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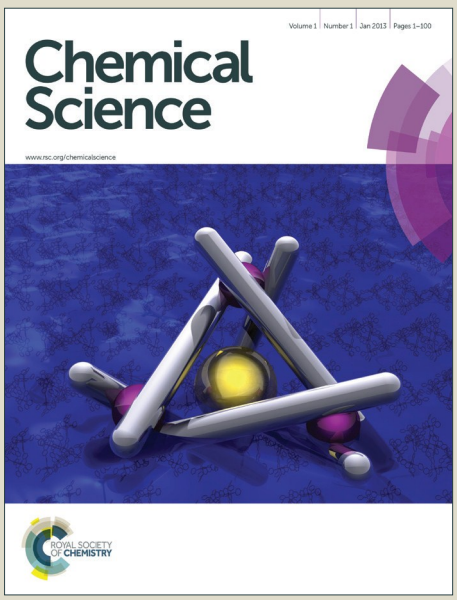

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ARTICLE

Asymmetric [3+2] Cycloaddition of Donor-Acceptor Aziridines with Aldehydes *via* Carbon–Carbon Bond Cleavage

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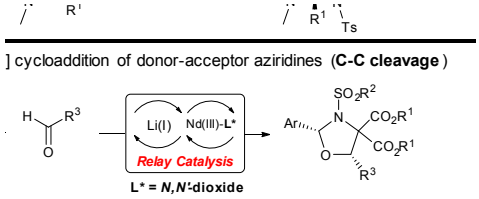
An enantioselective [3+2] annulation of donor-acceptor aziridines with aldehydes has been realized using $Nd(OTf)_3$/*N,N*′-dioxide/$LiNTf_2$ catalyst system, providing various chiral *cis*-1,3-oxazolidines in moderate to good yields with high level of stereocontrol. A relay catalytic process is proposed that $LiNTf_2$ promotes the formation of azomethine ylide intermediates, and chiral Nd(III)–*N,N*′-dioxide complex accelerates the asymmetric cycloaddition.

Introduction

The cycloaddition of aziridines is an attractive method to obtain various nitrogen-containing heterocycles.[1] Among them, highly enantioselective [3+2] cycloadditions via C–N bond cleavage of racemic aziridines have been realized. For example, the asymmetric cycloadditions of racemic vinyl aziridines with isocyanates and α,β-unsaturated ketones have been reported by Trost and Hou, respectively (Scheme 1a).[2] Very recently, Wang realized chiral copper(I) complex catalyzed [3+2] annulation of racemic 2-aryl-*N*-tosylaziridines with indoles (Scheme 1b).[3] As a type of donor-acceptor (DA) variation, 2,3-diester aziridines favor C–C bond heterolytic cleavage, and the formed transient azomethine ylide intermediates can undergo cycloadditions with various dipolarophiles (Scheme 1c). These transformations could be promoted by Lewis acid under mild condition in comparison with photochemically or thermally induced conditions.[4] Pioneering example is $ZnCl_2$ catalyzed cycloaddition between *N*-aryl-2,3-diester aziridines and electron-rich alkenes developed by Johnson.[5a] The Zhang group and others further explored Lewis acid accelerated cycloadditions of *N*-tosylaziridinedicarboxylates with aldehydes,[5b,c] imines,[5c,d] electron-rich alkenes,[5e] alkynes,[5f] 2,3-disubstituted indoles,[5g,h] donor-acceptor cyclopropanes,[5i] isocyanides[5j] and heterocumulenes.[5k]

Despite these important racemic examples, catalytic asymmetric [3+2] cycloadditions of DA aziridines are rare with the results of no more than 70% ee.[5b,d-f] Compared with their cousins DA cyclopropanes[6] and DA oxiranes,[7] the enantioselective [3+2] cycloadditions of aziridines are more difficult with considerable challenges: (1) The azomethine ylide via C–C bond cleavage is transient, being further converted to 2-amino malonate and aldehyde in the presence of unavoidable trace amount of water that prevent from cycloadditions.[5a,e] (2) DA aziridine has a relatively congested structure tethering four substituents on the three-membered ring, which hampers its interaction with a chiral catalyst. Additionally, the competitive coordination of aldehydes to the chiral catalyst is also a disadvantage to the yield and stereocontrol. Therefore, the asymmetric cycloadditions of DA aziridines require a powerful catalytic system enabling both C–C bond cleavage and enantiocontrol. Here we report a relay catalyst system of $Nd(OTf)_3$/*N,N*′-dioxide/$LiNTf_2$ for the asymmetric cycloaddition of DA aziridines with aldehydes (Scheme 1c).[8] The relay approach is to use an achiral metal salt in accelerating the formation of azomethine ylide intermediate, which is then transformed into a chiral catalytic environment to undergo asymmetric cycloaddition. Chiral *cis*-1,3-oxazolidines, which have emerged as crucial structural units in



Scheme 1. Asymmetric [3+2] cycloadditions of racemic aziridines

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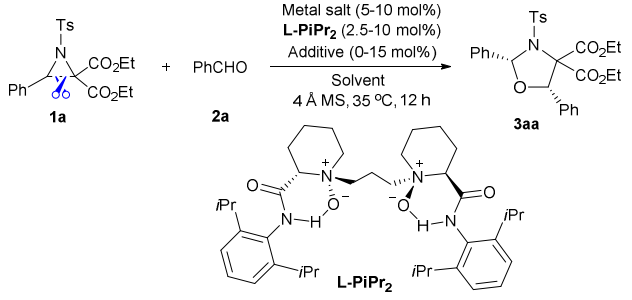
chiral catalysts and biologically active compounds[9] could be given in moderate to high yield and good enantioselectivity.

Results and discussion

We selected the model [3+2] annulation of DA aziridine **1a** with benzaldehyde **2a** as our starting point (see Table 1). In the presence of 10 mol% of *N*,*N*′-dioxide **L-PiPr$_2$** and 4 Å MS, metal salts which have been established as efficient Lewis acids for the catalytic racemic transformations were tested (entries 1-4). Disappointedly, low yields and enantioselectivities were obtained with $Sc(OTf)_3$, $Ni(ClO_4)_2$, $Zn(OTf)_2$ or $La(OTf)_3$ due to the decomposition of aziridine **1a**. $La(OTf)_3$/**L-PiPr$_2$** provided the *cis*-1,3-oxazolidines **3aa** in 14% yield with 36% ee in toluene at 35 °C. We surmised whether extra Lewis acid could assist to furnish the desired transformation.[7] Encouragingly, the addition of $LiNTf_2$ (10 mol%) was indeed beneficial for both the reactivity and enantioselectivity (entry 5). After examining a series of lanthanide metal salts (see the Supporting Information), $Nd(OTf)_3$ was selected as the best one, resulting in 30% yield and 71% ee (entry 6). Next, the systematical modification of *N,N′*-dioxides through alteration of the amino acid backbones and amide moieties, as well as the length of linkage showed **L-PiPr$_2$** was the optimized ligand (see the Supporting Information). Empirically changing the solvent to $CHCl_3$ instead of toluene improved the enantioselectivity to 85% ee (entry 7). Optimization of other reaction conditions by adjusting the ratio of $Nd(OTf)_3$ to **L-PiPr$_2$** (2:1), increasing the amount of $LiNTf_2$, 4 Å MS and aldehyde to speed up the reaction provided the product **3aa** in a good yield of 65% with 87% ee (entry 8). It should be considered that the azomethine ylide intermediate derived from DA aziridine was very unstable,

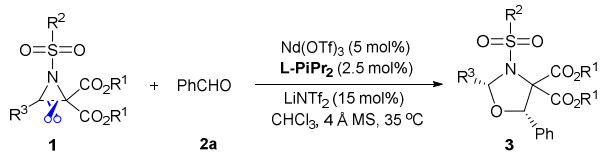
Table 1. Optimization of the reaction conditions.[a]

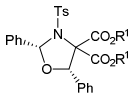
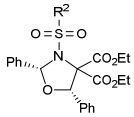
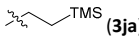
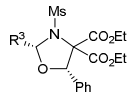
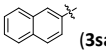


Entry	Metal salt	Additive	Solvent	Yield (%)[b]	ee (%)[c]
1	$Sc(OTf)_3$	-	Toluene	45	0
2	$Ni(ClO_4)_2{\cdot}6H_2O$	-	Toluene	20	-22
3	$Zn(OTf)_2$	-	Toluene	trace	-
4	$La(OTf)_3$	-	Toluene	14	36
5[d]	$La(OTf)_3$	$LiNTf_2$	Toluene	24	58
6[d]	$Nd(OTf)_3$	$LiNTf_2$	Toluene	30	71
7[d]	$Nd(OTf)_3$	$LiNTf_2$	$CHCl_3$	35	85
8[e]	$Nd(OTf)_3$	$LiNTf_2$	$CHCl_3$	65	87
9[e,f]	$Nd(OTf)_3$	$LiNTf_2$	$CHCl_3$	68	91
10[e,f,g]	$Nd(OTf)_3$	$LiNTf_2$	$CHCl_3$	68	91

[a] Unless otherwise noted, the reactions were performed with metal salt/**L*** (10 mol%, 1/1), 4 Å MS (20 mg), aziridine **1a** (0.1 mmol) and PhCHO **2a** (0.15 mmol) in solvent (1.0 mL) under nitrogen at 35 °C for 12 h. [b] Isolated yield by silica gel chromatography. [c] The ratio of *cis*/*trans* was >19:1 determined by ^{1}H NMR spectroscopy and ee values were determined by chiral HPLC analysis. [d] $LiNTf_2$ (10 mol%) was used. [e] $Nd(OTf)_3$/**L-PiPr$_2$** (5 mol%, 2/1), $LiNTf_2$ (15 mol%), 4 Å MS (100 mg), aziridine **1a** (0.1 mmol) and PhCHO **2a** (0.2 mmol) in $CHCl_3$ (0.75 mL). [f] Isolation by flash chromatography using basic Al_2O_3. [g] $Nd(OTf)_3$/**L-PiPr$_2$** (2.5 mol%, 2/1), $LiNTf_2$ (15 mol%).

Table 2. Substrate scope of donor-acceptor aziridines.[a]

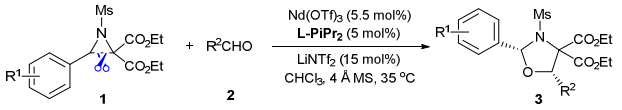


Entry	3	t (h)	Yield (%)[b]	ee (%)[c]
1	 Et (**3aa**)	12	68	91
2[d]	Me (**3ba**)	12	62	90
3[d]	*i*Pr (**3ca**)	14	40	72
4[d]	4-ClC_6H_4 (**3da**)	12	74	89
5	C_6H_5 (**3ea**)	12	70	90
6	 4-$MeOC_6H_4$ (**3fa**)	12	60	90
7	2-MeC_6H_4 (**3ga**)	38	54	76
8	2-$O_2NC_6H_4$ (**3ha**)	92	6[e]	62
9[d]	Me (**3ia**)	12	77	95
10[d]	 (**3ja**)	12	66	93
11[d]	4-ClC_6H_4 (**3ka**)	24	80	91
12[d]	3-ClC_6H_4 (**3la**)	24	78	92
13[d]	2-ClC_6H_4 (**3ma**)	40	71	88
14[d]	4-BrC_6H_4 (**3na**)	24	70	93
15[d]	 4-FC_6H_4 (**3oa**)	24	66	94
16[d,f]	4-$F_3CC_6H_4$ (**3pa**)	40	98	91
17	4-$O_2NC_6H_4$ (**3qa**)	36	84	87
18[g]	4-PhC_6H_4 (**3ra**)	12	70	93
19[d,g]	 (**3sa**)	12	94	93
20	cyclohexyl (**3ua**)	36	0	-

[a-c] Unless otherwise noted, the reaction conditions were the same as entry 10, Table 1. [d] The absolute configuration was assigned as (*2R*, *5S*) by CD analysis referred to **3sa** whose absolute configuration was determined by X-ray analysis.[11] [e] The yield was determined by ^{1}H NMR. [f] $Nd(OTf)_3$/**L-PiPr$_2$** (5 mol%, 2/1). [g] PhCHO (0.3 mmol, 3 equiv.).

thereby 2-fold excess of benzaldehyde **2a** was necessary to achieve this satisfying outcome. Furthermore, chromatography purification using basic Al_2O_3 as the stationary phase instead of silica gel, led to an encouraging outcome with 68% yield and 91% ee (entry 9). It might prevent the partial racemization of chiral *cis*-1,3-oxazolidines in silica gel. Notably, **L-PiPr$_2$** at a loading of 2.5 mol% was able to catalyse the reaction efficiently without any loss of the outcome (entry 10).

Table 3. Substrate scope of aldehydes.[a]



Entry	R^1	R^2	**1**:**2**	t (h)	Yield (%)[b]	ee (%)[c]
1[d]	H	4-ClC_6H_4	1:3	24	70 (**3ib**)	90
2[e]	3-Cl	3-ClC_6H_4	1:2	66	38 (**3lc**)	89
3[f]	4-Cl	4-MeC_6H_4	1:2	24	51 (**3kd**)	84
4[f]	4-Cl	3-MeC_6H_4	1:1.5	24	73 (**3ke**)	94
5[f]	3-Me	3-MeC_6H_4	1:2	12	51 (**3te**)	92
6[f]	4-Cl	3-$MeOC_6H_4$	1:2	24	70 (**3kf**)	93
7[f]	4-Cl	3-Thienyl	1:1.5	27	84 (**3kg**)	91
8[g]	4-Cl	2-Furyl	1:1.5	27	93 (**3kh**)	94
9[f]	4-Cl		1:2	30	84 (**3ki**)	55
10	4-Cl	cyclohexyl	1:2	40	trace	-

[a] Unless otherwise noted, the reactions were performed with $Nd(OTf)_3$ (5.5 mol%), **L-PiPr$_2$** (5 mol%), $LiNTf_2$ (15 mol%), 4 Å MS (100 mg), aziridine **1** (0.1 mmol) and aldehyde **2** in $CHCl_3$ (0.75 mL) under nitrogen at 35 °C for the indicated time. [b] Isolated yield by flash chromatography using basic Al_2O_3. [c] Determined by chiral HPLC analysis. [d] $Nd(OTf)_3$/**L-PiPr$_2$** (2.5 mol%, 2/1) was used. [e] $Nd(OTf)_3$/**L-PiPr$_2$** (5 mol%, 2/1) was used. [f] The absolute configuration was assigned as (*2R*, *5S*) by CD analysis referred to **3sa**. [g] With the absolute configuration of (*2R*, *5R*).

Examples of asymmetric [3+2] annulation of DA aziridines **1** with benzaldehyde **2a** promoted by the $Nd(OTf)_3$/$LiNTf_2$/**L-PiPr$_2$** catalyst system are summarized in Table 2. For the ester moieties, the methyl group had less influence on the outcome, while isopropyl group was detrimental to both the reactivity and enantioselectivity (entries 1-3). And other benzenesulfonyl motifs were well tolerated except that 2-methyl and 2-nitro substituent slowed down the reaction in a diminished yield and ee value, which might result from the steric hindrance at *ortho*-position (entries 4-8). It was noteworthy that methanesulfonyl substituent could make the result rise up to 77% yield and 95% ee (entry 9). Moreover, 2-trimethylsilylethanesulfonyl group, which proved to be readily cleaved under mild condition[10] also suited for the catalyst system (entry 10). Subsequently, a variety of electron-withdrawing substituted aryl aziridines provided the cycloadducts in 66–98% yields and 87–94% ee (entries 11-17). The position of the substituent had some influence on the enantioselectivity, and the *ortho*-substituted one required elongating the reaction time and gave a reduced ee value (entries 11-13). The aryl substituent could be replaced by the biphenyl or naphthalene-2-yl group, and the desired products were obtained in high yields and enantioselectivities albeit in need of 3-fold excess of benzaldehyde **2a** (entries 18-19). It might avoid the competitive annulations of the aldehydes from the decomposition of DA aziridines **1r** and **1s** with the corresponding DA aziridines. The alkyl substituted aziridine was inert and none of the corresponding 1,3-oxazolidine generated (entry 20). The result should be caused by its poor stabilization of the azomethine ylide intermediate compared to the aryl substituted ones. Overall, only *cis*-1,3-oxazolidines were detected. The absolute configuration of the product **3sa** was determined to be (*2R*, *5S*) by X-ray crystal analysis.[11]

The reaction also tolerated diverse aromatic aldehydes (see Table 3). In order to reach satisfactory reactivity and enantioselectivity, the amount of $Nd(OTf)_3$, **L-PiPr$_2$** and aldehydes needed to be adjusted. A variety of electron acceptor or donor substituted benzaldehydes provided *cis*-1,3-oxazolidines in moderate to high yields (38-73%) with good enantioselectivities (84-94% ee) (entries 1-6). Remarkably, heteroaromatic aldehydes (such as furan-2-carbaldehyde and thiophene-3-carbaldehyde) delivered the desired products in high yields (84-93%) and enantioselectivities (91-94% ee) (entries 7-8). Additionally, cinnamaldehyde displayed high reactivity but with moderate ee value (entry 9). Only trace amount of the expected adduct was detected using aliphatic aldehyde (entry 10). Similarly, only *cis*-1,3-oxazolidines were attained. To evaluate the synthetic utility of this catalyst system, a gram-scale preparation of **3kh** was undertaken, resulting in an outcome of 93% yield, >19:1 dr and 93% ee.

To gain insights into the reaction process, several control experiments were conducted. In the standard reaction condition, excessive aldehyde **2h** was used and the desired *cis*-product **3kh** was given in 93% yield and 94% ee (Table 3, entry 8). When the ratio of the aziridine **1k** to **2h** increased, the enantioselectivity of the product **3kh** maintained and the remaining aziridine **1k** was a racemate (Figure 1a).[12a] It indicates that the reaction performs through the formation of azomethine ylide intermediate.[13]

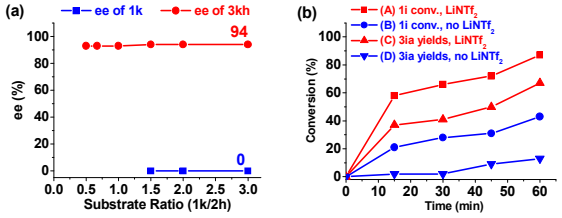
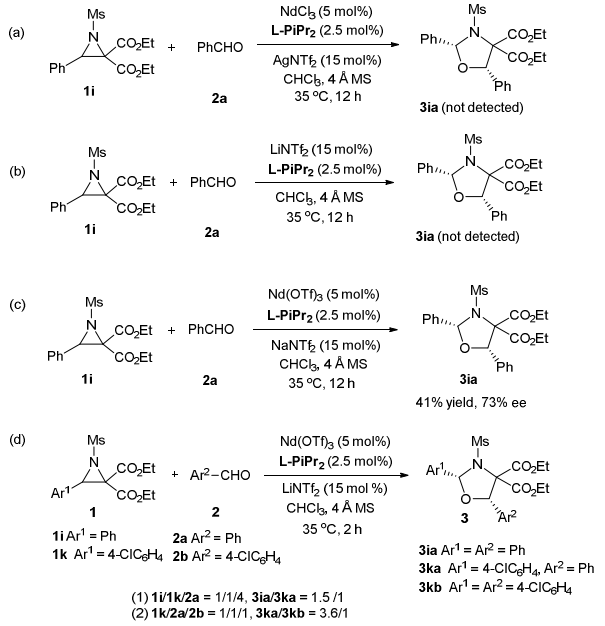


Figure 1. (a) Ee traces of the product **3kh** and the substrate **1k** of the reaction. (b) Reaction time profile of the reactions with or without $LiNTf_2$.

To better understand the catalyst systems, HRMS experiments were further explored. ESI-MS species assigned to [**L-PiPr$_2$**+Li^+]$^+$ and [**L-PiPr$_2$**+Nd^{3+}+OTf^-]$^{2+}$ were detected from the separate mixtures of the ligand with each of the metal salts. However, upon mixing the three components together (**L-PiPr$_2$**/$Nd(OTf)_3$/$LiNTf_2$ = 1/1.1/3), only the signals related to the complexes of **L-PiPr$_2$**/Nd(III) were observed (See the

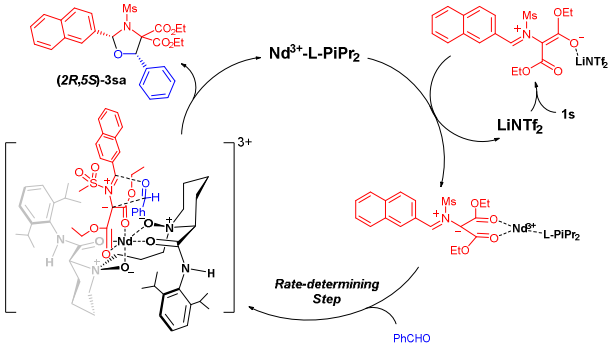
Supporting Information), elucidating the high stereocontrol might originate from chiral Nd(III) complex of **L-PiPr$_2$**.

Next, the primary action of the catalyst components was studied. When the mixture of $NdCl_3$/$AgNTf_2$/**L-PiPr$_2$** or $LiNTf_2$/**L-PiPr$_2$** was used, none of the desired [3+2] cycloadduct but byproducts were detected (Scheme 2a and 2b). In addition, the utilization of $NaNTf_2$ replacing $LiNTf_2$ reduced the results (41% yield/73% ee vs 77% yield/95% ee, Scheme 2c). It implies that the lithium salt does not merely provide a counter-anion or participate in the cycloaddition step. Reaction time profile of the transformation between aziridine **1i** and benzaldehyde **2a** showed that the *cis*-1,3-oxazolidine **3ia** formed gradually accompanying the consumption of aziridine **1i**. It was also evident from Figure 1b that the reaction rate was faster in the presence of $LiNTf_2$ than absence. ^{1}H NMR spectroscopy study of aziridine **1r** revealed that $LiNTf_2$ could obviously accelerate the generation of 4-PhC_6H_4CHO and $MsNHCH(CO_2Et)_2$, which was given from azomethine ylide trapped by water. Therefore, it is reasonable to conclude that $LiNTf_2$ could benefit the cleavage of the aziridine to generate azomethine ylide intermediate (See the Supporting Information).[14] Moreover, competitive reactions documented that the rate of cycloaddition was more sensitively influenced by the electronic nature of aldehydes (Scheme 2d).[12b,15] It implies that aldehydes function as electron rich dipolarphiles and the cycloaddition step is more likely to be the rate-determining step in comparison with the carbon-carbon cleavage in this case.



Scheme 2. Control experiments

Based on above mentioned results and our previous study of *N,N'*-dioxide–metal complex catalysis,[8] we proposed a dual Lewis acids relay catalysis process (Scheme 3).[16] Firstly, with the assistant of $LiNTf_2$, the carbon-carbon bond of DA aziridine cleaves to form the dipole intermediate. It is caught by the chiral Nd(III)/**L-PiPr$_2$** complex due to the strong bidentate coordination of the two ester groups to the metal center. A concert [3+2] cycloaddition occurred enantioselectively to give *cis-(2R, 5S)*-1,3-oxazolidine **3sa**, liberating the catalysts.



Scheme 3. A plausible catalytic cycle.

Conclusions

In summary, we have disclosed an enantioselective [3+2] annulation of donor-acceptor aziridines with aldehydes through C–C bond cleavage. $LiNTf_2$ and chiral *N,N'*-dioxide/$Nd(OTf)_3$ complex worked as relay catalysts to promote the reaction under mild reaction conditions. The protocol allowed an efficient production of a variety of enantiomerically enriched *cis*-1,3-oxazolidines. Additional research in the expansion of asymmetric transformations of DA aziridines to other dipolarphiles is underway.

Acknowledgements

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Notes and references

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