate 1[a–d]

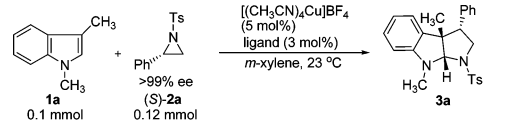


[a]Reactions were performed under conditions identical to those of Table 2 for the reaction times specified. [b]All the reactions showed dr >20:1 as estimated by ^{1}H NMR analysis of the crude mixture. [c]Isolated yields. [d]Determined by chiral HPLC.

Scheme 2. Scale-up Reaction and Product Transformation



Scheme 3. Control Experiments



ring were well-tolerated in the reaction (**3u**–**3x**). Notably, indoles with a phenyl group at the 3-position have been problematic and thus rarely used in dearomatic annulation reactions of indoles under Lewis or Brønsted acid catalysis.[17] While in our case, the product **3x** could be obtained in 83% yield and 89% ee. Moreover, 1,2,3-trisubstituted indole was also well-tolerated in the reaction, providing the pyrroloindoline **3y** bearing two contiguous tetrasubstituted carbon centers in excellent yield and with almost complete enantiocontrol. The absolute configuration of the product **3q** was determined by X-ray crystallographic analysis.

The chiral pyrroloindoline products **3** bearing a unique substitution are not easily accessible by other methods, which is one of the advantages of the method.[18] To demonstrate the practicality of the method, a gram-scale synthesis of the product **3w** was performed with almost the same excellent yield and stereoselectivity (Scheme 2). Moreover, the Ts group could be easily removed following a known procedure[19] to provide the free amine **4** in an unoptimized yield of 70% with no loss in both the diastereo- and enantioselectivity.

Next, some control experiments were performed to shed some light on the stereochemical course of the reaction (Scheme 3). Using the enantiopure aziridine (*S*)-**2a** derived from L-phenyl glycinol, we found that the use of (*R*)-XylBINAP or racemic Cy_3P as the ligand provided comparably excellent yields and stereoselectivities. In contrast, when (*S*)-XylBINAP was used, a sluggish reaction and poor stereoselectivity were observed. Notably, the structure of the aziridine predominated in determining the absolute figuration of the major product. Such results support that racemic aziridines undergo a simple kinetic resolution process in the asymmetric catalytic reaction. Reduced diastereo- and enantioselectivity were obtained when the reaction was run with $[(CH_3CN)_4Cu]BF_4$ alone, suggesting slightly partial racemization of the aziridine. The appreciably higher yield and stereoselectivity obtained in the presence of Cy_3P might be partly ascribed to the extenuated Lewis acidity of the combination of a Cu(I) salt and a phosphine, which might favor the nucleophilic attack of the aziridine by a "soft" carbon nucleophile (indoles) to give a cleaner reaction, while the lower solubility of the nonligated Cu(I) salt in *m*-xylene might also be partly responsible for its lower efficiency. The above results also suggest that the reaction initiated with an S_N2-type nucleophilic attack of the indole to the 2-position of the aziridines in a stereoinvertive manner. However, as the actual structure of the catalytic active Cu(I) species and its activation mode of the racemic *N*-Ts aziridines remain unclear at this time, further experiments would be necessary to elucidate the origin of the stereoselectivity of the reaction.

In conclusion, the asymmetric Lewis acid catalyzed [3 + 2] annulation reaction of indoles and 2-aryl-*N*-tosylaziridines was developed. The combination of commercially available Cu(I) salts and chiral diphosphine ligands was first identified as an efficient chiral Lewis acid catalyst for the asymmetric transformations of racemic aziridines via kinetic resolution, enabling facile accesses to a variety of chiral pyrroloindolines with a unique substitution type in a highly convergent and stereoselective way. Efforts toward a deeper understanding of the reaction mechanism and the application of this methodology to develop other useful asymmetric transformations of aziridines are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05820.

Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra, HPLC traces of all products (PDF)
CIF for compound **3q** (CIF)
Spectral data (ZIP)

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Notes

The authors declare no competing financial interest.

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(16) An alkyl substituent on the nitrogen atom of indoles seemed to be necessary for the reaction. *N*-Boc-3-methyl indole hardly underwent the reaction. *N*-Unprotected 3-methyl indole gave the desired product in very poor yield and enantioselectivity (21% yield, 24% ee, and >20:1 dr), together with some unidentified side products. The nucleophilicity of the NH functionality in the indole substrate and/or the initial annulation product toward aziridines might be responsible for the low yield, as supported by the almost full consumption of the aziridine **2a** (2.2 equiv) and ^{1}H NMR analysis of the complex mixture of the side products.

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