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Asymmetric synthesis of isochromanone derivatives *via* trapping carboxylic oxonium ylides and aldol cascade†

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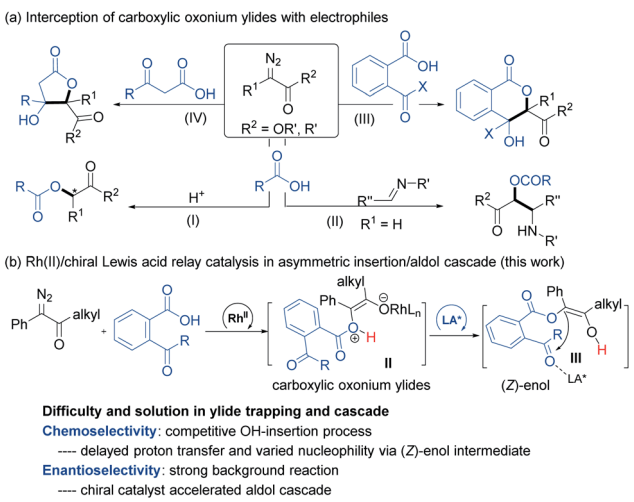
An efficient asymmetric synthesis of isochromanone derivatives was realized through *Z*-selective-1,3-OH insertion/aldol cyclization reaction involving acyclic carboxylic oxonium ylides. The combination of achiral dirhodium salts and chiral *N*,*N*′-dioxide–metal complexes, along with the use of α-diazoketones instead of α-diazoesters, enables the cascade reaction efficiently. A variety of benzo-fused δ-lactones bearing vicinal quaternary stereocenters were obtained with good to excellent enantioselectivity, bypassing the competitive 1,1-OH insertion and racemic background aldol reaction.

Introduction

Transition-metal-catalyzed insertion of carbenes into heteroatom–hydrogen bonds (X–H, X = N, O, S, *etc.*)[1] to form highly active onium ylides, undergoing either enantioselective insertion reaction[2] or interception by electrophiles,[3] has received considerable attention for effective construction of structurally complex molecules.[4] To this end, enantioselective trapping of oxonium ylides initiated by the insertion of phenols and alcohols, one of the most common and important species, has been well studied.[5] However, carboxylic oxonium ylides are largely undeveloped (Scheme 1a),[6,8] and sporadic racemic cascade reactions by bypassing the competitive O–H insertion step (path I)[7] have been disclosed, such as intermolecular trapping with imines (path II)[6a] and intramolecular aldol cascade to produce lactones (path III and IV).[6c] The enantioselective trapping of carboxylic oxonium ylides is rare with difficulties such as (1) low pK_a values of protonated carboxylic acids in the zwitterionic intermediate leads to a rapid proton shift;[8] (2) changing the electronics of the diazo-derived rhodium carbenoid to delay the proton shift and to facilitate additional cascade results in a strong racemic background reaction. Till recently, a representative capture of carboxylic oxonium ylides with imines for synthesis of chiral γ-butenolides was reported by Hu and coworkers, in which cycloprop-2-ene-1-carboxylic acids were employed as cyclic carboxylic oxonium ylide precursors.[9]

In the course of our study related to the enantioselective O–H insertion reaction of carboxylic acid[10] and dual metal complex relay catalysis,[11] we are interested in trapping acyclic carboxylic oxonium ylides *via* an asymmetric cascade reaction to obtain chiral isochromanones with two vicinal quaternary centers. The δ-lactone moiety is attractive in food additives, pharmaceuticals and natural products.[12] Nevertheless, to control the stereoselectivity of this cascade reaction, a chiral catalyst must engage in the final aldol reaction. The combination of dirhodium salt and the chiral Lewis acid catalyst would be a good choice. The chiral Lewis acid is able to do some multi-tasking under competition with the dirhodium catalyst: enhancing the electrophilicity of the ketone to facilitate the aldol addition to overtake the 1,1-OH insertion; directing the facial selectivity during the cyclization. On the other hand, we propose that the



Scheme 1 The reactions involving carboxylic oxonium ylides.

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† Electronic supplementary information (ESI) available: ^{1}H,$^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR and HPLC spectra (PDF). X-ray crystallographic data for **C1** and **F3**. **C1** (CCDC: 2004207) and **F3** (CCDC: 2085693). CCDC 2004207 and 2085693. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc06025b

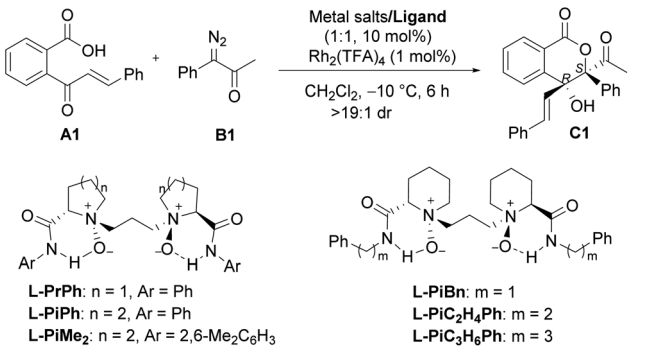
use of α-diazoketones instead of α-diazoesters would result in the formation of a transient (*Z*)-type enol intermediate for the aldol cascade (Scheme 1b), which has been proved in rhodium carbenoid-initiated Claisen rearrangement[13] and others.[14] Herein, we report the combination of achiral dirhodium salt and chiral *N*,*N*′-dioxide-Fe(III) or Sc(III) complex[15] catalyzed cascade 1,3-OH insertion/asymmetric aldol cyclization reaction of ketoacids with α-diazoketones. The corresponding optically active benzo-fused δ-valerolactones were obtained in excellent diastereo- and enantioselectivity.

Results and discussion

We initiated the investigation of the model reaction between 2-cinnamoylbenzoic acid (**A1**) and 1-diazo-1-phenylpropan-2-one (**B1**) in dichloromethane at −10 °C, using $Rh_2(TFA)_4$ and $Sc(OTf)_3$ complexes of chiral *N*,*N*′-dioxide ligands as the catalytic system. The influence of chiral ligand structures on enantioselectivity and reactivity was evaluated (Table 1, entries 1–5). It was found that both the amino acid backbones and the amide subunits can have significant influence on the enantioselectivity (entries 1–3). L-Proline derivative and hindered amides were disadvantageous to the enantiocontrol. Phenylmethanamine-based **L-PiBn** and phenylethanamine-based **L-PiC$_2$H$_4$Ph** showed remarkably increased enantioselectivity (entries 4 and 5). Moreover, the screening of a series of metal salts combined with *N*,*N*′-dioxide **L-PiC$_2$H$_4$Ph** (entries 5–8) showed that $Fe(OTf)_3$ could improve the yield to 84% with maintaining the ee value. It was interesting that $Fe(OTf)_2$ yielded only a racemic product (entry 7). Noteworthily, an excess amount of $Fe(OTf)_3$ benefited the reactivity, and a 91% yield with 97% ee was obtained for the lactone **C1** even at an amount of 2 mol% catalyst loading (entries 9 and 10), meanwhile, only a trace amount of 1,1-OH insertion intermediate **D1** was observed. In all cases, lactone was isolated as a single diastereoisomer (>19 : 1 dr), and the absolute configuration of **C1** was determined to be (3*S*,4*R*) by X-ray diffraction crystal analysis.[16] Comparatively, other chiral ligands, such as BOX or PyBOX instead of *N*,*N*′-dioxide, or chiral $[Rh_2(S\text{-}DOSP)_4]$ independently were employed, but low yields and ee values were observed for the product **C1** (see the ESI for details†). The screening of other achiral rhodium salts gave similar ee values indicating that rhodium salts only took part in O–H insertion to generate oxonium ylides, implying the merit of dual catalysis. It was noteworthy that the addition of α-diazoketone performed in the one-pot and slow-addition procedure was unnecessary.

With the optimized reaction conditions in hand (Table 1, entry 10), the scope of cinnamoylbenzoic acid derivatives was examined first. As shown in Table 2, all the substrates containing electron-donating or electron-deficient substituents at the *ortho*-, *meta*-, or *para*-positions of the terminal-aryl group tolerated well, delivering **C2–C10** in 50–92% yields with

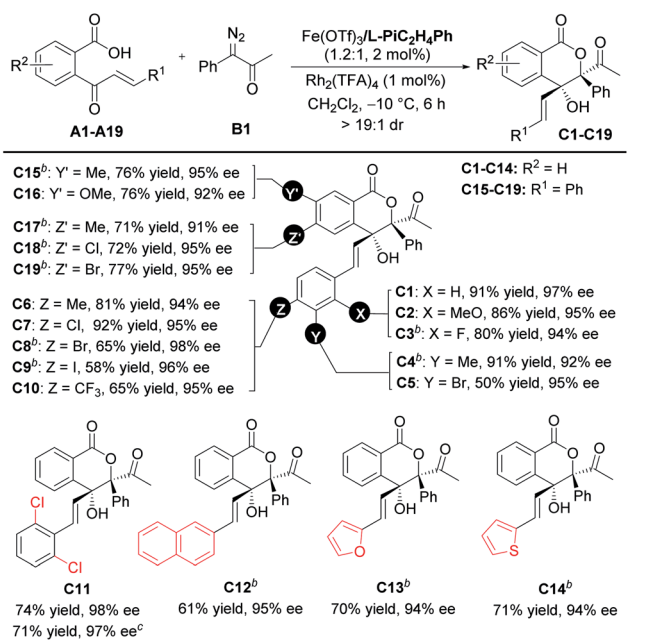
Table 1 Optimization of reaction conditions[a]



Entry	Metal salts	Ligand	Yield[b] (%)	ee[c] (%)
1	$Sc(OTf)_3$	**L-PrPh**	34	6
2	$Sc(OTf)_3$	**L-PiPh**	40	66
3	$Sc(OTf)_3$	**L-PiMe$_2$**	25	8
4	$Sc(OTf)_3$	**L-PiBn**	66	94
5	$Sc(OTf)_3$	**L-PiC$_2$H$_4$Ph**	75	97
6	**$Fe(OTf)_3$**	**L-PiC$_2$H$_4$Ph**	**84**	**97**
7	$Fe(OTf)_2$	**L-PiC$_2$H$_4$Ph**	67	0
8	$Co(OTf)_2$	**L-PiC$_2$H$_4$Ph**	57	80
9[d]	$Fe(OTf)_3$	**L-PiC$_2$H$_4$Ph**	91	97
10[e]	**$Fe(OTf)_3$**	**L-PiC$_2$H$_4$Ph**	**91**	**97**

[a] Unless otherwise noted, all reactions were carried out with **A1** (0.10 mmol), **B1** (2.0 equiv.), metal salts/ligand (1 : 1, 10 mol%), and $Rh_2(TFA)_4$ (1 mol%), in CH_2Cl_2 (2.0 mL) at −10 °C for 6 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis in a chiral stationary phase. All dr values were up to >19 : 1 detected by ^{1}H NMR. [d] $Fe(OTf)_3$ (12 mol%). [e] $Fe(OTf)_3$/**L-PiC$_2$H$_4$Ph** (1.2 : 1, 2 mol%).

Table 2 Substrate scope of the cinnamoylbenzoic acid derivatives[a]



[a] Unless otherwise noted, all reactions were carried out with **A** (0.10 mmol), **B1** (2.0 equiv.), $Fe(OTf)_3$/**L-PiC$_2$H$_4$Ph** (1.2 : 1, 2 mol%), and $Rh_2(TFA)_4$ (1 mol%), in CH_2Cl_2 (2.0 mL) at −10 °C for 6 h. Isolated yields. The ee value was determined by HPLC analysis. All dr values were up to >19 : 1 detected by ^{1}H NMR. [b] $Fe(OTf)_3$/**L-PiC$_2$H$_4$Ph** (1.2 : 1, 4 mol%). [c] **A11** (3.0 mmol) and **B1** (2.0 equiv.) in CH_2Cl_2 (60 mL) for 12 h.

excellent enantioselectivities (92–98%). The 3-bromo substituted **C5**, 4-bromo-substituted **C8** and 4-iodo-substituted **C9** were obtained in lower yield than others, due to the increased amount of the interrupted 1,1-OH insertion products. The large-scale synthesis of the lactone **C11** proceeded smoothly with good yield and excellent enantioselectivity (0.963 g, 71% yield, 97% ee). In addition, 2-naphthyl, 2-furanyl and 2-thiophenyl substituted cinnamoylbenzoic acids also performed well, delivering the corresponding products **C12–C14** with good outcomes (61–71% yields, 94–95% ee). Furthermore, these cinnamoylbenzoic acid derivatives bearing electron-donating or electron-withdrawing groups at 4- or 5-positions of the phenyl ring were suitable to synthesize lactones **C15–C19** in good yields with excellent ee values.

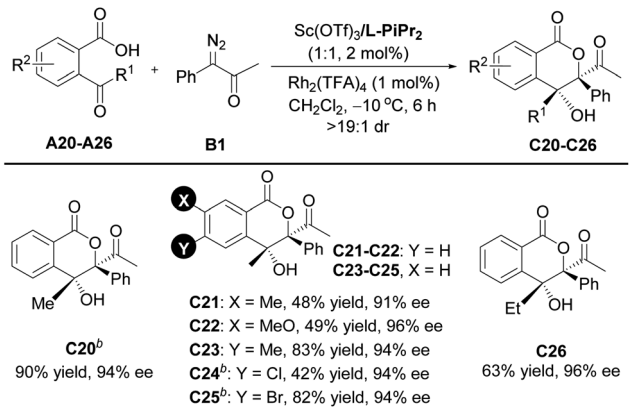
Encouraged by the above results, further efforts were made to expand the scope of ketoacids. A series of γ-ketoacids **A20–A26** were explored (Table 3). By switching the catalyst to the $Sc(OTf)_3$/**L- PiPr$_2$** complex, the cascade cyclization reaction with diazoketone **B1** could efficiently construct the desired products **C20–C26** in 42–90% yields with 91–96% ee values.

Subsequently, the scope with respect to the diazoketones was investigated (Table 4). All of the tested α-diazophenylpropanones (R^2 = Me, R^1, and **B2–B11**) reacted smoothly in 6 h to afford the corresponding chiral lactones **C27–C36** in good to high yields with excellent enantioselectivities. The electronic properties of the substituents at the *para*- or *meta*-position on the phenyl ring of the diazoketones hardly affected the yields and enantioselectivities. 2-Naphthalenyl-bearing diazoketone performed the reaction well to generate **C37** in 89% yield and 94% ee. We also studied the effect of the carbonyl substituent, and good enantioselectivities (72–93% ee) were obtained when R^2 was either an alkyl group (**C38–C41**) or aryl group (**C42–C46**). It should be mentioned that the loading of the Lewis acid catalyst and subunits of the ligand needed to be adjusted in some cases. For instance, 3-phenylpropanamine-based ligand **L-PiC$_3$H$_6$Ph** was used instead to guarantee the good enantioselectivity. The electron-deficient substituent on 2-cinnamoylbenzoic acid could offset the loss of enantioselectivity caused by 4-chlorobenzoyl substitution (**C44** and **C45** *vs.* **C43**).

As shown in Scheme 2a, hydrogenation of **C1** in the presence of Pd/C afforded derivative **F1** in 96% yield with 97% ee. Upon addition of *m*CPBA, **C1** could also be easily converted to an epoxide **F2** (88% yield, 87 : 13 dr, 99% ee). Reduction of **C1** by $NaBH_4$ delivered alcohol **F3** in high diastereo- and enantioselectivities (91% yield, 97% ee).[16]

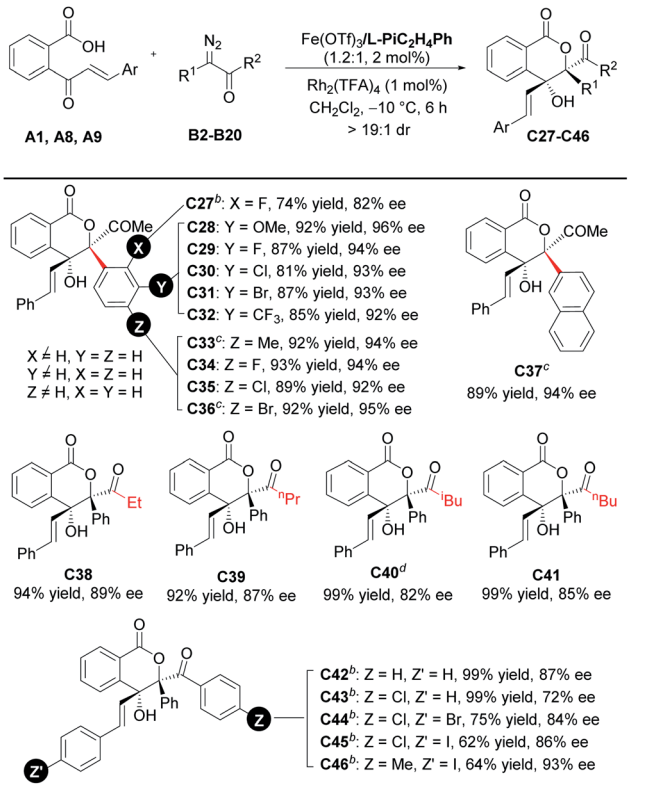
In order to understand the catalytic mechanism, we set out several control experiments (Scheme 2b–d). Intriguingly, when methyl 2-diazo-2-phenylacetate **B21** was subjected to the standard catalytic system instead of α-diazoketone **B1**, the corresponding lactone product **C47** was isolated in 99% yield as a racemate (Scheme 2b). Next, we probed into the role of each catalytic component and it could be seen from Scheme 2c that without the chiral Lewis acid, the 1,1-OH insertion intermediate **D1** was coproduced in varying amounts even at low reaction temperature. Favoring a ligand-accelerated process, the 1,1-OH insertion product **D1** was nearly bypassed. Nevertheless, the 1,1-OH insertion intermediate **D1** produced none of lactone **C1** when exposed to the standard reaction conditions, even in the

Table 3 Substrate scope of the sample γ-ketoacids[a]

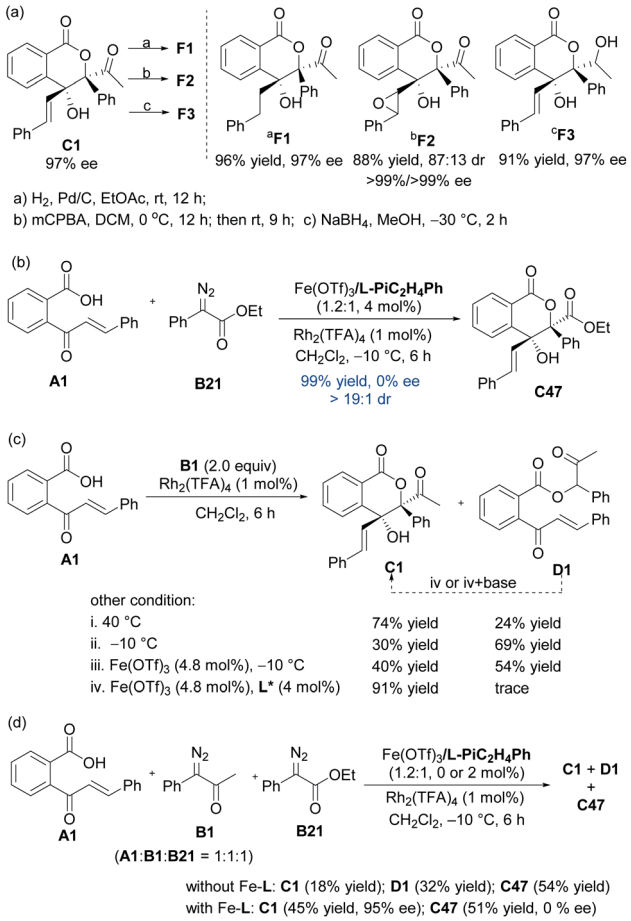


[a] Unless otherwise noted, all reactions were carried out with **A** (0.10 mmol), **B1** (2.0 equiv.), $Sc(OTf)_3$/**L-PiPr$_2$** (1 : 1, 2 mol%), and $Rh_2(TFA)_4$ (1 mol%), in CH_2Cl_2 (2.0 mL) at −10 °C for 6 h. Isolated yields and ee value was determined by HPLC analysis. All dr values were up to >19 : 1 detected by ^{1}H NMR. [b] $Sc(OTf)_3$/**L-PiPr$_2$** (1 : 1, 4 mol%).

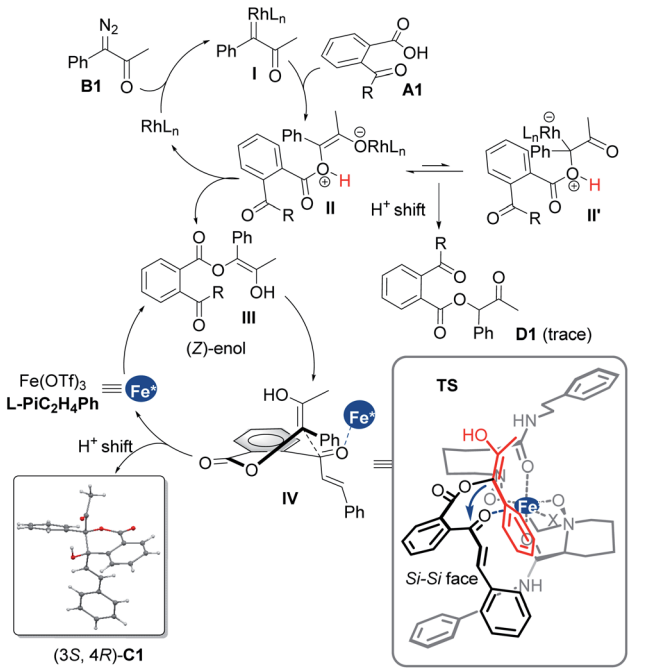
Table 4 Substrate scope of the diazoketones[a]



[a] As same as footnote a in Table 2. [b] $Fe(OTf)_3$/**L-PiC$_3$H$_6$Ph** (1.2 : 1, 4 mol%). [c] $Fe(OTf)_3$/**L-PiC$_2$H$_4$Ph** (1.2 : 1, 4 mol%). [d] $Fe(OTf)_3$/**L-PiC$_3$H$_6$Ph** (1 : 1, 5 mol%).



Scheme 2 Transformation of the products and the control experiments.



Scheme 3 Possible asymmetric catalytic model.

presence of a base. This result suggested that the sequential transformations were not the case for the generation of **C1**.

The comparison experiment by mixing substrate **A1**, α-diazoketone **B1** and α-diazoester **B21** manifested that the rate of the cascade reaction of α-diazoesters exceeded α-diazoketones (Scheme 2d), and the generation of lactone from α-diazoesters occurred more readily than α-diazoketone *via* the intramolecular Mukaiyama aldol type reaction of metal ketene acetal with the $Rh_2(TFA)_4$ catalyst or spontaneously. The strong competition of the $Rh_2(TFA)_4$-involved racemic process might decrease the enantioselectivity in the reaction of α-diazoester **B21** even at −60 °C (see the ESI for details†). Furthermore, the combination of other dirhodium salts and the chiral ferric catalyst led to complete conversion, containing racemic **C47** and minor 1,1-OH insertion intermediates (see the ESI for details†). The prediction of the pK_a value *via* Luo's molecular prediction platform[17] showed that the enol intermediate of α-diazoester **B21** is slight lower than the corresponding intermediates of α-diazoketones (see the ESI for details†). These results clearly indicate that stabilized ylide species affect the addition step in these cases.

Based on these results and our previous studies,[11,15] a possible catalytic cycle with a favorable transition-state model is illustrated in Scheme 3. Initially, nitrogen is extruded from the diazoketone compound to generate a Rh(II)-carbenoid intermediate **I**, engaging the carboxylic acid to form the rhodium-associated ylide species **II′** and its isomer **II**. Bypassing tautomerization to afford the inertial 1,1-OH insertion byproduct **D1**, a (*Z*)-enol intermediate **III** is generated upon a 1,4-H shift to release the rhodium catalyst.[11d,13,14] Furthermore, in the existence of chiral Lewis acid, which could coordinate with the carbonyl group of species **III** to advance the subsequent aldol reaction through the intermediacy of **IV**, where a half-chairlike transition state possesses axially disposed (*Z*)-enol substituents and vinyl substituents of ketones.

Speeding the aldol cascade and transfer of the stereochemistry lie in the chiral ferric catalyst with external subunits of the ligand. The tetra-dentate coordination of **L-PiC$_2$H$_4$Ph** to ferric ions leads to an octahedral complex, preserving two similar sites at equatorial position for the coordination of the intermediates. As shown in **TS**, the two amide arms adpot reverse extension, leaving space to emplace both 2-acetylbenzoic acid **A** and α-diazoketone **B**. The *Re*-face of the ketone species bonds will be blocked by the below amide. Therefore, the favorable *Si*–*Si* facial approach produces the (3*S*,4*R*)-product **C1** as the major isomer with excellent diastereo- and enantioselectivities after tautomerization and regeneration of the ferric catalyst.

Conclusions

In summary, a highly efficient asymmetric cascade O–H insertion/aldol cyclization of ketoacids with diazoketones was achieved with a Rh(II)/chiral *N*,*N*′-dioxide-Fe(III) or Sc(III) complex bimetallic relay catalytic system. Asymmetric intramolecular aldol addition of (*Z*)-enols which are generated from

readily accessible ketoacids and α-keto Rh-carbenoids *via* acyclic carboxylic oxonium ylides was accomplished for the first time. A range of optically active lactone derivatives with two adjacent quaternary–quaternary stereocenters was afforded with good to excellent yields and stereoselectivities. A plausible catalytic cycle along with a working model was proposed to explain the formation of enantioenriched products according to the experimental evidence and single crystal data.

Data availability

Further details of experimental procedure, ^{1}H, $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR, HPLC spectra and X-ray crystallographic data for **C1** and **F3** are available in the ESI.†

Author contributions

J. W. L. performed the experiments and prepared the ESI† and paper. S. Y. W. and C. L. H. repeated some experiments. X. M. F. and X. H. L. supervised the project. X. M. F. and X. H. L. helped with modifying the paper and ESI.†

Conflicts of interest

There are no conflicts to declare.

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