Chemical Science

EDGE ARTICLE

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Cite this: Chem. Sci., 2020, 11, 3068

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Chiral *N*,*N*[']-dioxide/Mg(OTf)₂ complex-catalyzed asymmetric [2,3]-rearrangement of *in situ* generated ammonium salts⁺

Qianchi Lin, ^(b) Bowen Hu, ^(b) Xi Xu, ^(b) Shunxi Dong, ^(b) Xiaohua Liu ^(b)* and Xiaoming Feng ^(b)*

to illustrate the reaction process and the origin of stereoselectivity.

Received 16th December 2019 Accepted 18th February 2020

DOI: 10.1039/c9sc06342k

rsc.li/chemical-science

Introduction

[2,3]-Rearrangements have been regarded as a class of synthetically powerful organic transformations due to their inherently high efficiency.¹ In particular, [2,3]-rearrangement of ammonium ylides has been extensively investigated for rapid construction of valuable nitrogen-containing molecules.² It is highly attractive to disclose asymmetric versions of such intriguing rearrangement,3-5 but only a few examples concerning the catalytic enantioselective [2,3]-rearrangement of ammonium ylides have been reported to date.⁵ In 2014, Smith and co-workers demonstrated the first example of chiral isothiourea-catalyzed [2,3]-rearrangement of allylic ammonium ylides to gain optically enriched syn-configured α-amino acid derivatives (Scheme 1a).5a In 2017, they developed an elegant tandem in situ protocol utilizing Pd/chiral isothiourea relay catalysis, which provides a direct method for the synthesis of syn-a-amino acid derivatives from N,N-disubstituted glycine aryl esters and allylic phosphates (Scheme 1b).5e Recently, the group of Song reported an interesting study on an isothiourea catalyzed asymmetric [2,3]-rearrangement reaction of propargyl ammonium salts, which allows access to optically active allenyl α -amino amides.^{5f} Despite these impressive advances, there is still room for further development. For instance, chiral isothiourea is a unique catalyst with which syn- α -amino acid derivatives were preferentially afforded in current reports.5a-e Given the wide and versatile use of α -amino acids in organic

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China. E-mail: liuxh@scu.edu.cn; xmfeng@scu.edu.cn synthesis and pharmaceutical chemistry,⁶ it is highly desirable to search for new catalytic systems for [2,3]-rearrangement of ammonium ylides in terms of the catalyst, substrate scope and the method of ammonium ylide formation, as well as stereo-divergence of products.⁷

Inspired by the achievements in enantioselective [2,3]-rearrangement^{1-5,8} and our ongoing interest in synthesis of unnatural α -amino acid derivatives,⁹ we envisaged that chiral *N*,*N'*dioxide-metal complex catalysts¹⁰ developed by our group would be potentially useful in promoting asymmetric [2,3]rearrangement of allylic ammonium ylides upon rationally introducing pyrazoleamide groups.¹¹ As depicted in Scheme 1c, pyrazoleamide ammonium salts generated from glycine



Scheme 1 [2,3]-Rearrangements of allylic ammonium ylides.



pyrazoleamides and allyl bromides were achieved by employing a chiral N,N'-dioxide/Mg^{II} complex as

the catalyst. This protocol provided a facile and efficient synthesis route to a series of $anti-\alpha$ -amino acid

derivatives in good yields with high stereoselectivities. Moreover, a possible catalytic cycle was proposed



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[†] Electronic supplementary information (ESI) available: [¹H, ¹³C{¹H} and ¹⁹F{¹H} NMR, HPLC spectra, and CD spectra (PDF). X-ray crystallographic data for **4u** (CIF)]. CCDC 1960932. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc06342k

pyrazoleamides 1 and allyl bromides 2 were selected as the precursors of [2,3]-rearrangement. It was thought that such allylic ammonium salts could be activated by bidentate coordination with the chiral N,N'-dioxide-metal complex and then subjected to deprotonation with the assistance of an external base to afford ammonium ylides, which subsequently undergo [2,3]-rearrangement to deliver non-racemic α -amino acid derivatives. There are some difficulties associated with the catalytic asymmetric [2,3]-rearrangement, such as the compatibility of all reactants with the catalyst^{5a,f} and the background reaction in the presence of the external base.12 Herein, we wish to disclose our effort toward one-pot asymmetric [2,3]rearrangement of in situ formed allylic ammonium ylides. Chiral N, N'-dioxide/Mg(OTf)₂ (ref. 13) was found to promote the diastereo- and enantioselective rearrangement efficiently, and various anti-a-amino acid derivatives14 were readily obtained in good yields with high stereoselectivities (up to 95% yield, >19:1 anti: syn and 98.5: 1.5 er) from easily available glycine pyrazoleamides and allyl bromides.

Results and discussion

In the initial study, *N*,*N*-dimethylglycine pyrazoleamide (1a) and cinnamyl bromide (2a) were selected as the model

substrates to optimize the reaction conditions. The preliminary study indicated that the tandem ammonium salt formation/[2,3]-rearrangement took place well in the presence of an external base, and the desired product 3a was isolated in 91% yield with a 1:1 anti: syn ratio by using diisopropylamine as the base (see page 9 in the ESI[†] for more details). This result showed the difficulty in achieving the asymmetric version of such one-pot transformation. For the purpose of determination of the er value, compound 3a was converted to 4a quantitatively with MeOH at 60 °C for further analysis. Next, different metal salts coordinated with chiral N,N'-dioxide L-PrMe₂ were examined in CH₂Cl₂ at 30 °C (Table 1, entries 1-4). $Mg(OTf)_2$ performed better than other metal salts, giving the desired rearranged product 3a in 91% yield, 1.8 : 1 anti : syn, and 67.5: 32.5 er for the major diastereomer (Table 1, entry 3). The complex of Mg(NTf)₂ provided a comparable result (Table 1, entry 4). Subsequently, the amide moiety in the ligand was evaluated, and it was found that sterically bulky 1-adamantyl amine derived L-PrAd afforded better stereoselectivities (Table 1, entry 7 vs. entries 5 and 6). Further investigations on the chiral backbone in the ligand showed that the L-ramiprilderived L-RaAd was superior to the L-proline-derived L-PrAd and (S)-pipecolic acid-derived L-PiAd in terms of enantioselectivity (91% yield, 3 : 1 anti : syn, and 81 : 19 er; entries 7-9).



Entry	Metal salt	Ligand	Yield of $3\mathbf{a}^{b}$ (%)	anti : syn of $3a^c$	er of $4\mathbf{a}^d$
1	Sc(OTf) ₃	L-PrMe ₂	77	1:1	race/race
2	Ni(OTf)2	L-PrMe ₂	90	1.1:1	54:46/57.5:42.5
3	$Mg(OTf)_2$	L-PrMe ₂	91	1.8:1	67.5:32.5/67.5:32.5
4	Mg(NTf)2	L-PrMe ₂	93	1.6:1	65.5:34.5/64.5:35.5
5	$Mg(OTf)_2$	L-PrEt ₂	99	3:1	61:39/80:20
6	$Mg(OTf)_2$	L-PrtBu	90	2:1	56.5:43.5/52.5:47.5
7	$Mg(OTf)_2$	L-PrAd	98	5:1	75.5:24.5/57:43
8	$Mg(OTf)_2$	L-PiAd	94	2:1	52.5 : 47.5/race
9	$Mg(OTf)_2$	L-RaAd	91	3:1	81:19/54.5:45.5
10^e	$Mg(OTf)_2$	L-RaAd	99	13:1	93.5:6.5
$11^{e,f}$	$Mg(OTf)_2$	L-RaAd	82	12:1	95.5:4.5
$12^{e,f,g}$	Mg(OTf) ₂	L-RaAd	94	>19:1	97:3

^{*a*} Unless otherwise noted, all reactions were carried out with **1a** (0.10 mmol), **2a** (0.10 mmol), iPr_2NH (0.15 mmol) and metal salt/ligand (1 : 1, 10 mol%) in CH₂Cl₂ (1.0 mL) at 30 °C for 14 h. ^{*b*} Isolated yield of **3a**. ^{*c*} Determined by ¹H NMR. ^{*d*} Determined by HPLC on a chiral stationary phase. ^{*e*} Carried out in MeCN. The metal salt/ligand was pretreated in CH₂Cl₂. ^{*f*} -20 °C for 24 h. ^{*g*} NaBAr₄^{*F*} {NaB[3,5-(F₃C)₂C₆H₃]₄} (20 mol%) was added. The metal salt/ligand/NaBAr₄^{*F*} was pretreated in EtOAc instead of CH₂Cl₂. *T* = trifluoromethanesulfonyl.

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Other reaction parameters were investigated and the solvent was proven to play a significant role in the reaction. With MeCN as the solvent, the amino acid derivative **3a** was produced in 99% yield with 13 : 1 *anti* : *syn* and 93.5 : 6.5 er for the major diastereomer (entry 10). The enantioselectivity could be further enhanced when the reaction was performed at decreased temperature $(-20 \ ^{\circ}C)^{15}$ while a slightly lower yield was obtained (82% yield, 12 : 1 *anti* : *syn*, 95.5 : 4.5 er; entry 11). To our delight, the addition of NaBAr₄^F as an additive and preparation of the catalyst in EtOAc produced optimized results (entry 12; 94% yield, >19 : 1 *anti* : *syn*, 97 : 3 er).

Moreover, when the product with a low *anti* : *syn* ratio was subjected to the reaction conditions, it was found that both *anti* : *syn* ratios and er values did not change. This result implied that an ultimately high *anti* : *syn* ratio was obtained during the [2,3]-rearrangement rather than epimerization of the product during the reaction (for further details, see ESI,† page 11).

With the optimized reaction conditions in hand, the substrate scope of [2,3]-rearrangement was screened (Table 2). Varying *N*-substituents in the glycine pyrazoleamides had no effect on the *anti* : *syn* ratio of the reaction (>19 : 1 in all cases).



^{*a*} All reactions were carried out with L-RaAd/Mg(OTf)₂/NaBAr^F₄ (1 : 1 : 2, 10 mol%), **1** (0.2 mmol), **2** (0.2 mmol), and iPr₂NH (0.3 mmol) in MeCN (2.0 mL) at -20 °C. Isolated total yield of product **3**. The *anti* : *syn* ratio was determined by ¹H NMR analysis. The er value was determined by HPLC on a chiral stationary phase. ^{*b*} Isolated yield of the major diastereomer **3**. ^{*c*} er value of product **4**.

However, the reactivity and enantioselectivity dropped sharply with the increase of the ring size and steric hindrance of Nsubstituents (3a-3e). As shown in Table 2, the use of glycine pyrazoleamides bearing symmetrical N,N-dialkyl substituents, such as N,N-diethylglycine pyrazoleamide, gave the desired product 3b in 64% yield with a 95 : 5 er value. Cyclic N-piperidinyl and N-azepanyl substituents were also tolerated in this reaction, delivering the products 3c and 3d in moderate yields with satisfactory enantioselectivities. Lower yield (27% yield) with a good enantiomeric ratio (92:8 er) was obtained for product 3e bearing a N-heterocycle (morpholinyl) substituent. Next, the reaction of 1a with allyl bromide compounds 2 bearing different cinnamic aryl substituents was evaluated. Both the position and electronic properties of substituents had obvious effects on the reaction. Meta-substituted (E)-(3bromopropenyl)benzenes afforded the corresponding products (3g and 3o) with better results than those with substituents at ortho- or para-positions (3f, 3h, 3n, 3p). Generally, the substrate with an electron-rich group transformed into the rearrangement product with a slightly higher anti : syn ratio than the substrate with an electron-deficient group (3h and 3p). Other para-halogen-substituted aryl rings, including 4-FC₆H₄, 4-BrC₆H₄, and 4-IC₆H₄ delivered the expected products (3j-3l) in 57-70% isolated yields of the major diastereomers with 90.5:9.5 to 96:4 er. The presence of the 4-F₃CC₆H₄ substituent led to acceptable outcomes (3m, 57% yield, 4:1 anti : syn and 92 : 8 er). The allyl bromide compounds bearing a 2-naphthyl group and heteroaromatic ring could also perform well to yield the desired products (3q-3s) with high diastereo- and enantioselectivities. Moreover, the allyl bromide compound 2 bearing a styryl functional group was suitable for the current reaction, producing the amino acid derivative 3t in 82% yield with >19 : 1 anti : syn and 97 : 3 er. In addition, this rearrangement process of N,N-dimethylglycine pyrazoleamide 1a with cinnamyl bromide bearing a methyl on the double bond gave the amino acid derivative 3u in excellent yields (95% yield, >19:1 anti: syn and 98.5:1.5 er). Unfortunately, when cyclohexyl-substituted allyl bromide was employed, only a trace amount of the desired product (3v) was detected even with a prolonged reaction time (7 days). The absolute configuration of product 4u was determined to be (2R,3S) by X-ray crystallography analysis,16 and the others were assigned by comparing their CD spectra with that of 3u (see pages 96-105 in the ESI[†] for more details).

To illustrate the potential utility of the methodology, a scaleup synthesis of **3r** was carried out under the optimized reaction conditions. As illustrated in Scheme 2a, 3 mmol of compound **1a** reacted smoothly with equal amounts of allyl bromide **2n**, furnishing the desired product **3r** in 89% yield with >19 : 1 *anti* : *syn* and 98 : 2 er. Further transformations of the product **4a** were conducted (Scheme 2b). Compound **4a** was easily reduced to **5a** in 88% yield with maintained stereoselectivities (>19 : 1 *anti* : *syn*, 96.5 : 3.5 er) by treatment with 10% Pd/C in methanol. Additionally, the reduction of **4a** with LiAlH₄ generated the corresponding alcohol **6a** in 71% yield (>19 : 1 *anti* : *syn*, 97.5 : 2.5 er).



Scheme 2 (a) Scale-up synthesis of **3r**; (b) further transformation of product **4a**.

Based on previous work,¹⁷ the proposed catalytic cycle and a possible working mode of the enantioselective [2,3]rearrangements of ammonium ylides are depicted in Scheme 3. Initially, the reaction of *N*,*N*-dimethylglycine pyrazoleamide (1a) and cinnamyl bromide (2a) produced the corresponding ammonium salt I which was activated by bidentate coordination with the *N*,*N*'-dioxide-metal complex and subjected to deprotonation with the assistance of iPr₂NH to afford metal bonded ammonium ylide II. Due to the steric repulsion of the aryl group of the cinnamyl moiety of the substrate with the octahydrocyclopenta[*b*] pyrrole unit in the ligand L-RaAd as well as the pyrazoleamide unit in the *exo*-transition state,¹⁴ the rearrangement occurred preferentially to afford the *anti*-configured α -amino acid derivative (2*R*,3*S*)-3a, which was consistent with the experimental results.



Scheme 3 The proposed catalytic cycle and working mode.

Conclusions

We have successfully developed the first Lewis acid catalyzed asymmetric [2,3]-rearrangement of quaternary ammonium ylides formed *in situ* from glycine pyrazoleamides and allyl bromides. The *N*,*N*'-dioxide/Mg(OTf)₂ catalytic system benefited the rearrangement process efficiently, providing diverse chiral *anti*- α -amino acid derivatives in good yields with high stereo-selectivities (up to 95% yield, >19 : 1 *anti* : *syn* and 98.5 : 1.5 er). Besides, the potential use of the current method was illustrated by gram-scale synthesis and further transformations of products. A possible catalytic cycle along with the working mode was proposed to elucidate the reaction process and chiral induction. Further investigations on other reactions enabled by chiral *N*,*N*'-dioxide–metal complex catalysts are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We appreciate the National Natural Science Foundation of China (No. 21625205 and 21772127) for financial support.

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