Asymmetric Catalysis Hot Paper

How to cite:
International Edition: doi.org/10.1002/anie.202102054
German Edition: doi.org/10.1002/ange.202102054

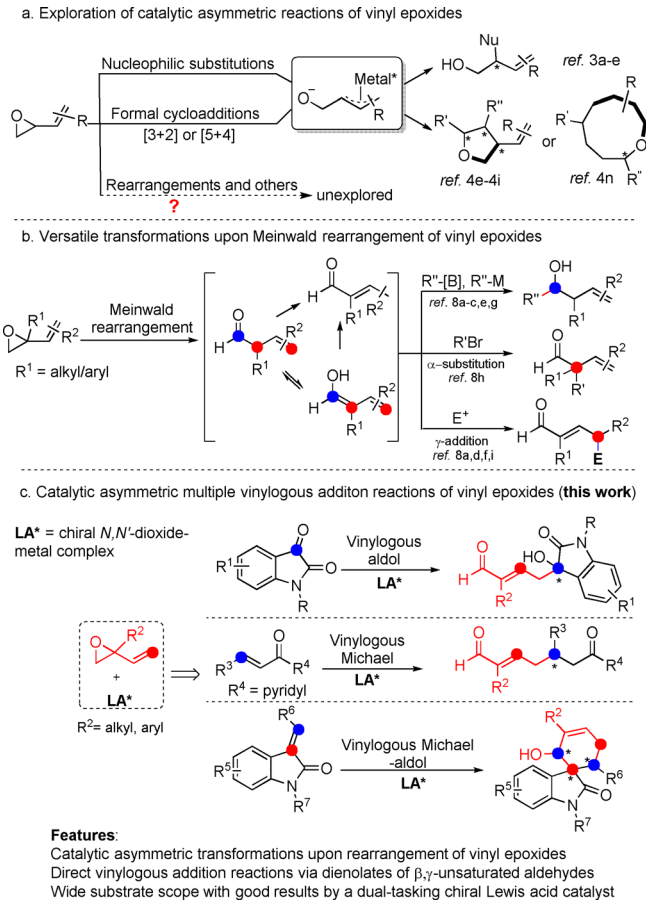
Asymmetric Catalytic Vinylogous Addition Reactions Initiated by Meinwald Rearrangement of Vinyl Epoxides

*Jinxiu Xu, Yanji Song, Jun He, Shunxi Dong, Lili Lin, and Xiaoming Feng**

Abstract: *The first catalytic asymmetric multiple vinylogous addition reactions initiated by Meinwald rearrangement of vinyl epoxides were realized by employing chiral N,N′-dioxide/Sc^{III} complex catalysts. The vinyl epoxides, as masked β,γ-unsaturated aldehydes, via direct vinylogous additions with isatins, 2-alkenoylpyridines or methyleneindolinones, provided a facile and efficient way for the synthesis of chiral 3-hydroxy-3-substituted oxindoles, α,β-unsaturated aldehydes and spirocyclohexene indolinones, respectively with high efficiency and stereoselectivity. The control experiments and kinetic studies revealed that the Lewis acid acted as dual-tasking catalyst, controlling the initial rearrangement to match subsequent enantioselective vinylogous addition reactions. A catalytic cycle with a possible transition model was proposed to illustrate the reaction mechanism.*

Introduction

The chemistry of vinyl epoxides is very attractive for their easy preparation and multifunctional reactivities in the synthesis of various bioactive heterocyclic molecules and natural products.[1,2] Vinyl epoxides are uniquely characterized by the connected reactivities of the oxirane ring and the double bond, which are not offered by either one of them separately. The well-developed nucleophilic ring-opening substitutions[3] and formal cycloaddition reactions[4] (Scheme 1a) could go through a chiral zwitterionic metal-π-allyl intermediate to deliver useful chiral β-substituted homoallylic alcohols[3a–e] and heterocyclic skeletons.[4e–i,n] Besides, the rearrangements of vinyl epoxides provide access to a number of functionalized carbon skeletons,[2,5] among them, the Meinwald rearrangement[6] has been frequently employed in total synthesis and attracted widespread attention.[7] Through Meinwald rearrangement (Scheme 1b), the in situ generated α-aryl/alkyl β,γ-unsaturated aldehydes could react with nucleophiles at the aldehyde functional group to furnish homoallylic alcohols, or could isomerize into masked dienolates to construct functional aldehydes via transformations at either α-position or γ-position. Several elegant works have been reported by the Lautens group and others in exploring



Scheme 1. Reactions about vinyl epoxides.

their versatile reactivities.[8] To the best of our knowledge, the catalytic asymmetric vinylogous transformations of vinyl epoxides upon Meinwald rearrangement remain elusive. The difficulties exist in the reaction, include: 1) the unstability of the β,γ-unsaturated aldehyde intermediate, which tend to isomerize into more conjugated but less reactive α,β-unsaturated aldehydes, 2) the competitive side reactions,[5j,8a] as well as 3) the difficulty in controlling the chemoselectivity and stereoselectivity at the same time.

The catalytic asymmetric vinylogous reaction serving as a powerful tool to construct highly functionalized optically pure γ-functionalized α,β-unsaturated carbonyl compounds has been widely documented in the last decades.[9] The enolizable π-extended carbonyl and dienolsilane analogues were frequently employed in these reactions, but for the α-substituted β,γ or α,β-unsaturated aldehydes, direct vinylogous additions have been scarcely reported for their

[*] J. X. Xu, Y. J. Song, J. He, Prof. Dr. S. X. Dong, Prof. Dr. L. L. Lin, Prof. Dr. X. M. Feng
Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University
Chengdu 610064 (China)
E-mail: xmfeng@scu.edu.cn
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202102054.

relatively low γ-reactivity and intrinsical competition reactions. Only a few successful examples by using chiral amines catalyst through dienamine intermediates have been reported by Melchiorre group, Chen group and others.[10] Chiral *N*,*N*′-dioxide-metal complexes[11] developed by our group, have been proven to be efficient in asymmetric addition reactions and others. Combining with the unique characters of the Meinwald rearrangement of vinyl epoxides, we conceived that the chiral *N*,*N*′-dioxide-metal complexes acted as suitable chiral Lewis acid to control both the Meinwald rearrangement of vinyl epoxides and the subsequent transformations (Scheme 1c). Herein, we set out to develop efficient chiral *N*,*N*′-dioxide-metal catalytic systems for the asymmetric Meinwald rearrangement/vinylogous cascade reactions of vinyl epoxides with isatins, 2-alkenoylpyridines and methyleneindolinones. Vinyl epoxides served as masked vinylogous enolate species, providing a facile and efficient way for vinylogous-aldol, vinylogous-Michael and formal [4+2] cycloaddition reactions. A number of α,β-unsaturated aldehyde derivatives and cyclohexene derivatives were obtained in high efficiency and stereoselectivities, which are truly important motifs in valuable molecule skeletons.[9,12–13]

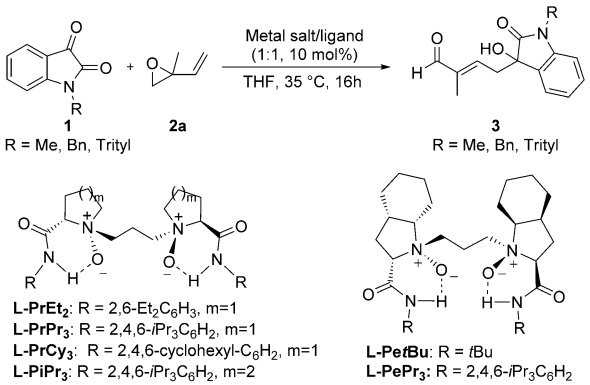
Results and Discussion

In the initial studies, the Meinwald rearrangement/vinylogous aldol cascade reaction of isatin **1a** with vinyl epoxide **2a** was used as model reaction to optimize the reaction conditions (Table 1). Firstly, various metal salts combined with *N*,*N*′-dioxide **L-Pe*t*Bu** were tested in THF at 35 °C (entries 1–3). It showed that the complexes of $Mg(OTf)_2$ or $Ni(OTf)_2$ gave extremely low yields and *ee*. The complex of $Sc(OTf)_3$ gave 3-hydroxy-3-substituted oxindole **3a** in 47% yield with 30% *ee* (entry 3). The low yields are due to the unproductive loss of **2a**, while **1a** could be recovered. Then, the structure of the chiral *N*,*N*′-dioxide ligands by coordinating with $Sc(OTf)_3$ was evaluated (entries 4–7). It was found that the L-proline-derived **L-PrPr$_3$** gave better results than the L-pipecolic acid derived **L-PiPr$_3$** and L-perindopril-derived **L-PePr$_3$** (entry 6 vs. entries 4, 5). Changing the amide moiety to 2,4,6-cyclohexyl phenyl led to higher yield and *ee* (92% yield and 75% *ee*; entry 7). Comparatively, when chiral BOX, PyBOX or BINOL ligand was used as the ligand, moderate yields but low *ee* values were achieved (See the Supporting Information for details). N-Protected group (R) of isatin **1** was another key parameter in influencing the outcomes of this cascade reaction (entries 7–9). N-Benzyl isatin **1b** significantly improved the enantioselectivity to 87% *ee* (entry 8) The more steric N-triphenylmethyl isatin **1c** could afford the 3-hydroxy-3-substituted oxindole **3c** in 96% yield with 98% *ee* (entry 9). The catalyst loading could be reduced to 2.5 mol%, and the results were kept if the amount of **2a** reduced to 1.5 equivalent and the reaction temperature increased to 50 °C (entry 10).

With the optimized reaction conditions in hand (Table 1, entry 10), the substrate scope of aldol cascade reactions was evaluated (Scheme 2). A series of 3-hydroxy-3-substituted oxindoles were obtained.[12] Isatins with electron-withdrawing or electron-donating groups at 5, 6 or 7-positions, could be smoothly transformed into the corresponding products (**3e**–**3k**) in 86–99% yields with 86–98% *ee*. While R^2 in vinyl epoxide was phenyl, the corresponding product **3d** could be obtained in 36% yield with 97% *ee*. The decreased yield was caused by the steric hindrance between two substrates. The absolute configuration of product **3c** was determined to be (*S*,*E*) by X-ray crystallography analysis.[14]

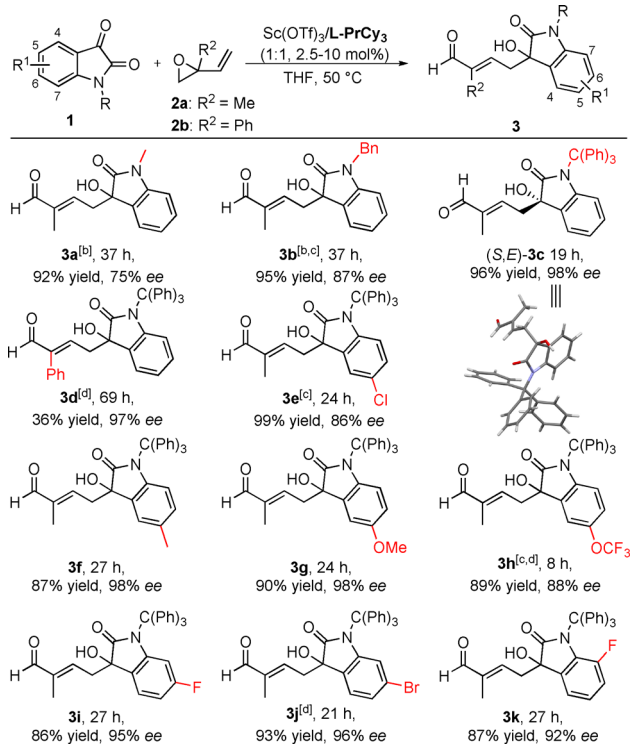
Encouraged by aboved results, the Meinwald rearrangement/vinylogous Michael reaction of 2-alkenoylpyridine **4** with vinyl epoxide **2** was examined (Scheme 3). By switching the ligand to **L-PrEt$_2$**, lowering the temperature to 10 °C and adding 5 mol% 3-chlorobenzoic acid, the alkenoylpyridine **4a** reacted with vinyl epoxide **2a** to deliver the γ-functionalized α,β-unsaturated aldehyde **5a** in moderate results. However, when R^2 was phenyl (**2b**), product **5b** was obtained in 82% yield with 94% *ee*. The addition of 3-chlorobenzoic acid could shorten the reaction time, which might be because it can facilitate the enolization of β,γ-unsaturated aldehyde and release the chiral Lewis acid catalyst. Then, variation of 2-alkenoylpyridines by reacting with **2b** revealed that regardless of the electronic nature or position of the substituents on the β-phenyl (R^3) had little effect on the enantioselectivity. The products **5c**–**5e** could be obtained in 92–94% *ee*, but yields were influenced by the steric hindrance and electronic nature significantly. 2-Naphthyl, 3-thienyl and 3-furyl substituted substrates were also suitable, affording **5f**–**5h** in 71–

Table 1: Optimization of reaction conditions.

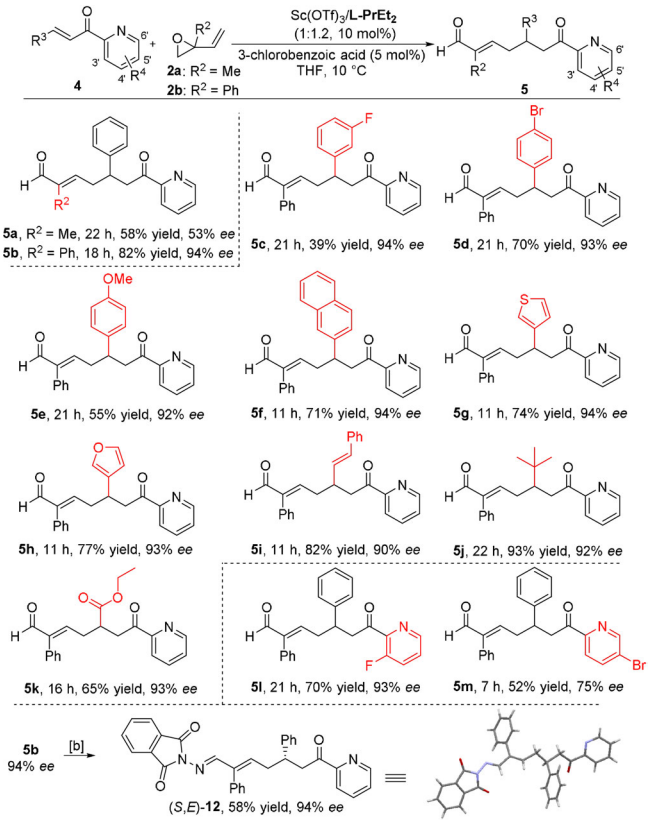


Entry[a]	Metal salt	Ligand	R (**1**)	Yield [%][b]	*ee* [%][c]
1	$Mg(OTf)_2$	**L-PetBu**	Me (**1a**)	trace	–
2	$Ni(OTf)_2$	**L-PetBu**	Me (**1a**)	23	2
3	$Sc(OTf)_3$	**L-PetBu**	Me (**1a**)	47	30
4	$Sc(OTf)_3$	**L-PiPr$_3$**	Me (**1a**)	49	30
5	$Sc(OTf)_3$	**L-PePr$_3$**	Me (**1a**)	61	21
6	$Sc(OTf)_3$	**L-PrPr$_3$**	Me (**1a**)	71	42
7	$Sc(OTf)_3$	**L-PrCy$_3$**	Me (**1a**)	92	75
8	$Sc(OTf)_3$	**L-PrCy$_3$**	Bn (**1b**)	95	87
9	$Sc(OTf)_3$	**L-PrCy$_3$**	Trityl (**1c**)	96	98
10[d]	$Sc(OTf)_3$	**L-PrCy$_3$**	Trityl (**1c**)	96	98

[a] Unless otherwise noted, all reactions were carried out with metal salt/ligand (10 mol%, 1.0/1.0), **1** (0.10 mmol) and **2a** (3.0 equiv) in THF (1.0 mL) at 35 °C for 16 h. [b] Yield of the isolated **3**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] **2a** (1.5 equiv), $Sc(OTf)_3$/**L-PrCy$_3$** (2.5 mol%), reacted at 50 °C for 17 h. Bn = Benzyl, Trityl = Triphenylmethyl, THF = Tetrahydrofuran.



Scheme 2. Substrate scope of the Meinwald rearrangement/vinylogous aldol reaction. [a] Unless otherwise noted, all reactions were carried out with Sc(OTf)$_3$/**L-PrCy$_3$** (2.5 mol%, 1.0/1.0), **1** (0.10 mmol) and **2** (0.15 mmol) in THF (1.0 mL) at 50°C. *E*/*Z* > 20:1 in all cases. The yields were the isolated product. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] **2a** (0.30 mmol). [c] 17:1 *E*/*Z*. [d] 10 mol% Sc(OTf)$_3$/**L-PrCy$_3$**.

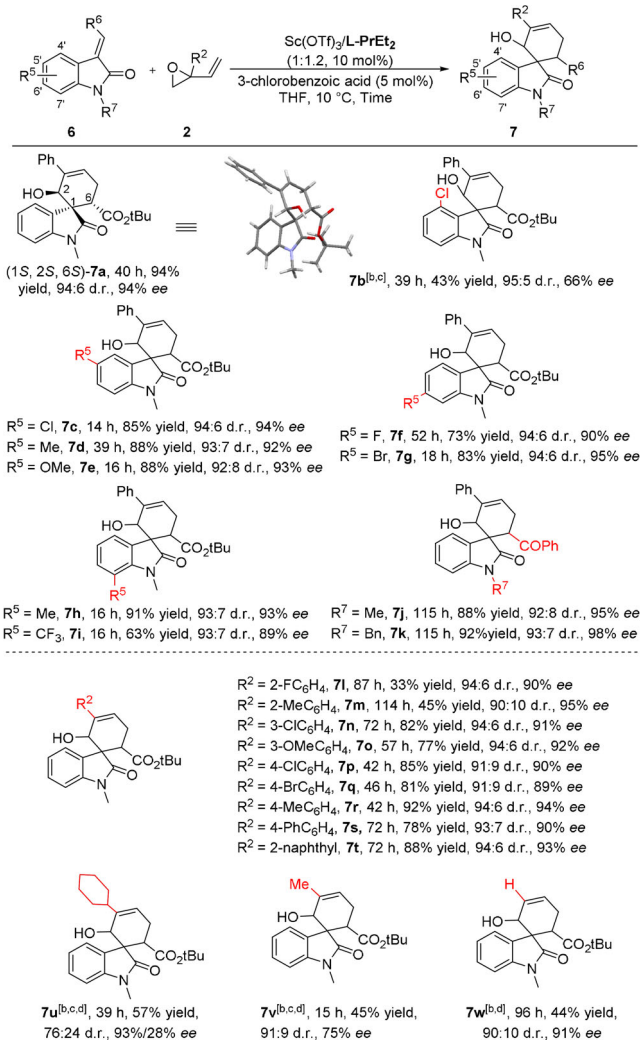


Scheme 3. Substrate scope of the Meinwald rearrangement/vinylogous Michael reaction. [a] All reactions were carried out with Sc(OTf)$_3$/**L-PrEt$_2$** (10 mol%, 1.0/1.2), 3-chlorobenzoic acid (5 mol%), **4** (0.1 mmol) and **2** (0.2 mmol) in THF (1.0 mL) at 10°C. *E*/*Z* > 20:1 in all cases. The yields were the isolated product. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] *N*-Aminophthalimide (1.0 equiv), EtOH, reflux.

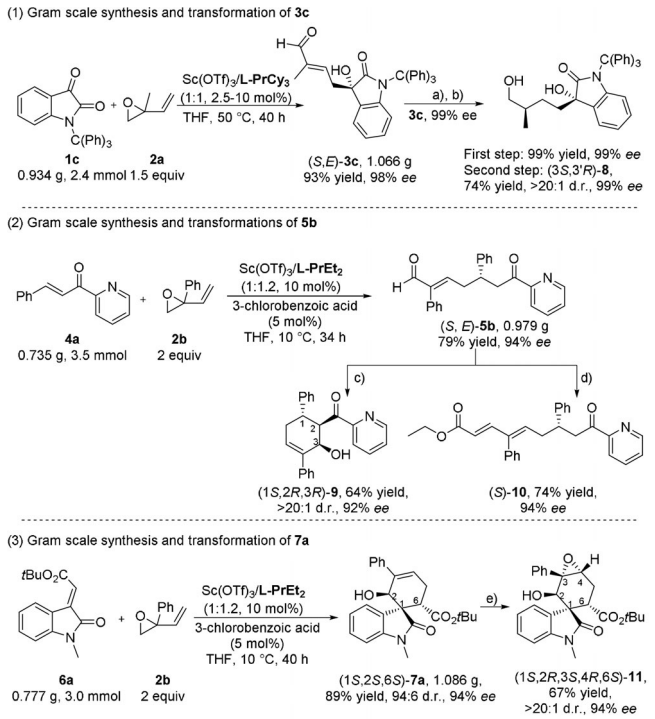
77% yields and 93–94% *ee*. Moreover, 2-alkenoylpyridines bearing styryl, alkyl or ester substituent at R^3 position were also tolerated in this reaction system, delivering the products (**5i**, **5j** and **5k**) in 65–93% yields with 90–93% *ee*. Additionally, substrates bearing 3′-F or 5′-Br group on the pyridine ring could also form the desired product in acceptable results (**5l** and **5m**). If pyridyl substituent was replaced by phenyl, bidentate pyrazolyl or pyridine N-oxide, trace or few desired products were detected, which indicates that the crucial factor for the reaction is the higher reactivity caused by the electron-withdrawing pyridine substituent rather than the bidentate association by the catalyst (See Supporting Information for details). The absolute configuration of **5b** was assigned to be (*S*,*E*) by X-ray analysis of the single crystal of its hydrazone derivative **12** prepared by a condensation with *N*-aminophthalimide.[14]

Methyleneindolinones were also applied, which underwent formal [4+2] cycloaddition reaction after the Meinwald rearrangement, delivering spiro-cyclohexene indolinone derivatives (Scheme 4). Methyleneindolinones **6** bearing electron-donating or electron-withdrawing groups at 5′,6′,7′-positions of indolinone proceeded well to give spiro-cyclohexene indolinones **7a**, **7c**–**k** in good yields with excellent d.r. (92:8–94:6) and *ee* values (89–98% *ee*). **7b** with a chloro-substituent at 4′-position was transformed in lower yield and *ee* (43% yield and 66% *ee*), which might be caused by the increased steric hindrance. With regard to vinyl epoxides **2**, *meta*- or *para*-substituted aryl R^2 delivered the corresponding products **7n**–**7s** in 77–92% yields with 91:9–94:6 d.r. and 89–94% *ee*. Vinyl epoxides with *ortho*-substituted phenyl (**7l** and **7m**) transformed in much lower yields. In addition, 2-naphthyl-substituted vinyl epoxide proceed well to afford **7t** in 88% yield with 94:6 d.r. and 93% *ee*. Alkyl (cyclohexyl and methyl) substituted vinyl epoxides were amenable to the present reaction, delivered spiro-cyclohexene indolinones in moderate results (**7u** and **7v**). 1,2-Epoxybutene transformed to the product **7w** in 44% yield with 90:10 d.r. and 91% *ee*. The absolute configuration of **7a** was unambiguously determined to be (1*S*,2*S*,6*S*) by X-ray crystallographic analysis.[14]

To illustrate the potential synthetic utility of the current catalytic system, gram-scale synthesis and some transformations of the products were performed (Scheme 5). The gram scale synthesis of all the three Meinwald rearrangement/vinylogous addition reactions performed well. Two consecutive reduction of 3-hydroxy-3-substituted oxindoles **3c** could afford 1,5-dihydroxy compound **8** with 74% yield. Ring closure of **5b** under basic condition produced **9** in 64% yield. Following by a well-established Wittig reaction, the chiral 1,9-dicarbonyl compound **10** was afforded in 74% yield. Furthermore, oxidation of **7a** with *m*CPBA generated polysub-



Scheme 4. Substrate scope of the Meinwald rearrangement/formal [4+2] cycloaddition reaction. [a] Unless otherwise noted, all reactions were carried out with $Sc(OTf)_3$/**L-PrEt$_2$**(10 mol%, 1.0/1.2), 3-chlorobenzoic acid (5 mol%), **6** (0.1 mmol) and **2** (0.2 mmol) in THF (1.0 mL) at 10 °C. The yields were the isolated major diastereomer. The d.r. values were determined by ^{1}H NMR analysis of crude product. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] 35 °C. [c] $Sc(OTf)_3$/**L-PiEt$_2$** (10 mol%, 1.0/1.2). [d] **2** (3.0 equiv).



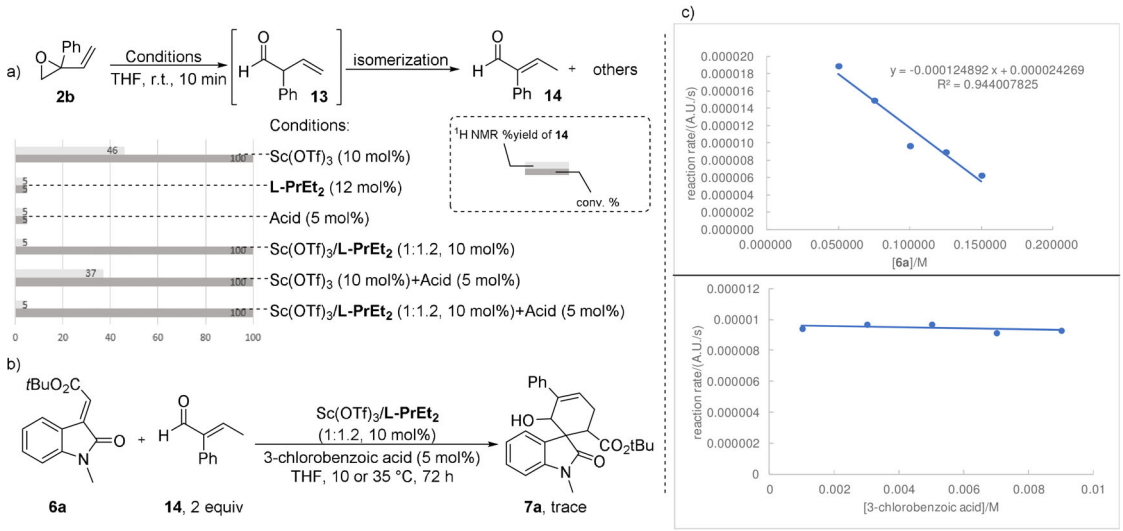
Conditions and reagents: a) $NaBH_4$ (2.2 equiv), MeOH, 0 °C; b) Pd/C, H_2, MeOH, r.t.; c) LiCl (2.0 equiv), DBU (2.0 equiv) $(EtO)_2P(O)CH_2CO_2Et$ (2.0 equiv), CH_3CN, r.t.; d) Ph_3PCHCO_2Et (2.4 equiv), CH_2Cl_2, r.t.; e) *m*-CPBA (3.0 equiv), CH_2Cl_2, 0 °C to r.t.

Scheme 5. Gram scale synthesis and further transformations.

stituted epoxide **11** in 67% yield. All these transformations could occur smoothly without any erosion of the enantioselectivity, and with excellent diastereoselectivities.[15]

To gain insight into the mechanism of these rearrangement/ vinylogous type cascade reactions, control experiments and kinetic studies were conducted in the reaction between methyleneindolinone **6a** and vinyl epoxide **2b** (Scheme 6). Since α-aryl β,γ-unsaturated aldehydes would isomerize to more stable conjugate α,β-unsaturated aldehydes,[16] α-aryl α,β-unsaturated aldehyde **14** which was in fact observed in the reaction system was selected to explore influencing factors in Meinwald rearrangement (Scheme 6a). In the presence of $Sc(OTf)_3$, 46% yield of **14** could be determined by ^{1}H NMR analysis after 10 min. While in the presence of **L-PrEt$_2$**/$Sc(OTf)_3$ complex, the epoxide was consumed quickly but the transformed components were complex. Besides, 3-chlorobenzoic acid and **L-PrEt$_2$** could not solely accelerate transformations of vinyl epoxide **2b**. These results indicated that *N,N'*-dioxide/Sc^{III} complex could suppress the isomerization of active β,γ-unsaturated aldehyde intermediate and accelerate the subsequent vinylogous reaction after the Meinwald rearrangement of vinyl epoxide. On the other hand, more stable α-aryl α,β-unsaturated aldehyde **14** could not participate in the following vinylogous reaction even warming the reaction temperature to 35 °C (Scheme 6b).

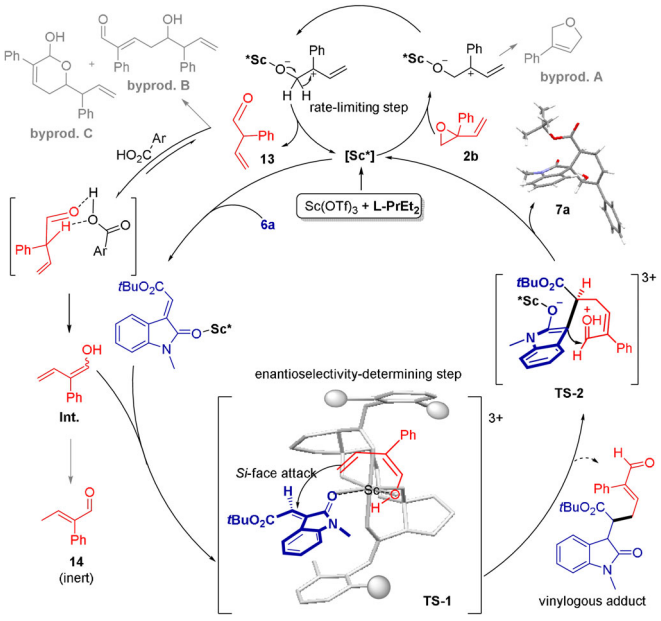
Kinetic experiments of initial rate kinetic analysis with reaction of **6a** and **2b** through the ReactIR instrument showed first-order dependences of the reaction rate on the concentration of both **2b** and the chiral catalyst (see Supporting Information for more details). This feature of kinetics indicates that the process of Meinwald rearrangement is involved in the rate-limiting step. However, the correlation between the reaction rate and the concentration of methyleneindolinone **6a** showed an inverse relationship (Scheme 6c). These data implied that the vinylogous step was more rapid than the rearrangement of vinyl epoxide, although the pre-coordination of methyleneindolinone **6a** to the chiral scandium(III) center might relax the promotion ability of $Sc(OTf)_3$/**L-PrEt$_2$** complex in the process of Meinwald rearrangement to some extent, overwhelmed the side reactions as well. In view of that the diastereoselectivity arises from the second reaction, the chiral catalyst must also be involved in the following addition transformation. Additionally, the kinetic profile of Meinwald rearrangement/formal [4+2] cycloaddition reaction showed a zero-order dependence on 3-chlorobenzoic acid (Scheme 6c), so the role of acid might be to facilitate the enolization of α-aryl β,γ-unsaturated



Scheme 6. Control experiments and kinetic studies.

aldehyde **13** and release the chiral Lewis acid catalyst for the second cycle. Furthermore, a linear relationship between the *ee* of ligand **L-PrEt$_2$** and product **7a** was found (see Supporting Information for more details), implying that enantiodetermining active catalyst was likely a mono-chiral *N*,*N*′-dioxide-scandium complex.

Based on the above analysis, determination of the absolute configuration of the products and previous studies,[8,9,17,18] a possible catalytic cycle with a transition-state mode was proposed (Scheme 7). First, the chiral *N*,*N*′-dioxide **L-PrEt$_2$** and metal salt coordinated in situ to form chiral metal complex [**Sc***]. Then, with the assistance of [**Sc***], vinyl epoxide **2b** smoothly went through Meinwald rearrangement to form α-aryl β,γ-unsaturated aldehyde **13**, then isomerized to its dienolate intermediate **Int.** with the assistance of acid, releasing the chiral [**Sc***] to undergo enantioselective reaction. Next, the catalyst-bonded α,β-unsaturated carbonyl compound **6a** and dienolate would occur γ-addition reaction. The dienolate prefers to attack **6a** from its β-*Si*-face (**TS-1**) because the *Re*-face was strongly blocked by the nearby aryl ring of **L-PrEt$_2$**. Next, diastereoselective intramolecular addition reaction performs via **TS-2** to yield the desired product **7a**.



Scheme 7. The proposed reaction mechanism.

Conclusion

The first catalytic asymmetric multiple vinylogous addition reactions initiated by Meinwald rearrangement of vinyl epoxides were realized via employing chiral *N*,*N*′-dioxide/Sc^{III} complex catalysts. By reacting with isatins, 2-alkenoylpyridines or methyleneindolinones, a series of chiral 3-hydroxy-3-substituted oxindoles, α,γ-difunctionalized α,β-unsaturated aldehydes and spiro-cyclohexene indolinones were observed in good yields with excellent enantioselectivities and diastereoselectivities. Kinetic studies suggested that the process of Meinwald rearrangement is involved in the rate-limiting step. The Lewis acid acts as dual-tasking catalyst, controlling the initial rearrangement step to match subsequent enantioselective vinylogous addition reactions. Further investigations on other type reactions of vinyl epoxides are underway.

Acknowledgements

We appreciate the National Natural Science Foundation of China (No. 21890723 and 21871188) for financial support.

Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · Meinwald rearrangement ·

vinyl epoxides · vinylogous reactions · α-aryl/alkyl β,γ-unsaturated aldehyde

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[15] The absolute configuration of **9** was determined to be (1*S*, 2*R*, 3*R*) from NOESY spectra. The absolute configuration of **11** was determined to be (1*S*, 2*R*, 3*S*, 4*R*, 6*S*) from NOESY spectra.

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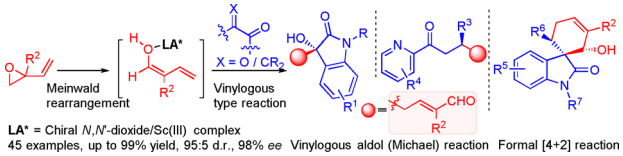
Manuscript received: February 9, 2021
Accepted manuscript online: April 7, 2021
Version of record online: ■■ ■■, ■■■■

Research Articles

Asymmetric Catalysis

J. X. Xu, Y. J. Song, J. He, S. X. Dong, L. L. Lin, X. M. Feng* ——— ▮▮▮▮–▮▮▮▮

Asymmetric Catalytic Vinylogous Addition Reactions Initiated by Meinwald Rearrangement of Vinyl Epoxides



The first catalytic asymmetric multiple vinylogous addition reactions initiated by Meinwald rearrangement of vinyl epoxides were realized by employing chiral *N*,*N*′-dioxide/Sc^{III} complexes as catalysts. Direct vinylogous additions via dienolates of β,γ-unsaturated aldehydes were realized. A series of chiral α,β-unsaturated aldehydes and spiro-cyclohexene indolinones were synthesized in good yields with excellent stereoselectivity.