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Magnesium Catalysis Mediated Tetrazoles in Desymmetrization Reaction of Aziridines

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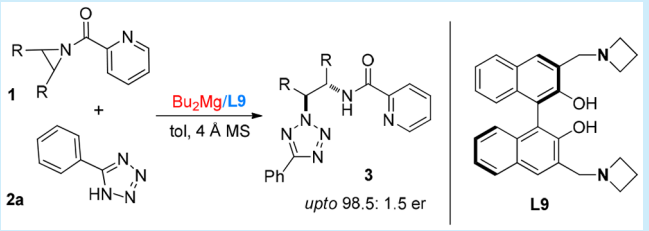
Supporting Information

ABSTRACT: A magnesium-catalyzed asymmetric ring-opening reaction of aziridines with substituted tetrazoles is reported. The current protocol proceeds smoothly and gives the corresponding desymmetrization products in high yields and good enantioselectivities. A new chiral ligand was synthesized from azetidine and (*R*)-BINOL and was employed in the current in situ generated magnesium catalyst. The Mg(II)-mediated desymmetrization reaction could be performed on gram scale under mild conditions and was transformed to chiral alkyl amines by a deprotection process.



Nitrogen-containing heterocycles and their derivatives are widely distributed in numerous naturally occurring compounds, many of which exhibit significant biological properties.[1] In this regard, substituted tetrazoles are valuable nitrogen-containing heterocycles to medicinal chemistry and often act as key pharmacophores in many drugs, such as losartan and valsartan, antagonists of angiotensin II receptor.[2] As such, the introduction of tetrazoles into more complex skeletons is meaningful for discovering of pharmaceutical candidates,[3] and it would be highly desirable to construct enantioenriched structures while equipping substituted tetrazoles in one single step. However, to date, there are limited examples established for substituted tetrazoles in asymmetric reactions. In the documented methods, catalytic asymmetric reactions concerning substituted tetrazoles is narrow, often restricted to asymmetric conjugate reactions to different acceptors by metal or organocatalysis methods since the seminal work accomplished by Jacobsen and co-workers in 2005.[4,5] Very recently, Piotrowski and co-workers reported an interesting three-component reaction between substituted azoles, aldehydes, and different acylation reagents in the presence of Lewis base catalysts. This reaction could be used to synthesize valuable substituted tetrazoles by capping of the equilibrating azole-aldehyde adducts.[6] Considering our ongoing works on ring-opening reactions of three-membered rings[7] and inspired by the well-documented studies on asymmetric reactions of aziridines,[8,9] herein we report the participation of substituted tetrazoles in the desymmetrization reaction of aziridines for the first time.

On the basis of our recent efforts to investige magnesium catalysis in asymmetric synthesis,[10] the initial experiment began by evaluating a series of chiral ligands in the Mg(II)-mediated desymmetrization of aziridine **1a** with tetrazole **2a**. The initial trial of oxazoline−OH ligand **L1** and some simple BINOL derivatives did not give more promising er values, although the transformation proceeded smoothly in the presence of these magnesium catalysts under mild conditions (Table 1, entries 1−4; Scheme 1, **L1**−**L4**). Next, we examined chiral ligands derived from BINOL by introduction of C_2-symmetric Brønsted bases on the naphthol rings, and it was observed that these ligands (**L5**−**L8**) gave more potential results when amine groups were equipped on the phenol ligands. We supposed heterocyclic rings on the ligands should act not only as steric hindrance groups, but also as Brønsted bases to activate tetrazoles during the ring-opening process. We then wondered it would be helpful to reduce the members of the heterocyclic rings, letting tetrazoles be activated via hydrogen bond function but not stemmed by the heterocyclic rings' structure during the coordination process. To our delight, a new ligand **L9** synthesized from (*R*)-BINOL and azetidine showed superior ability in introducing high level of enantioselectivities compared with other chiral ligands by simply reducing the heterocyclic rings' cubage (Scheme 2). On the other hand, the ligand **L10** synthesized from imidazole did not give higher enantioselectivities, perhaps owing to its relatively weaker basicity.

Next the detailed conditions were further optimized. Solvent screening to others, such as xylenes, PhCl, THF, DCM, and ether, did not give more favorable results as shown in Table 1, and it was observed that polarity solvents dramatically decreased the enantioselectivities of the reaction, which might be due to the solvent's coordination effects (Table 1, entries 11−16). Other magnesium salts such as $Mg(OTf)_2$ or $Mg(OAc)_2$ would lead to low selectivities. Further optimization progress found the introduction of molecular sieves into the reaction led to higher er values (Table 1, 19−22).[11]

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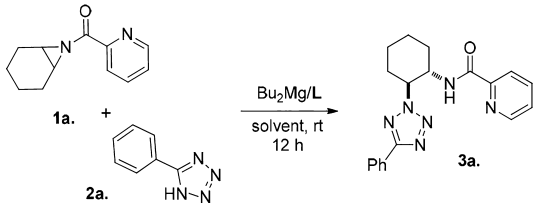
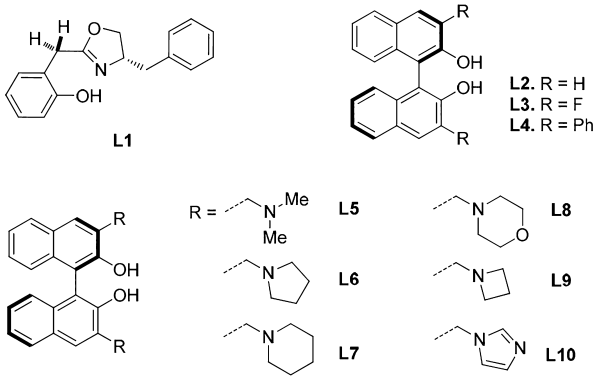
Table 1. Optimization of the Tetrazole-Involved Desymmetrization Reaction[a]



entry	ligand	solvent	additives	er[b]
1	**L1**	tol		54:46
2	**L2**	tol		60:40
3	**L3**	tol		51.5:48.5
4	**L4**	tol		53:47
5	**L5**	tol		65:35
6	**L6**	tol		69:31
7	**L7**	tol		62.5:37.5
8	**L8**	tol		65:35
9	**L9**	tol		90:10
10	**L10**	tol		63.5:36.5
11	**L9**	xylene		87.5:12.5
12	**L9**	*o*-xylene		87.5:12.5
13	**L9**	PhCl		70:30
14	**L9**	DCM		60:40
15	**L9**	THF		59:41
16	**L9**	ether		50:50
17	**L9**	tol		62.5:37.5[c]
18	**L9**	tol		56.5:43.5[d]
19	**L9**	tol	3 Å MS	94.5:5.5
20	**L9**	tol	4 Å MS	97.5:2.5
21	**L9**	tol	5 Å MS	97:3
22	**L9**	tol	13x MS	87.5:12.5

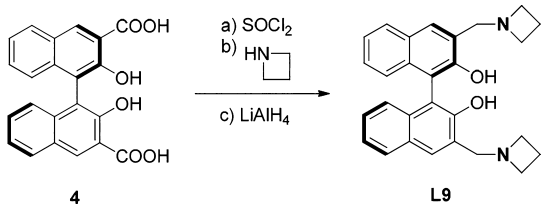
[a]Reactions were performed with aziridine (**1a**, 0.10 mmol) and tetrazole (**2a**, 0.12 mmol) in toluene (1.0 mL) in the presence of Bu_2Mg (20 mol %) and **L** (20 mol %). [b]The er value of **3a** was analyzed by chiral stationary-phase HPLC. [c]Using $Mg(OTf)_2$ instead of Bu_2Mg. [d]Using $Mg(OAc)_2{\cdot}4H_2O$ instead of Bu_2Mg.

Scheme 1. Chiral Ligands Prepared for the Reaction

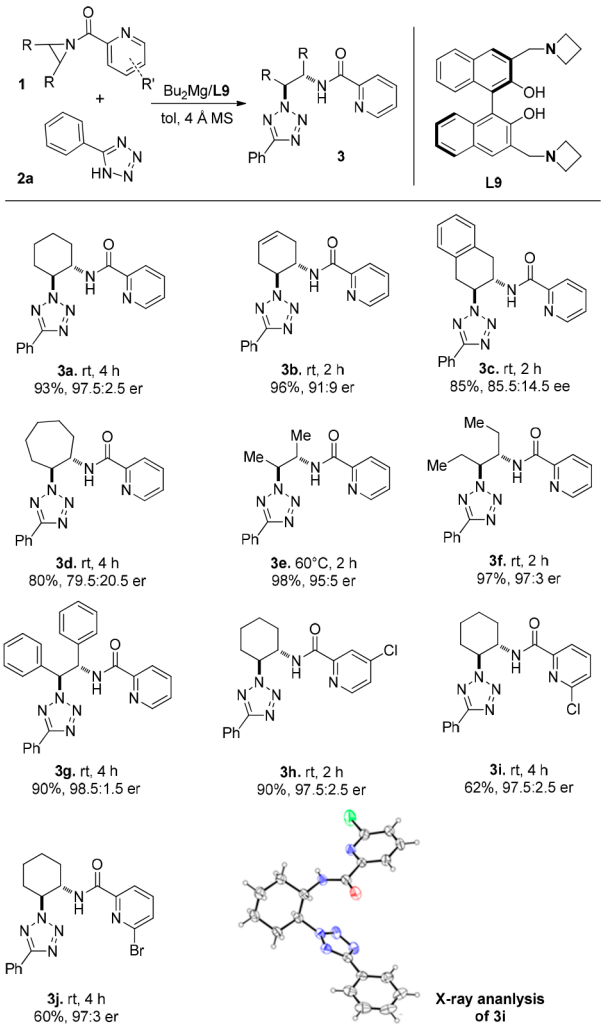


With these optimized conditions, we explored the scope of this Mg(II)-mediated tetrazole-involved desymmetrization reaction. First, *meso*-aziridines with cyclic and acyclic structures were combined with phenyl-substituted tetrazole **2a** after the ring-opening process mediated by the in situ generated bifunctional magnesium catalyst, leading to the desired enantioenriched heterocyclic products in high yields and moderate to excellent er values (Scheme 3). The absolute configuration of the desymmetrization products was determined by the X-ray crystallographic analysis of **3i** with a halogenated protected group.[12]

Scheme 2. Synthesis Process of Ligand L9



Scheme 3. Substrate Scope and X-ray Crystallographic Analysis of the Desymmetrization Product



Then a series of substituted tetrazoles were synthesized and participated in the desymmetrization reaction. Aryl groups with different electronic effects were tolerable but led to the corresponding ring-opening products with different enantioselectivities. Introduction of alkyl groups into the azole's ring did not affect the reaction's efficiency and resulted in moderate or higher er values, which might depend on the steric hindrance effects (Scheme 4).

Furthermore, the tetrazole-involved desymmetrization reaction was carried out on gram scale by utilization of 10 mol % in situ generated magnesium catalyst, leading to the ring-opening

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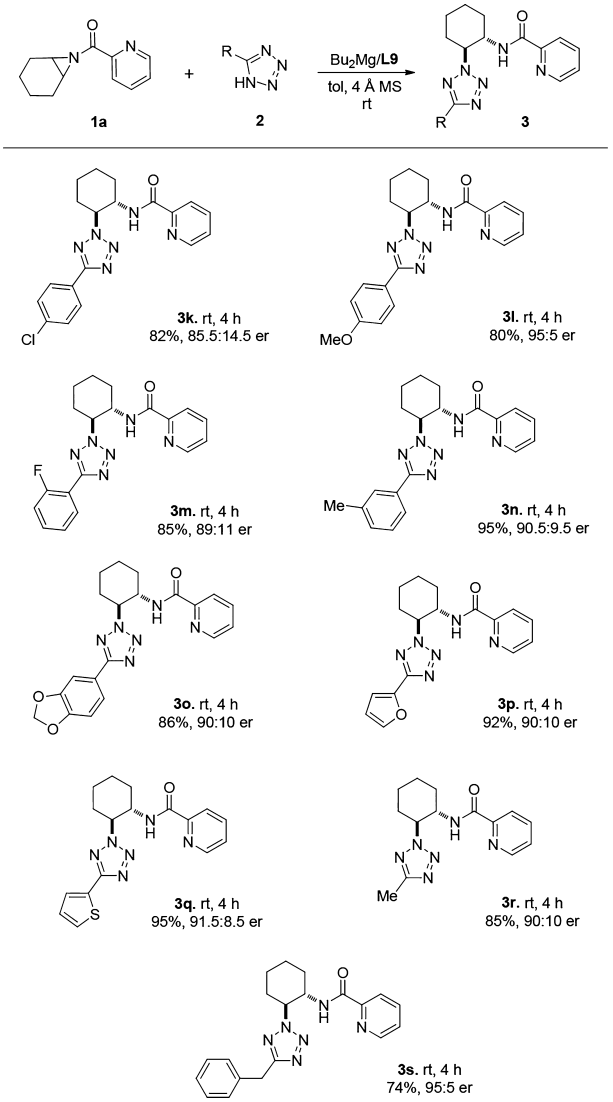
Scheme 4. Substrate Scope of the Tetrazole-Involved Desymmetrization Reaction

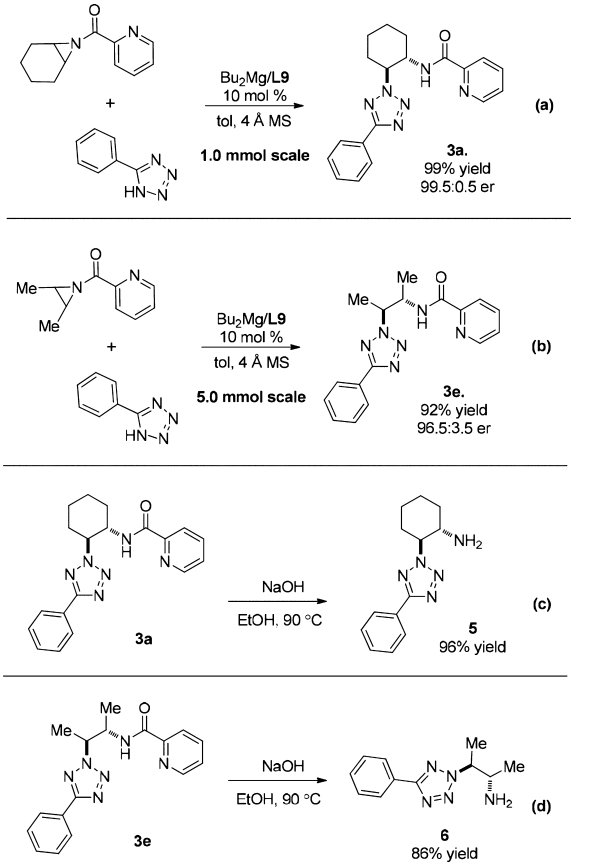


products in **3a** in an excellent yield and enantioselecitivity. The deprotection process proceeded smoothly by treating **3** with NaOH at 90 °C, generating the chiral amine **5** and **6** in almost quantitive yield (Scheme 5).

Finally, a proposed mechanism is proposed in Figure 1. The N-heterocyclic ring on phenol ligand **L9** is supposed to act as a C_2-symmetric Brønsted base that could coordinate with tetrazoles by a hydrogen bond. Thus, use of these N-heterocyclic rings would have more positive effects on introduction of high levels of enantioselectivity. The in situ generated magnesium catalysts from this type of ligands are highly effective via the bifunctional catalysis route.

In summary, we have reported a desymmetrization reaction of *meso*-aziridines with substituted tetrazoles mediated by a newly developed magnesium catalyst.[13] A series of enantioenriched heterocyclic compounds relying on the successful development of a bifunctional chiral ligand **L9** were generated. The catalytic desymmetrization reaction could be performed on gram scale, and the protection group is smoothly removed to generate chiral alkyl amines. Further investigation of bifunctional magnesium catalysts will be undertaken in our future work.

Scheme 5. Gram-Scale Synthesis and Further Transformations of the Desymmetrization Products



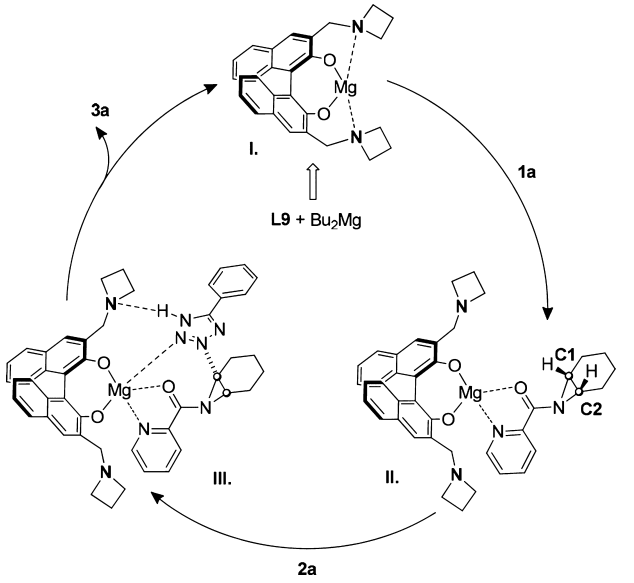


Figure 1. Proposed mechanism of the Mg(II)-mediated desymmetrization reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01333.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Crystallographic data of **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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