Synthetic Methods

DOI: 10.1002/anie.201410257

Intermolecular Enantioselective Dearomatization Reaction of β-Naphthol Using *meso*-Aziridine: A Bifunctional In Situ Generated Magnesium Catalyst**

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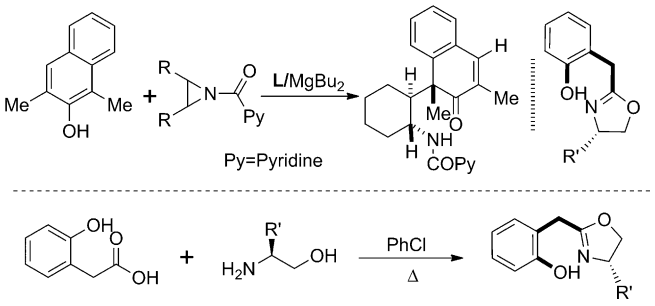
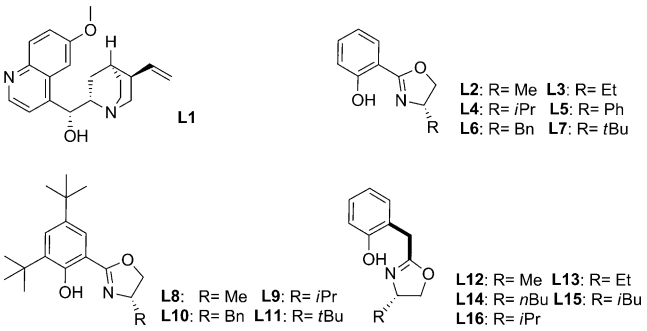
Abstract: *A direct, facile, and highly diastereo- and enantioselective dearomatization reaction of β-naphthol derivatives with aziridines has been developed for the first time. A newly designed Box–OH ligand was employed for an in situ generated magnesium catalyst and proved to be efficient. The corresponding dearomatization product was transformed into a polycyclic scaffold and polyhydroxylated compound. ^{1}H NMR studies revealed the activation mode of the dearomatization process of β-naphthols, and a clear positive nonlinear effect was observed in the reaction, and provides insight into the coordination environment around the Mg^{II} center and the possible active species.*

The enantioselective dearomatization reactions of phenols and their analogues are developed as powerful methods for building of stereoframeworks from simple planar aromatic structures.[1] And this strategy has also been applied to the synthesis of several natural products.[2] Recently, the enantioselective oxidative dearomatization reactions of phenols have been well documented and great achievements have been realized.[3] However, there are limited reports on non-oxidative conditions for the asymmetric dearomatization of phenol derivatives, especially for intermolecular pathways.[4,5] In 2013, Toste and co-workers demonstrated an asymmetric fluorinative dearomatization of phenols by using a binol-derived phosphate.[6] And very recently, You and co-workers described a direct intermolecular asymmetric allylic dearomatization of β-naphthol derivatives for the first time.[7] Still, to the best of our knowledge, there have been no other reports on other types of direct asymmetric dearomatization reactions between phenol derivatives and electrophiles under non-oxidative conditions. Herein, we report a direct and enantioselective intermolecular dearomatization of β-naphthol derivatives through a ring-opening reaction of *N*-(2-*p*icolinoyl)-*meso*-aziridines[8] using a newly designed Box–OH ligand (Scheme 1).

At the outset, we utilized an in situ generated magnesium catalyst,[9] including $MgBu_2$ and quinine (**L1**; Scheme 2) as the



Scheme 1. Intermolecular dearomatization of β-naphthols with aziridines.



Scheme 2. Development and screening of chiral ligands.

chiral ligand, which was reported by us previously.[8e] However, the reaction only gave the desired ring-opening product **3a** with disappointing results (Table 1, entry 1). After screening a series of Box–OH type chiral ligands in the model reaction, we found that the reactions employing ligands derived from salicylic acid did not provide more promising results (entries 2–11). We then turned our attention to synthesizing a new type of Box–OH chiral ligand derived from *o*-hydroxy-phenylacetic acid.[10] Fortunately, the diastereo- and enantioselectivities were efficiently enhanced

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[**] This work was supported by NSFC (21432003, 81473095, 21202071, 91213302), the National S&T Major Project of China (2012ZX09504001-003), and the Program for Changjiang Scholars and Innovative Research Team in University (IRT1137).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201410257.

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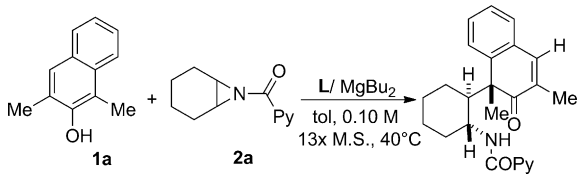
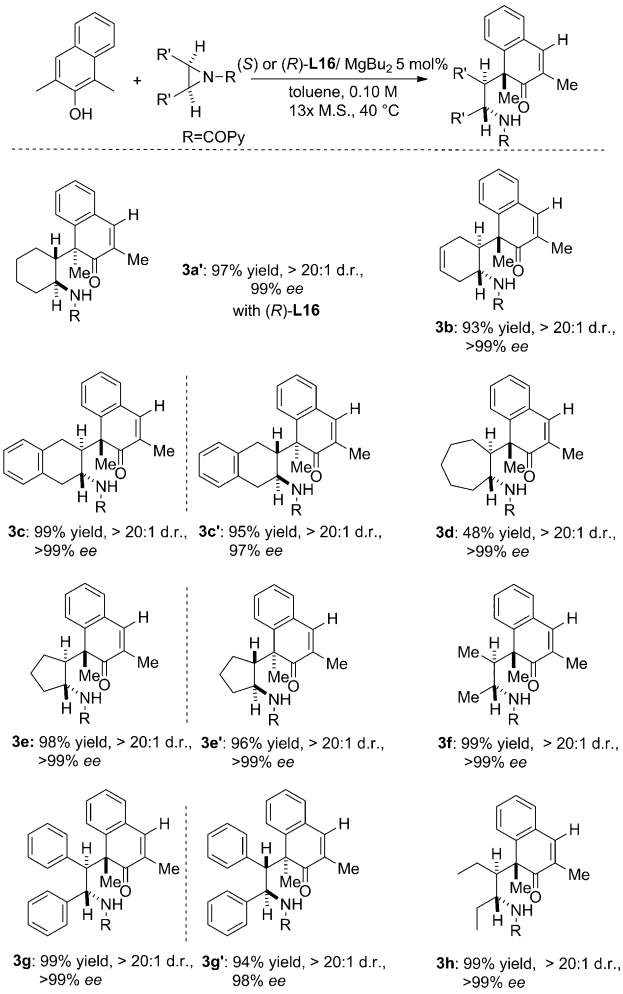
Table 1: Optimization studies of the dearomatization reaction of **1a**.



Entry[a]	L	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**L1**	85	1:1	0, 0
2	**L2**	83	1.1:1	0, 29
3	**L3**	77	2.0:1	4, 37
4	**L4**	85	3.5:1	33, 2
5	**L5**	84	7.9:1	21, 0
6	**L6**	86	2.1:1	6, 20
7	**L7**	84	4.0:1	2, 33
8	**L8**	77	1:3.2	19, 0
9	**L9**	81	1:2.3	0, 59
10	**L10**	80	0.9:1	0, 0
11	**L11**	83	5.0:1	0, −6
12	**L12**	93	>20:1	94, –
13	**L13**	82	>20:1	86, –
14	**L14**	87	>20:1	91, –
15	**L15**	99	>20:1	90, –
16	**L16**	98	>20:1	>99, –
17	**L16** (10 mol%)	97	>20:1	>99, –
18	**L16** (5 mol%)	97	>20:1	>99, –
19	**L16** (2 mol%)	41	>20:1	92, –
20	**L16** (1 mol%)	trace	–	–
21[e]	–	85	–	–
22[f]	**L16** (20 mol%)	n.r.	–	–

[a] Reactions were performed with **1a** (0.20 mmol), aziridine **2a** (0.10 mmol) in toluene (1.0 mL) in the presence of $MgBu_2$ (20 mol%) and ligand (20 mol%). [b] Yield of isolated product. [c] Diastereomeric ratios were determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixtures. [d] Determined by HPLC using a chiral stationary phase. Values are given for both diastereoisomers. [e] Reaction carried without chiral ligand. [f] Reaction carried without $MgBu_2$. M.S. = molecular sieves.



Scheme 3. Substrate scope of the dearomatization reaction. Reactions were performed with **1a** (0.40 mmol), aziridine (0.20 mmol), and M.S. (200 mg) in toluene (2.0 mL) in the presence of $MgBu_2$ (5 mol%) and **L16** (5 mol%).

when the new ligands were introduced into the dearomatization reaction (entries 12–16). And the loading of the catalyst could be reduced to 5 mol% without noticeable deterioration in yield and enantioselectivity (entries 17–20).

With the optimal reaction conditions in hand, we examined the applicability of other *meso*-aziridines in the asymmetric dearomatization reactions using the β-naphthol **1a**. As summarized in Scheme 3, other bicyclic *meso*-aziridines were well accommodated, and excellent diastereo- and enantioselectivities were uniformly observed (**3a–e**). However, the yield of **3d** was comparably low and might be due to ring strain. Furthermore, acyclic aziridines were also good electrophiles in these dearomatization reactions (**3f–h**). To our delight, the enantiotropic ring-opening adducts could be obtained with similar results when using (*R*)-**L16** as the chiral ligand (**3a′**, **3c′**, **3e′**, **3g′**).

Next, we explored the substrates scope with a variety of β-naphthols (Table 2). β-Naphthols bearing 3-Et, 3-Ph, 3-Cl, 3-Br, and 3-I groups generally led to the corresponding dearomatized products in excellent diastereo- and enantioselectivities (>99% *ee*) with high yields (entries 1 and 3–7). 3-Phenylethynyl- and 3-TMS-substituted naphthols were also good substrates for the reaction with respect to the good chemical yields and enantioselectivities (entries 2 and 8). For β-naphthols bearing bulkier substituents, such as ethyl, *n*-propyl, and *n*-heptyl at C1, the ring-opening products were generated smoothly with excellent enantioselectivities (entries 9–11). The absolute configuration of the dearomatized product **3q** was determined by X-ray anomalous dispersion.[11] It is noteworthy that the asymmetric dearomatization also occurred with 3-(H)-2-naphthols in good enantioselectivities but with lower yields and diastereoselectivities (entries 12 and 13).

We next sought to demonstrate the synthetic utility of the obtained polycyclic compound through the dearomatization reactions. The ketone carbonyl in **3a** was reduced with $LiAlH_4$, and the alcohol **4** subsequently underwent an intramolecular cyclization reaction treated with $SOCl_2$ to furnish the polycyclic product **6** in 96% yield, albeit with lower diastereoselectivity (Scheme 4a). The structure of **6** was confirmed by X-ray crystallographic analysis[11] to contain a [6-6-5] tricyclic core skeleton which often appears in many natural products, such as cycloclavine, delavayine, and

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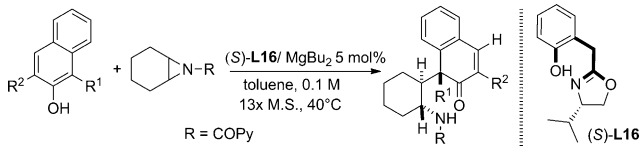
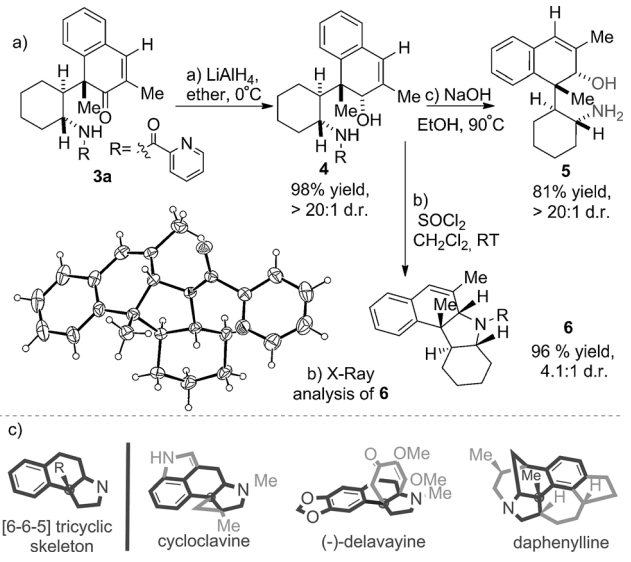
Table 2: Substrate scope of the dearomatization reaction with respect to β-naphthol.



Entry[a]	**3** (R^1, R^2)	Yield [%]	d.r.	*ee* [%]
1	**3i** (Me, Et)	99	>20:1	>99
2	**3j** (Me, TMS)[d]	98	>20:1	>99
3	**3k** (Me, Cl)	72	>20:1	>99
4	**3l** (Me, Br)	83	>20:1	>−99[c]
5		80	>20:1	>99
6	**3m** (Me, I)	99	>20:1	>99
7	**3n** (Me, Ph)	99	>20:1	>99
8	**3o** (Me, PhC≡C)	94	4.6:1	>99
9	**3p** (Et, Me)	97	18:1	>99
10	**3q** (*n*Pr, Me)	99	14:1	98
11	**3r** (*n*Hep, Me)	99	11:1	97
12[b]	**3s** (Me, H)	59	14:1	91
13[b]	**3t** (*n*Hep, H)	74	11:1	>99

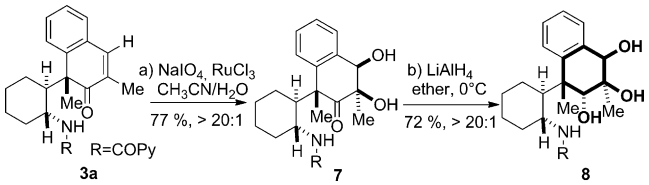
[a] Reactions were performed with **1a** (0.40 mmol), aziridine (0.20 mmol), and 13x M.S. (200 mg) in toluene (2.0 mL) in the presence of $MgBu_2$ (5 mol%) and **L16** (5 mol%). [b] The reaction was carried out with 20 mol% $MgBu_2$ and **L16**. [c] With (*R*)-**L16**. [d] TMS = trimethylsilyl.



Scheme 4. Straightforward transformation of **3a** into a polycyclic core skeleton and aminoalchols.

daphenylline (Scheme 4b,c).[12] And deprotection of **4** generated the aminoalcohol **5**. In contrast, direct dihydroxylation of **3a** followed by a reduction delivered the polyhydroxylated compound **8** (Scheme 5).[13]

To understand the activation mode of the dearomatization reaction mediated by the Box–OH/$MgBu_2$, further information about the activation process of phenol was provided by ^{1}H NMR studies of mixtures generated the from chiral ligand **L16**, $MgBu_2$, and **1a** (Figure 1). Signals corresponding to the phenolic hydroxy group in **L16** and **1a** disappeared after the introduction of $MgBu_2$ (The addition sequence is **L16**, **1a** and



Scheme 5. Transformation of **3a** into polyhydroxylated compound.

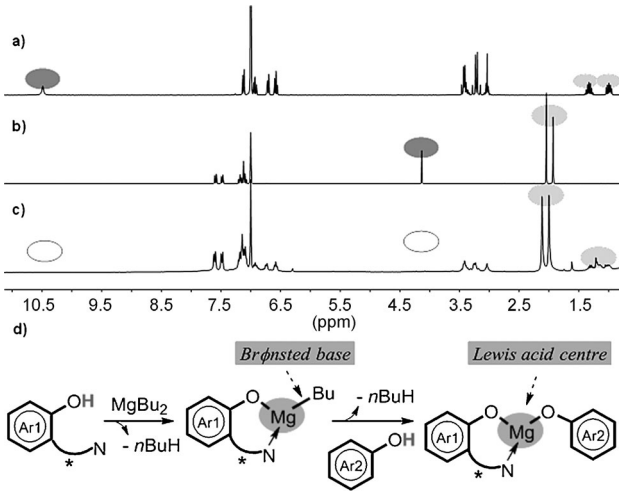


Figure 1. ^{1}H NMR studies. a) ^{1}H NMR spectrum of **L16** in C_6D_6. b) ^{1}H NMR spectrum of the β-naphthol **1a** in C_6D_6. c) ^{1}H NMR spectrum of the mixture from chiral ligand (**L16**), $MgBu_2$, and **1a** in C_6D_6. d) Proposed activation mode of the **1a**.

$MgBu_2$, as noted in Figure 1, and is in accord with the general sequence for normal reacions). Furthermore, there are obvious downfield shifts and changes in splitting which occur after the addition of $MgBu_2$. The ^{1}H NMR analyses seemed to indicate that the phenolic hydroxy groups in **L16** and **1a** were coordinated to magnesium after the neutralization process. Additionally, we speculated that the resulting Mg^{II} center could act as a Lewis acid to further activate aziridines through a coordination process.

To investigate the coordination environment around the Mg^{II} center and the possible active species, we studied the relationship between the *ee* values of the chiral ligand (**L16**) and the corresponding *ee* values of the product **3a**.[14] As seen from Figure 2, a clear positive nonlinear effect was observed in the enantioselective dearomatization of **1a** with **2a** when using the Mg^{II}/**L16** catalyst having varying *ee* values. The positive nonlinear effect revealed that the dearomatization reaction occurred in the presence of a dimeric Mg^{II} species. The heterochiral Mg^{II} complex was easily formed and bound tightly, thus leading to the heterochiral Mg^{II} complex showing low or even no catalytic activity for the reaction.

A plausible mechanism for this dearomatization reaction is postulated in Figure 3. The in situ formed precatalyst **A** can be generated after the reaction of **L16** with $MgBu_2$. The β-naphthol is activated as we discovered from the ^{1}H NMR studies. Then the aziridine coordinates to the Mg^{II} center to undergo ring-opening (**E**). Next another β-naphthol coordinates to the magnesium and releases the dearomatization

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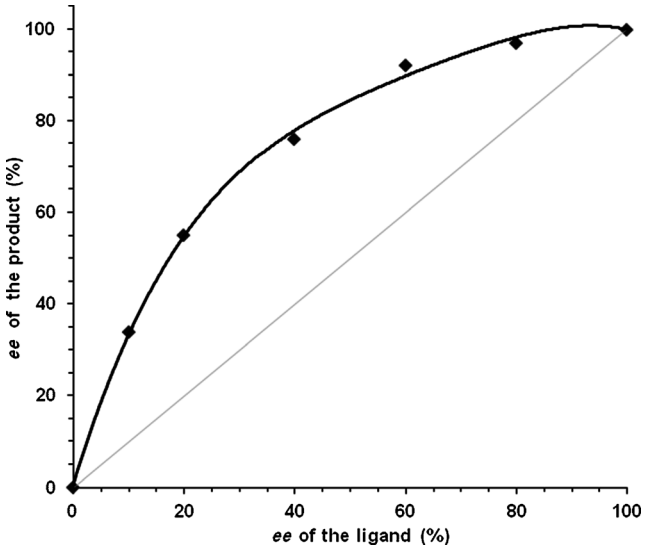

Figure 2. Result of nonlinear effects for the dearomatization of β-naphthol.

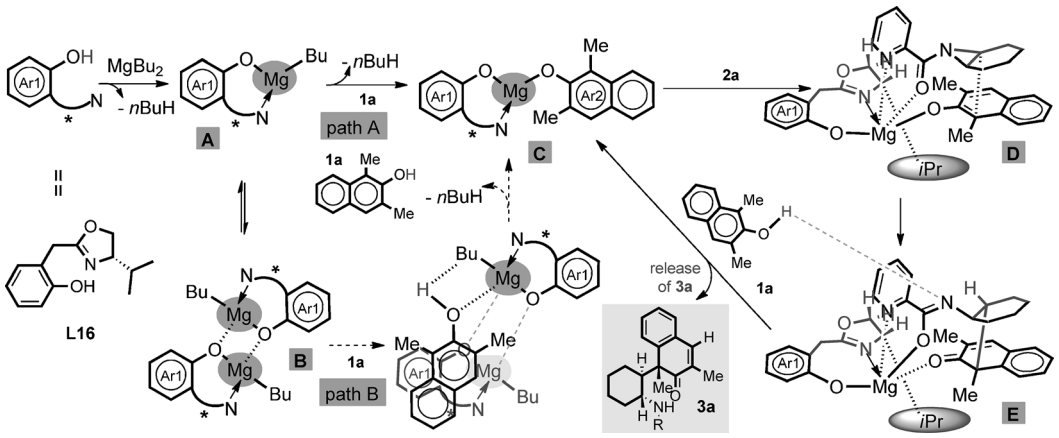

Figure 3. A plausible mechanism of the dearomatization reaction.

product **3a** to regenerate **C** (path A). In contrast, based on previous works on phenol/Mg crystallographic structure studies[15] and our aforementioned nonlinear studies, it is known that the dimeric Mg^{II} species are easily formed. We speculated that the homodimeric Mg^{II} species might also participate in the catalytic cycle by generating **C** through a commutative process with β-naphthol (path B).

In summary, we have developed a direct enantioselective dearomatization of β-naphthols with aziridines by using an in situ generated magnesium catalyst employing a new chiral Box–OH ligand. The enantioenriched products were subjected to reactions leading to polycyclic scaffolds and a polyhydroxylated compound. Further utility of the magnesium catalysis and evaluation of the biological activities of the polyhydroxylated compounds are currently underway in this lab.

Received: October 19, 2014
Revised: December 11, 2014
Published online: January 14, 2015

Keywords: arenes · aromaticity · intermolecular reactions · ligand design · magnesium

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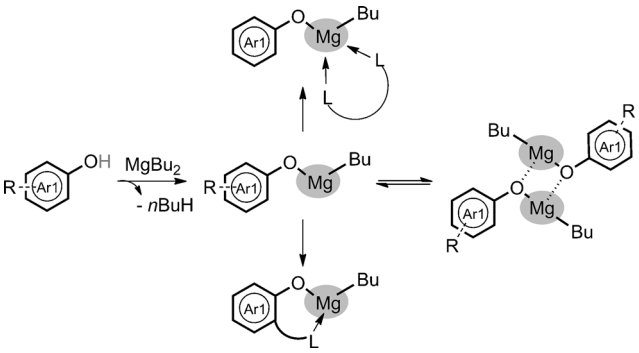

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