Asymmetric synthesis of dihydro-1,3-dioxepines by Rh(II)/Sm(III) relay catalytic three-component tandem [4 + 3]-cycloaddition†

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Heterocycles have been widely used in organic synthesis, agrochemical, pharmaceutical and materials science industries. Catalytic three-component ylide formation/cycloaddition enables the assembly of complex heterocycles from simple starting materials in a highly efficient manner. However, asymmetric versions remain a yet-unsolved task. Here, we present a new bimetallic catalytic system for tackling this challenge. A combined system of Rh(II) salt and chiral N,N0-dioxide–Sm(III) complex was established for promoting the unprecedented tandem carbonyl ylide formation/asymmetric [4 + 3]-cycloaddition of aldehydes and a-diazoacetates with b,g-unsaturated a-ketoesters smoothly, affording various chiral 4,5-dihydro-1,3-dioxepines in up to 97% yield, with 99% ee. The utility of the current method was demonstrated by conversion of products to optically active multi-substituted tetrahydrofuran derivatives.

A possible reaction mechanism was provided to elucidate the origin of chiral induction based on experimental studies and X-ray structures of catalysts and products.

Introduction

a-Diazo carbonyl compounds are widely used in organic synthesis due to their diverse reactivity profiles. In particular, formation of various ylides A between a-diazo carbonyl compounds and carbonyl, a–i imine or thiocarbonyl groups, followed by subsequent cycloaddition reactions provides a concise and efficient route to heterocyclic molecules with multiple stereocenters (Scheme 1a), and thus has attracted considerable attention in the past several decades. This strategy has been successfully applied to the total synthesis of complex natural products. Among them, catalytic asymmetric cycloadditions via intramolecular carbonyl ylide formation of functionalized diazo-compounds have been well-established using chiral diiridium salts or combined catalysts. On the other hand, the transformations of ylides initiated by an intermolecular reaction between an a-diazo carbonyl compound and aldehydes or imines have been extended to other reaction partners, including olefins, s–s alkynes, s–s aldehydes or ketones and amines, enabling rapid buildup of molecular complexity from simple starting materials (Scheme 1b).

However, to the best of our knowledge, the highly catalytic enantioselective versions have remained unknown to date. The difficulty stems mainly from the following: (1) the competing...
formation of epoxides or dioxolanes with additional aldehydes hampers the subsequent cycloaddition with dipolarophiles. (Scheme 1c) (2) Rhodium catalysts could induce a background reaction, and both a Rh-associated ylide and a free ylide were proposed in the catalytic cycloaddition process, while chiral dirhodium catalysts only provided poor enantioselectivity.

Experiments in the literature reveal that in some cases Lewis acid catalysts are able to accelerate the cycloaddition of the in situ generated carbonyl ylide with several dipolarophiles. Intrigued by the high performance of chiral N,N'-dioxide metal complex catalysts in cycloaddition reactions and others, we speculated that a bimetallic relay catalysis could potentially realize this challenging three-component tandem reaction. First, in the presence of an achiral dirhodium complex, the reaction of an aldehyde and 2-diazo compound leads to carbonyl ylide. Then a chiral Lewis acid catalyst preferably accelerates the subsequent stereoselective cycloaddition with a suitable dipolarophile, but not the side reactions. Herein, we wish to disclose our endeavor along this line. Rh2Piv4 and Sm(OtF)3/L4-PrPr2 combined catalysts were identified to be efficient for triggering an unprecedented enantioselective tandem ylide formation.[4+3]-cycloaddition reaction among β,γ-unsaturated α-ketoesters, aldehydes and α-diazoacetates. A number of chiral and densely functionalized 4,5-dihydro-1,3-dioxepines were obtained in high yield with excellent diastereoselective and enantioselective yield. (Scheme 1c). It was worth noting that 4,5-dihydro-1,3-dioxepines are important intermediates in the synthesis of γ-butyrolactone derivatives, 2-arylpropionic acids, and substituted tetrahydrofurans. Stereospecific conversion of the products to synthetically useful poly-substituted tetrahydrofuran derivatives, the formal [3+2] adducts, was established as well.

## Results and discussion

Our initial attempts involved using β,γ-unsaturated α-ketoester 1a as the model dipolarophile together with benzaldehyde (2a) and ethyl 2-diazo-2-phenylacetate (3a) to optimize the reaction conditions. As depicted in Scheme 1c, several competition pathways were possible including [3+2] of either a C=C bond or C=O bond, or [4+3] of C=C–C=O bond. The reaction took place smoothly under the influence of Rh2Piv4 and a chiral N,N'-dioxide L4-PrPr2/Yb(OtF)3 complex at –20 °C in dichloromethane, affording 4,5-dihydro-1,3-dioxepine through a new paradigm of [4+3] route in 58% isolated yield with 67% ee for the major diastereomer (Table 1). The 1H NMR spectrum of the crude mixture indicated that the other diastereomer of 1,3-dioxepine (ca. 18% yield) and [3+2] adduct III with the C=O group of the α-ketoester (ca. 7% yield) were generated as well (for more details, see Table S6 in the ESI†). Subsequent investigation indicated that lowering the temperature from –20 °C to –78 °C resulted in a highly diastereoselective process, and the desired [4+3] product 4a was yielded exclusively with maintaining the ee value (entry 2, 90% yield, 66% ee). Next, several rare-earth metal salts were tested with N,N'-dioxide L4-PrPr2 as the ligand (see the ESI for details†). It was found that Sm(OtF)3 gave a higher ee value (entry 3, 84% ee). Then, screening of the backbone of the ligands suggested that l-proline derived L4-PrPr2 afforded better results than (S)-piperidine-2-carboxylic acid or l-ramipril derived ones (entries 4 and 5). The length of the carbon tether of N,N'-dioxide ligands was found to have a significant influence on the outcomes, and a four-carbon linker was superior to three- or five-carbon ones in terms of yield and enantioselectivity (entry 3 vs. entries 6 and 7). Other chiral ligands, such as tBu-Box and DTBM-SEGP4OS, gave poor results (entries 8 and 9). Without Rh2Piv4, the three-component reaction did not occur at all, even when camphor sulfonic acid was used as the alternative for carbene generation from diazo compounds (see Table S6 in the ESI for details†). When the reaction was carried out with only Rh(n), a mixture of at least four isomeric products (I and III) was obtained (entry 10, 4a, trace yield). The use of chiral Rh3(S-DOSP), furnished a racemic product (see the ESI for more details†), implying that a free carbonyl ylide might be involved. Performing the reaction with Rh(n) and Sm(OtF)3 led to the consumption of the aldehyde and diazoester and the recovery of the ketoester, but only a trace amount of the cycloaddition adduct (entry 11) was obtained. The aforementioned results clearly indicated that the chiral Lewis acid catalyst accelerated

### Table 1  Optimization of the reaction conditions

| Entry | Metal salt | Ligand | T (°C) | Yield (%) | ee (%) |
|-------|------------|--------|--------|-----------|--------|
| 1     | Yb(OtF)3  | L4-PrPr2 | -20    | 58        | 67     |
| 2     | Yb(OtF)3  | L4-PrPr2 | -78    | 90        | 66     |
| 3     | Sm(OtF)3  | L4-PrPr2 | -4     | 90        | 84     |
| 4     | Sm(OtF)3  | L4-PrPr2 | -78    | 68        | 32     |
| 5     | Sm(OtF)3  | L4-PrPr2 | -78    | 50        | 26     |
| 6     | Sm(OtF)3  | L4-PrPr2 | -78    | 38        | 26     |
| 7     | Sm(OtF)3  | L4-PrPr2 | -78    | 85        | 54     |
| 8     | Sm(OtF)3  | tBu-Box | -78    | 56        | 11     |
| 9     | Sm(OtF)3  | DTBM-SEGP4OS | -78 | 57       | 0      |
| 10    | —         | —       | -78    | Trace     | —      |
| 11    | Sm(OtF)3  | —       | -78    | Trace     | —      |
| 12    | Sm(OtF)3  | L4-PrPr2 | -78    | 92        | 99     |

a Unless otherwise noted, the reaction was carried out with Rh2Piv4 (0.75 mol%), metal salt/ligand (1 : 1.2, 10 mol%), β,γ-unsaturated α-ketoesters 1a (0.10 mmol), aldehyde 2a (3.0 equiv.) and α-diazo ester 3a (3.0 equiv.) at T °C for 10 h under a N2 atmosphere. b Isolated yield of the major diastereomer. c Determined by HPLC analysis on a chiral stationary phase. d 2a (4.0 equiv.) and 3a (4.0 equiv.).
the subsequent [4 + 3]-cycloaddition and controlled the chemoselectivity and stereoselectivity of this process. To our delight, increasing the amounts of 2a and 3a can elevate the enantioselectivity obviously, affording 4a in 92% yield and 99% ee (entry 12).

With the optimized conditions in hand, the substrate scope was next examined. As shown in Table 2, changing the ester group (R1') of the β,γ-unsaturated α-ketoester from a methyl to an isopropyl, a cyclopentyl or a benzyl group led to slightly reduced yields and ee values (4a–4d, 72–92% yield, 85–99% ee). The γ-aryl substituted β,γ-unsaturated α-ketoesters with electron-withdrawing or electron-donating substituents at 2-, 3-, and 4-positions of the phenyl group can react with benzaldehyde 2a and α-diazoester 3a smoothly to furnish the corresponding products 4e–4o in moderate to good yields (64–95% yield) and high ee values (80–99% ee). Generally, 2-substituted ones (1f and 1l) provided diminished yield and enantiomeric excess. Additionally, 2-naphthyl and heteroaromatic substrates were tolerated in this cascade reaction as well (4p–4r).

As shown in Table 2, changing the ester group (R1') of the β,γ-unsaturated α-ketoester from a methyl to an isopropyl, a cyclopentyl or a benzyl group led to slightly reduced yields and ee values (4a–4d, 72–92% yield, 85–99% ee). The γ-aryl substituted β,γ-unsaturated α-ketoester 1s was a competent reaction partner, providing the desired [4 + 3] adduct 4s in 94% yield and 99% ee. The absolute configuration of the major enantiomer of 4m was determined to be (2S,4S,5S) by X-ray diffraction analysis, and the others were assigned by comparing their CD spectra with those of 4m.25

Table 2  Substrate scope of β,γ-unsaturated α-ketoesters

| R1' | Yield (%) | ee (%) |
|-----|-----------|--------|
| Me  | 95        | 99     |
| iPr | 90        | 94     |
| C5H11 | 85    | 98    |
| C6H5 | 75        | 89     |

**Notes:** Unless otherwise noted, the reaction conditions were the same as those in Table 2. a β-Diazoester 3 (4.2 equiv.). b α-Diazoester 3 (3.7 equiv.). c Aldehyde 2 (4.2 equiv.) and Rh2Piv4 (1.5% mmol).

Next, various aldehydes 2a and α-diazoacetates 3 were tested (Table 3). According to the reactivity of the aldehydes, the amount of the α-diazoacetates was adjusted slightly in order to get high yield and ee. Satisfactorily, using β,γ-unsaturated α-ketoester 1a and α-phenyl diazoacetate 3a as the reaction partner, aryldaldehydes 2b–2h with different electron-withdrawing or electron-donating substituents were readily converted into the corresponding products 4t–4z (81–95% yield and 87–98% ee). In this case, para-chloro- or bromo-substituted ones exhibited low reactivity and enantioselective control. 1-Naphthaldehyde 2i and cyclohexyl formaldehyde 2j were compatible in the current transformation, delivering the adducts 4aa and 4ab with good results. Furthermore, changing the phenyl group on the α-diazoacetates 3 had a limited influence on the reaction, regardless of the position and electronic effect of substituents on the phenyl group (4ac–4al, 88–97% yield, 89–99% ee). Benzyl substituted α-diazoacetate was suitable as well, affording the product 4am with 84% ee. However, low yield (31% yield) was obtained due to the elimination reaction of the α-diazoacetate.26

To illustrate the utility of the current methodology, further conversion of the 4,5-dihydro-1,3-dioxepines 4 was carried out. As shown in Table 4, compound 4a was stereospecifically
transformed into tetrahydrofuran (THF) derivative 5a with four continuous stereogenic centers in the presence of methanesulfonic acid at 60 °C. Under such conditions, representative products 4 with different substituents rearranged to THF-derivatives 5 in high yield (84–93% yield) without loss of enantioselectivity (97–99% ee). Interestingly, compounds 5 were the formal [3 + 2]-adducts of carbonyl ylide B with the C=C double bond of the β,γ-unsaturated α-ketoester (Scheme 1c, II), which could make up for the lack of the catalytic asymmetric version of the related [3 + 2] cascade reaction.5 The absolute configuration of 5a was assigned as (2S,3S,4R,5R) on the basis of the absolute configuration of 4a and the relative configuration of racemic 5a.6 The others were assigned by comparing their CD spectra with those of 5a. In addition, the alkenyl ester group in compound 4a was reduced by LiAlH₄ (2.2 equiv.) to give the alcohol 6a in 76% yield with 99% ee (Scheme 2, left). Hydrogenation of 4a with Pd/C and H₂ yielded the saturated 1,3-dioxepane 7a in 98% yield, 2 : 1 dr and 99/99% ee value (Scheme 2, right).

In order to understand the chiral induction of the N,N'-dioxide–Sm[III] Lewis acid catalyst, we got the crystals of the Sm[III] complexes of chiral N,N'-dioxides L₄-PrPr₂ with different lengths of the carbon tether (n = 3, 4, or 5).6,14 The X-ray crystal structures show that each N,N'-dioxide coordinates as a tetradeptate ligand to Sm[III] with two amine oxide oxygen atoms and two amide oxygen atoms, forming a square antiprismatic geometry version through the coordination with four additional species. It is interesting that L₄-PrPr₂ is noteworthy in view of the angles between O²⁻–Sm–O²⁻ (narrowest, 138.5°) and O³⁻–Sm–O⁴⁻ (widest, 94.4°), and the shortest bond distance of O²⁻–Sm (2.393 and 2.423 Å) and O⁴⁻–Sm (2.266 and 2.286 Å) in comparison with L₃-PrPr₂ and L₅-PrPr₂ (see the ESI for more details†). It implies that the alkyl linker between the two amine oxides affects both the geography and the electronic nature of the catalyst, delivering distinct activity and stereoselectivity.

Based on the absolute configuration of the products and control experiments, a possible reaction pathway was proposed (Scheme 3). Initially, free carbonyl ylide B is generated in situ from α-diazoacetate 3a and aldehyde 2a with the assistance of achiral Rh(n). Considering the fact that excess amounts of aldehyde and α-diazoacetate are advantageous to improve the enantioselectivity, we speculated that interaction between carbonyl ylide intermediate B and chiral Sm[III]–N,N'-dioxide exists, which is also supported by the operando IR experiment (see the ESI for details†). The high-coordination number of the rare-earth metal complex catalyst enabled the activation of the β,γ-unsaturated α-ketoester with Sm[III]/L₄-PrPr₂ in a bidentate-bonding manner at the same time. Therefore, a possible working mode was set forth to explain the stereoselectivity of the cycloaddition step. Due to the steric hindrance of the 2,6⁻Pr₂C₆H₃ moiety in the chiral N,N'-dioxide ligand, the β-Re face of the unsaturated ketoester was blocked, leaving the less-hindered β-Si face available for attack by ylide B with its Re-Re face in an endo fashion.19 As a result, (2S,4S,5S)⁻4a was formed as the major enantiomer.

**Conclusions**

In summary, a highly efficient asymmetric cascade carbonyl ylide formation/[4 + 3]-cycloaddition reaction of β,γ-unsaturated α-ketoesters, aldehydes, and α-diazoacetates was realized...
by using a rhodium(III)/chiral N,N'-dioxide-Sm(III) complex bimetallic catalyst. Various chiral 4,5-dihydro-1,3-dioxepines were readily obtained in high yield with excellent ee values. Moreover, the 1,3-dioxepines can stereospecifically transform into multi-substituted tetrahydronorbornene derivatives efficiently. A plausible catalytic cycle along with a working mode was proposed to explain the formation of enantioenriched products according to the experimental evidence and single crystal data. Further uses of the bimetallic relay catalysis strategy in other reactions are under investigation.

Author contributions

C. R. X. performed the experiments. J. L. Q. repeated data. S. X. D. participated in structure characterization and discussion. Y. Q. Z. analyzed the X-ray diffraction crystal data. X. M. F. and X. H. L. supervised the project. X. M. F., X. H. L., S. X. D. and C. R. X. co-wrote the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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18 X-ray crystal structures indicated that the chiral pocket changed with the catalysts bearing different carbon tethers of chiral ligands (see the ESI, page S15†). Further studies are needed to illustrate the effect of the catalyst structure on diastereo- and enantioselectivity.

19 Both endo and exo-selectivity were observed in previous studies (endo, 6a, f–i; exo, 6e).