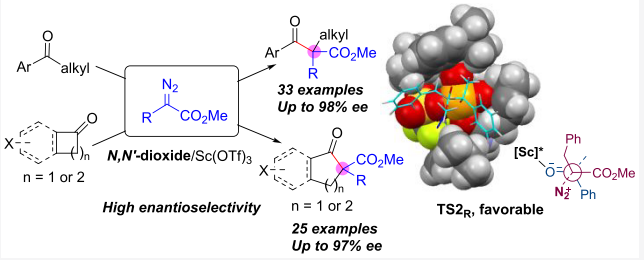
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Article

Catalytic Asymmetric Homologation of Ketones with α-Alkyl α-Diazo Esters

Fei Tan,[‖] Maoping Pu,[‖] Jun He, Jinzhao Li, Jian Yang, Shunxi Dong, Xiaohua Liu,* Yun-Dong Wu,* and Xiaoming Feng*

Cite This: J. Am. Chem. Soc. 2021, 143, 2394−2402
Read Online

ABSTRACT: The homologation of ketones with diazo compounds is a useful strategy to synthesize one-carbon chain-extended acyclic ketones or ring-expanded cyclic ketones. However, the asymmetric homologation of acyclic ketones with α-diazo esters remains a challenge due to the lower reactivity and complicated selectivity. Herein, we report the enantioselective catalytic homologation of acetophenone and related derivatives with α-alkyl α-diazo esters utilizing a chiral scandium(III) *N*,*N*′-dioxide as the Lewis acid catalyst. This reaction supplies a highly chemo-, regio-, and enantioselective pathway for the synthesis of optically active β-keto esters with an all-carbon quaternary center through highly selective alkyl-group migration of the ketones. Moreover, the ring expansion of cyclic ketones was accomplished under slightly modified conditions, affording a series of enantioenriched cyclic β-keto esters. Density functional theory calculations have been carried out to elucidate the reaction pathway and possible working models that can explain the observed regio- and enantioselectivity.



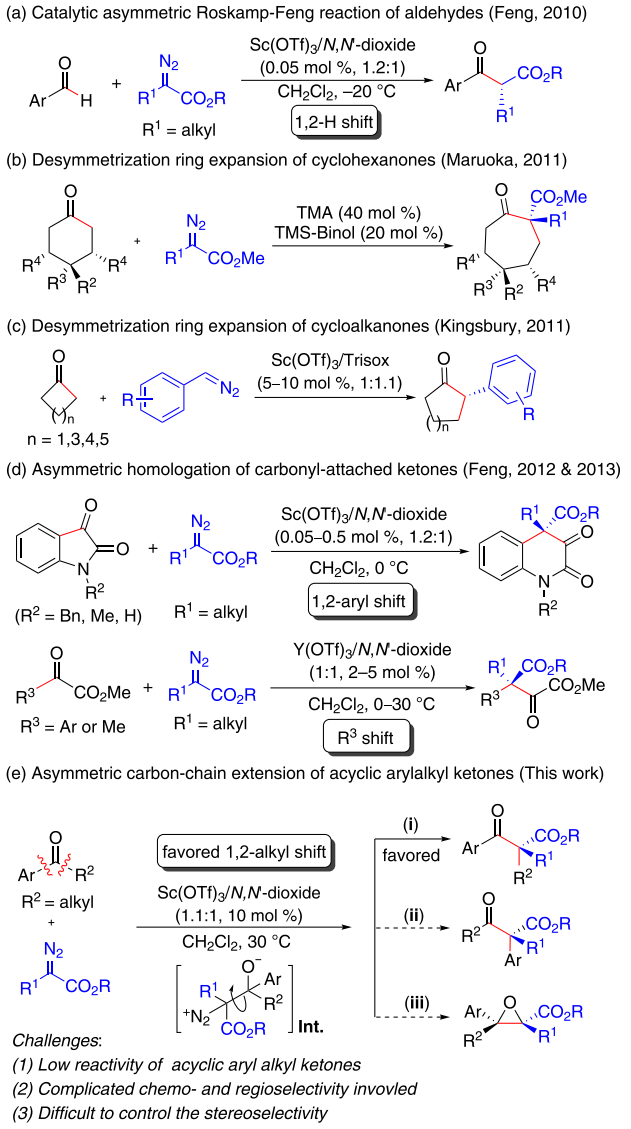
1. INTRODUCTION

The homologation of aldehydes or ketones with diazo compounds represents one of the most efficient and straightforward routes to one-carbon chain extension or ring expansion at the carbonyl moiety.[1−10] Mechanistically, this type of reaction is triggered by the nucleophilic addition of the diazoalkyl carbon to a carbonyl group, followed by a 1,2-shift with the concerted extrusion of N_2. This strategy has been frequently used in the synthesis of biologically active compounds and complex natural products.[11−15] With the discovery of well-defined Lewis acid promoters and catalysts,[5] asymmetric versions of homologation of aldehydes have been extensively investigated over the past decade (Scheme 1a).[16−21] In contrast, enantioselective homologation of ketone substrates[6] has mainly focused on either symmetrical cyclic ketones[22−24] or electronically activated ketones[25−27] with an electron-withdrawing carbonyl substituent. The Maruoka group reported a desymmetrizing asymmetric ring expansion of cyclohexanones with α-diazoacetates catalyzed by a chiral aluminum Lewis acid, and various chiral quaternary β-keto esters and medium-ring ketone products were provided (Scheme 1b).[23] Kingsbury and co-workers realized a highly enantioselective desymmetrization of cycloalkanones with substituted diazomethanes utilizing a chiral Sc(III)-trisox catalyst; upon several studies of racemic versions, an array of enantioenriched tertiary α-aryl cycloalkanones was readily afforded (Scheme 1c).[24] Later, the Feng group described the enantioselective intermolecular homologation of isatins[25] and α-ketone esters[26] with α-diazo esters (Scheme 1d) which were represented as electronically activated and readily bidentate-coordinated ketones. Despite such progress, the challenge remaining in this research field is the asymmetric intermolecular homologation of acyclic aryl alkyl ketones (Scheme 1e).[6] The difficulties mainly stem from the following issues. (1) The acyclic aryl alkyl ketones exhibit low reactivity to undergo the nucleophilic addition of α-diazo esters.[5,6] (2) The chemo- and regioselectivity associated with the homologation reaction of acyclic arylalkyl ketones is complex, in view of the possible rotation of a carbon−carbon bond in the intermediate or reversible addition of a α-diazo ester to a carbonyl group. Once the intermediate **Int**. was formed, both R^2 and the Ar group have the possibity of migrating, resulting in the formation of a mixture of products (path i or ii). Additionally, the nucleophilic attack of an oxygen anion to the diazoalkyl carbon would generate the epoxide byproduct (path iii).[1,5,6,28] (3) The facial selection of both ketones and α-diazo esters through differentiation of two sterically hindered groups is difficult, which has a decisive influence on the regio- and enantioselectivity.[3−6]

Received: December 6, 2020
Published: January 28, 2021

https://dx.doi.org/10.1021/jacs.0c12683
J. Am. Chem. Soc. 2021, 143, 2394−2402

Scheme 1. Enantioselective Homologation of Aldehydes or Ketones with Diazo Compounds



On the basis of the reaction mechanism and previous work,[17,25−27,29] we envisioned that a judicious selection of diazo reagents and chiral catalysts may provide a possible approach to address the above problem. The efficient activation of aryl alkyl ketones with a strong Lewis acid catalyst is necessary to improve their electrophilicity.[5,6,27] Concurrently, the chiral catalyst should be capable of not only differentiating the prochiral faces of both diazo esters and aryl alkyl ketones but also limiting the rotation of the zwitterionic intermediate, thus accelerating the final rearrangement through a stereoscopic confinement effect.[30−35]

Herein, we wish to disclose our endeavor along this line. A chiral scandium(III)-*N*,*N*′-dioxide Lewis acid catalyst[36−42] has been identified to be efficient in promoting the title reaction. Various enantiomerically enriched *β*-keto esters with quaternary stereocenters were afforded in high yield with excellent regioselectivity and enantioselectivity under mild conditions. In addition, cyclic ketones are suitable substrates under slightly modified conditions, yielding the desired ring-expanded cyclic *β*-keto esters in moderate yield with high enantioselectivity. Theoretical calculations were performed to illustrate the role of the catalyst as well as the origin of the observed regio- and enantioselectivity.

2. RESULTS AND DISCUSSION

2.1. Homologation of Aryl Alkyl Ketones with *α*-Diazo Esters. To assess our hypothesis, we began by evaluating the effects of Lewis acid catalysts on the enantioselective homologation of acetophenone (**1a**) and methyl *α*-benzyl-*α*-diazoacetate (**2a**) in dichloromethane. It was found that both the metal salt and the ligand (Figure 1)

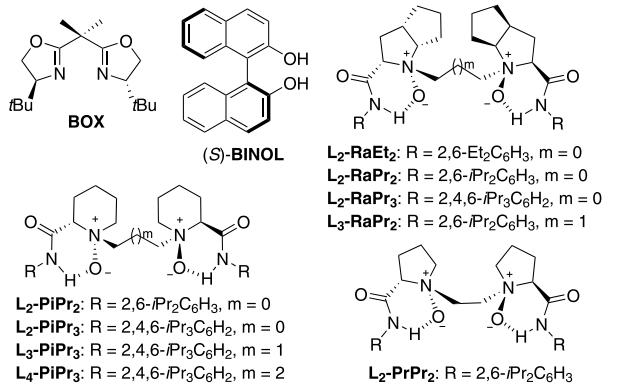
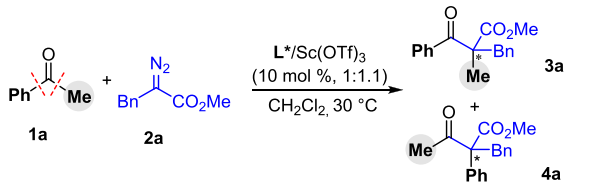


Figure 1. Chiral ligands used in the reaction.

had a significant influence on the reactivity. Almost no reaction occurred in the presence of scandium triflate without a ligand or other metal salt bonded *N*,*N*′-dioxide complexes (Table 1, entry 1, and the Supporting Information). The investigation of

Table 1. Optimization of the Homologation of Acetophenone 1a with *α*-Diazo Ester 2a[a]

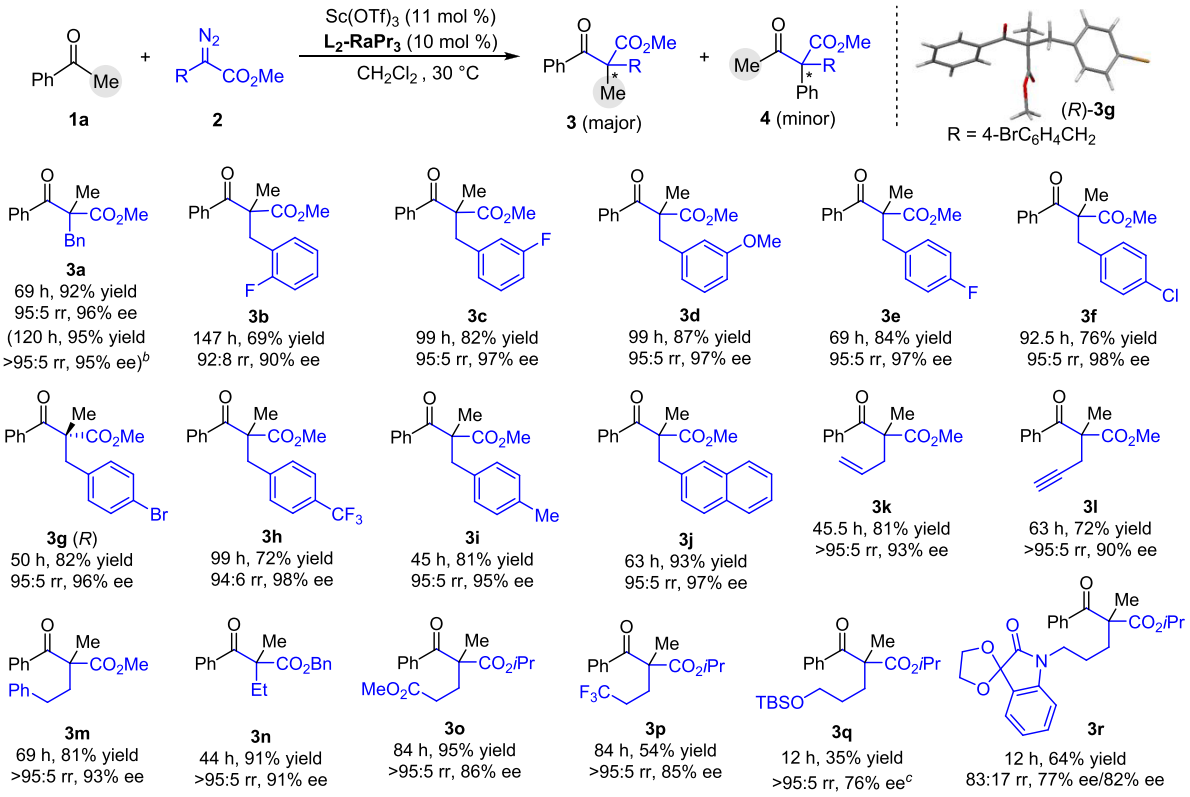


entry	L*	yield (%)	rr (3a:4a)	ee of 3a (%)
1	none	NR		
2	**BOX**	NR		
3[b]	(*S*)-**BINOL**	trace		
4	**L$_3$-PiPr$_3$**	58	95:5	84
5[c]	**L$_4$-PiPr$_3$**	26	90:10	94
6	**L$_2$-PiPr$_3$**	87	95:5	86
7	**L$_2$-PiPr$_2$**	76	91:9	81
8	**L$_2$-PrPr$_2$**	33	91:9	80
9	**L$_2$-RaPr$_2$**	75	92:8	94
10	**L$_3$-RaPr$_2$**	38	89:11	88
11[b]	**L$_2$-RaPr$_2$**	70	92:8	94
12[d]	**L$_2$-RaPr$_2$**	77	92:8	94
13[e]	**L$_2$-RaPr$_3$**	92	95:5	96

[a]Unless otherwise noted, all reactions were performed with Sc(OTf)$_3$ (11 mol %), ligand (10 mol %), **1a** (0.10 mmol), and **2a** (1.0 equiv) in CH_2Cl_2 (0.5 mL) at 30 °C for 45 h. Isolated yields of the mixture of **3a** and **4a** are given. The regio ratio (rr) was determined by ^{1}H NMR analysis, and the ee value was determined by HPLC analysis on a chiral stationary phase. [b]Sc(OTf)$_3$ (10 mol %). [c]117 h. [d]Sc(OTf)$_3$ (10 mol %) and La(OTf)$_3$ (1 mol %). [e]**2a** (1.1 equiv) for 69 h.

https://dx.doi.org/10.1021/jacs.0c12683
J. Am. Chem. Soc. 2021, 143, 2394−2402

Table 2. Scope of α-Diazo Esters 2 with Acetophenone 1a[a]



[a]Unless otherwise noted, all reactions were performed with $Sc(OTf)_3$ (11 mol %), $\mathbf{L_2}$-$\mathbf{RaPr_3}$ (10 mol %), **1a** (0.10 mmol), and **2** (0.11 mmol) in CH_2Cl_2 (0.5 mL) at 30 °C for the indicated time. Isolated yields of the mixture of **3** and **4** are given. The rr was determined by a ^{1}H NMR analysis, and the ee value was determined by HPLC analysis on a chiral stationary phase. [b]**1a** (5 mmol) and **2a** (5.5 mmol) were used. [c]The ee was detected after deprotection of product **3q**; see the Supporting Information for details.

other ligands used in previous studies indicated that the chiral complex **BOX**−$Sc(OTf)_3$ could not promote the reaction (Table 1, entry 2). Utilizing the (*S*)-**BINOL**−$Sc(OTf)_3$ combination in a 1:1 or 2:1 ratio led to the decomposition of diazo ester **2a**, and only a trace amount of the desired product was detected (Table 1, entry 3). To our delight, the reaction took place smoothly in the presence of the chiral *N*,*N*′-dioxide catalyst $\mathbf{L_3}$-$\mathbf{PiPr_3}$−$Sc(OTf)_3$, and the corresponding major product **3a** via methyl migration and the minor product **4a** via phenyl migration were isolated with a total 58% yield with high regioselectivity (95:5 rr) and a promising enantiomeric excess of 84% for **3a** (Table 1, entry 4). These results clearly showed that the chiral *N*,*N*′-dioxide was a robust and unique ligand for such a transformation. Subsequently, careful screening of chiral *N*,*N*′-dioxide ligands implied that the length of the carbon tether displayed a pronounced effect on the reactivity (Table 1, entries 4−6). The yield increased gradually with the linker decreasing from a four- to a two-carbon tether ($\mathbf{L_4}$-$\mathbf{PiPr_3}$ and $\mathbf{L_3}$-$\mathbf{PiPr_3}$ vs $\mathbf{L_2}$-$\mathbf{PiPr_3}$).[43] The ligand $\mathbf{L_2}$-$\mathbf{PiPr_3}$ gave the product in 87% yield, while the ligand $\mathbf{L_4}$-$\mathbf{PiPr_3}$ resulted in a 26% yield after extending the reaction time. Next, an examination of amino acid backbones of the chiral *N*,*N*′-dioxide ligands with a two-carbon linker showed that the *L*-ramipril-derived *N*,*N*′-dioxide $\mathbf{L_2}$-$\mathbf{RaPr_2}$ was superior to others in terms of enantioselectivity, and a 94% ee value was obtained (Table 1, entry 9 vs entries 7 and 8). Comparably, the ligand $\mathbf{L_3}$-$\mathbf{RaPr_2}$ optimized in our previous studies[17,25,27] led to an obvious decrease in yield, regioselectivity, and enantioselectivity (Table 1, entry 10 vs entry 9). It was noteworthy that, although $Sc(OTf)_3$ itself was unable to promote the reaction, an excess amount of the metal salt (1 mol %) in the presence of the ligand was beneficial to the reactivity, since a somewhat lower yield with retained enantioselectivity was obtained with a 1:1 ratio of metal salt to *N*,*N*′-dioxide (entry 11 vs entry 9; 75% vs 70%). Such a positive effect of excess metal precursor on the yield was observed as well when $La(OTf)_3$ (1 mol %) was added to the reaction system (entry 12 vs entry 11; 77% vs 70% yield).[44,45] Finally, the 1,2-methyl-shift product **3a** was obtained in high yield along with good regioselectivity (95:5 rr) and excellent enantioselectivity (96% ee) by employing the more sterically hindered $\mathbf{L_2}$-$\mathbf{RaPr_3}$ as the ligand and a slight excess of diazo ester (1.1 equiv) after 69 h (entry 13).

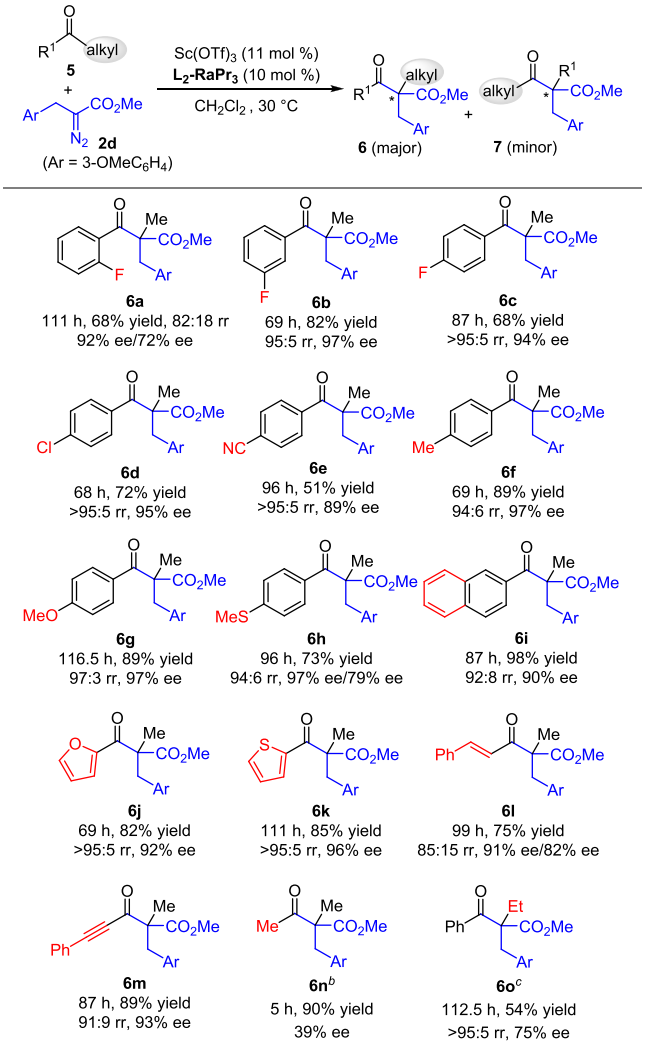
2.2. Substrate Scope. With the optimized conditions in hand (Table 1, entry 13), a broad range of α-benzyl α-diazo esters (**2a**−**i**) were investigated with acetophenone (**1a**) (Table 2). All of them underwent the homologation in good yield (69−92%) with high regioselectivity (Me-shift products; 92:8 to 95:5 rr) and excellent enantioselectivity (90−98% ee). It was found that the position of the substituent at benzyl moiety had a significant influence on the reactivity. An α-diazo ester with a 2-fluorophenyl group showed much lower reactivity, and moderate yield with good regioselectivity and ee value (**3b**; 69% yield, 92:8 rr, 90% ee) was obtained after a longer reaction time (147 h). The electronic nature of the substituent displayed a limited effect on the outcomes (**3c**,**d**; **3h**,**i**). The absolute configuration of the product **3g** was determined to be *R* by X-ray crystallographic analysis, and

https://dx.doi.org/10.1021/jacs.0c12683
J. Am. Chem. Soc. 2021, 143, 2394−2402

some other products exhibited a Cotton effect in the CD spectra similar to that of **3g** (for details, see the Supporting Information). A 2-naphthalenyl-substituted α-diazo ester gave a result comparable to that of a benzyl-substituted α-diazo ester. Moreover, allyl-, alkynyl-, phenylethyl-, and ethyl-substituted α-diazo esters were all well tolerated in the reaction, giving the corresponding products **3k**−**3n** in good yield (72−91% yield) with high regioselectivity (>95:5 rr) and enantioselectivity (90−93% ee). To our delight, highly functionalized α-alkyl α-diazo esters were suitable for this reaction, generating the desired products (**3o**−**r**) in moderate to high yield (35−95% yield) with good regioselectivity and slightly diminished enantioselectivity (83:17 to >95:5 rr, 76−86% ee). To demonstrate the practicability of this transformation, we carried out a gram-scale reaction under the standard conditions. Acetophenone **1a** (5 mmol, 0.60 g) reacted well with α-diazo ester **2a** (5.5 mmol, 1.05 g), delivering the desired product **3a** with the results maintained (1.34 g, 95% yield, >95:5 rr, 95% ee) after a prolonged reaction time (120 h).

Next, various aryl-/alkyl-substituted ketones **5** were examined (Table 3). For substituted acetophenone derivatives (**5a**−**f**), both the electronic and steric properties of the substitutions affected the outcomes of the reaction.[46] The yields of the electron-donating substituted acetophenones could be improved via prolonging the reaction time, while those of electron-deficient species could not be obviously enhanced. The reaction of 2-fluoroacetophenone was slower than those of 3- or 4-haloacetophenones. The desired 1,2-methyl-shift product **6a** was isolated in moderate yield (68%) with lower regioselectivity (82:18 rr) but high enantioselectivity (92% ee). It should be noted that the regioselective isomers could be separated after reduction of the ketone moiety to the corresponding alcohol with $NaBH_4$ (for more details, see page S10 in the Supporting Information). 4-Acetylbenzonitrile exhibited lower reactivity (**6e**; 51%) and enantioselectivity (89% ee), while *p*-tolylethanone performed the reaction with almost maintenance of the results (**6f**; 89% yield, 94:6 rr, 97% ee). 4-Methoxyphenylethanone with an electron-donating group reacted smoothly, and good results (**6g**; 89% yield and 97% ee) could be obtained with an extended reaction time. Notably, a methylthio group, a strongly coordinating moiety which could impair the activity of the metal catalyst, had a negligible effect on the reaction, and 4-methylthiophenylethanone could be transformed efficiently into the desired product **6h**. 2-Acetonaphthone was also suitable for this reaction, and an excellent yield (**6i**; 98%) with high regioselectivity (92:8 rr) and enantioselectivity (90% ee) were achieved. For heteroaryl-substituted ketones, equally good yields with high regioselectivity (**6j**,**k**; >95:5 rr) and ee values (92% and 96% ee, respectively) were obtained. Unsaturated α-methyl ketones, for instance, (*E*)-4-phenylbutenone and 4-phenylbutynone, were applicable substrates in the current reaction, and the desired products **6l**,**m** were afforded with good outcomes.[47] Interestingly, acetone can also undergo homologation with α-diazo ester **2d**, yielding the desymmetrization product **6n** in high yield (90% yield) but very low enantioselectivity (39% ee). To our delight, the reaction of propiophenone with **2d** took place with the use of the less bulky ligand $\mathbf{L_2}$-**RaEt**$_2$ instead, and the desired ethyl-shift product **6o** was isolated in moderate yield (54% yield) and ee value (75% ee). Other alkyl-substituted ketones, for instance, 1-phenylbutan-1-one, were investigated as well;

Table 3. Scope of Acyclic Ketones 5[a]



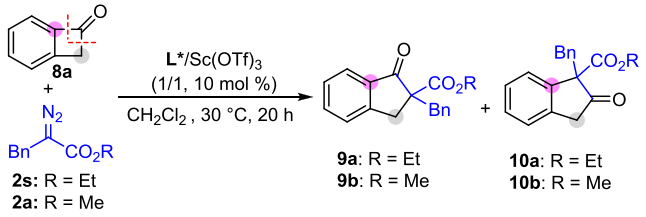
[a]Unless otherwise noted, all reactions were performed with $Sc(OTf)_3$ (11 mol %), $\mathbf{L_2}$-**RaPr**$_3$ (10 mol %), **5** (0.10 mmol), and **2d** (0.11 mmol) in CH_2Cl_2 (0.5 mL) at 30 °C for the indicated time. Isolated yields of a mixture of **6** and **7** are given . The rr was determined by a ^{1}H NMR analysis, and ee value was determined by HPLC analysis on a chiral stationary phase. [b]Acetone **5n** (50 μL) and **2d** (0.1 mmol). [c]$\mathbf{L_2}$-**RaEt**$_2$ (10 mol %) was used.

however, most of them exhibited extremely low reactivity (for more details, see page S7 in the Supporting Information). We envisaged that this dramatic effect could be attributed to steric repulsion. The modulation of the ligand might provide a potential solution to this issue, as indicated in the reaction with propiophenone (**6o**).

2.3. Homologation of Unsymmetrical Cyclic Ketones with α-Diazo Esters. Encouraged by the above results, the enantioselective ring expansion of unsymmetrical cyclic ketones and α-diazo esters was investigated. Initially, benzocyclobutenone (**8a**) and ethyl α-benzyl-α-diazoacetate (**2s**) were selected as the model substrates. In the presence of $Sc(OTf)_3$−$\mathbf{L_2}$-**RaPr**$_2$, the reaction occurred smoothly, generating the alkyl-shift product **9a** in 55% yield with 63% ee (Table 4, entry 1). The NMR spectrum of the crude reaction mixture indicated that the regioisomer **10a** formed via competitive aryl-shift process as well. However, the purification of regioisomer **10a** was unsuccessful due to the other undefined and

https://dx.doi.org/10.1021/jacs.0c12683
J. Am. Chem. Soc. 2021, 143, 2394−2402

Table 4. Optimization of the Homologation of Benzocyclobutenone 8a with α-Diazoester 2[a]



		9		10	
entry	L*	yield (%)	ee (%)	yield (%)[b]	ee (%)
1	L_2-$RaPr_2$	55	63	<30	33
2	L_2-$PiPr_3$	57	82	<30	68
3	L_3-$PiPr_3$	54	85	<39	87
4	L_4-$PiPr_3$	34	90	<43	94
5[c]	L_4-$PiPr_3$	52	92	<40	95

[a]Unless otherwise noted, all reactions were performed with $Sc(OTf)_3$ (10 mol %), ligand (10 mol %), **8a** (0.10 mmol), and **2s** (0.10 mmol) in CH_2Cl_2 (0.5 mL) at 30 °C for 20 h. Isolated yields are given. The ee values were determined by HPLC analysis on a chiral stationary phase. [b]The regioisomer **10** was mixed with other undefined byproducts. [c]$Sc(OTf)_3$ (11 mol %), **8a** (1.5 equiv), and **2a** (0.10 mmol) were used.

inseparable byproducts (for details, see the Supporting Information). Moreover, switching the ligand to L_2-$PiPr_3$ led to an enhancement of enantioselectivity of the alkyl-migration product **9a** (entry 2, 85% ee). When the length of the carbon tether in the chiral *N,N′*-dioxides was increased, a higher enantiomeric excess was afforded but with the decrease in yield (entries 2−4). The use of L_4-$PiPr_3$ gave the product **9a** in 34% yield with 90% ee (entry 4). Finally, by utilizing methyl α-benzyl-α-diazoacetate **2a**, 1.5 equiv of ketone **8a**, and 11 mol % $Sc(OTf)_3$, the ring expansion product **9b** was generated in 52% yield with 92% ee (entry 5).[50] There was no better result after further investigation of other reaction parameters (for details, see the Supporting Information).

2.4. Substrate Scope. After establishing the optimized conditions (Table 4, entry 5), we first examined the generality of α-diazo esters in the reaction with benzocyclobutenone (**8a**) (Table 5). Due to the polarity of aryl-shift products being similar to that of other byproducts, only alkyl-shift products **9** were isolated in most cases (for details, see the Supporting Information). A 2-fluorophenyl-bearing α-diazo ester showed a lower reactivity, affording a slight decrease in yield and ee value (**9c**; 39% yield, 85% ee). Meanwhile, in this case, pure regioisomer **10c** could be obtained in 46% yield with 91% ee. The absolute configuration of the corresponding products **9c** and **10c** were determined to be *R* via an X-ray crystallographic analysis, and most of the others had Cotton effects in the CD spectra similar to that of **9c** (for details, see the Supporting Information). For other substituted α-benzyl α-diazo esters, the electronic properties of a substituent at the *meta* or *para* position of the phenyl ring had a negligible effect on the enantioselectivity, generating the alkyl-shift products (**9d−m**) in modest yield and high ee value (37−47% yield, 90−92% ee). A 2-naphthyl-substituted α-diazo ester was well tolerated in the reaction (**9n**). Other α-diazo esters with unsaturated moieties, such as allyl or alkynyl, were compatible with this catalytic system (**9o,p**). Ethylphenyl-, dodecyl-, and methyl-substituted α-diazo esters showed higher reactivity, and the corresponding ring-expansion products (**9q−s**) were isolated in moderate yields with good ee values (21−51% yield, 89−92% ee).

Then, the representative cyclic ketones **11** were tested (Table 5). The reactions with 6-alkoxybenzocyclobutenone derivatives were smooth, yielding the desired products **12a−d** in acceptable yields (50−64% yield) with excellent ee values (90−97% ee). For the reaction of 5,6-dimethoxybenzocyclobutenone, the ligand L_2-$PiPr_3$ was used instead of L_4-$PiPr_3$ to afford a moderate yield and enantioselectivity (**12c**). Five-membered cyclic ketones are more challenging substrates according to the literature.[51] To our delight, 1-indanone can also undergo ring expansion smoothly with L_2-$PiPr_3$ as the ligand, forming the substituted 1-tetralone **12e** in good yield, regioselectivity, and enantioselectivity (60% yield, 91:9 rr, 88% ee). It should be noted that the α-amination product of 1-indanone was not detected at all,[52] which probably results from the change in ligand as well as the basic conditions in our previous study. In addition, 3-phenylcyclobutenone transformed into **12f** in moderate yield and ee (60% yield, 52% ee). Furthermore, the desymmetrization of cyclobutanone occurred under the standard conditions, generating the corresponding cyclopentanone derivative **12g** in high yield (86%) but with poor ee. Unfortunately, 1-tetralone, cyclopentanone, and cyclooctenone were sluggish in the current catalytic system (for more details, see the Supporting Information).

2.5. Mechanism Studies. To gain insights into the reactivity and the origin of enantioselectivity of the homologation of ketones, we carried out DFT calculations using the ligand L_2-$RaPr_2$. The discussion here is based on the data calculated on CPCM (dichloromethane) at the M06L/Def2-TZVP//B3LYP-D3/6-31G(d,p), SDD(Sc) level of theory. All of the calculations were performed using Gaussian 09 software; see the Supporting Information for details.[53]

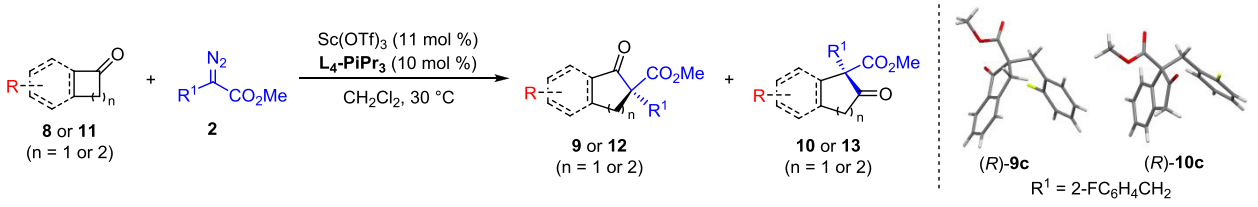
Although a water-bonded Sc(III) complex was crystallized (Figure 2, left),[29] the calculation result suggests that replacement of water by acetophenone gives a more stable species that can be considered as a reactive species for mechanistic investigations (for more details, see the Supporting Information). Next we examined the complexation of one acetophenone molecule to a chiral tetradentate *N,N′*-dioxide ligand bonded to Sc(III) (Figure 2). Two complexes, **Add** and **Add′** (Figure 2), are nearly energetically degenerate with a 0.8 kcal/mol difference. As such, both conformers were considered in the following steps. In addition, indirect evidence for the binding of TfO^- on Sc(III) is presented in the Supporting Information. Moreover, the coordination of an ester on Sc(III) was ruled out; see the Supporting Information for details.

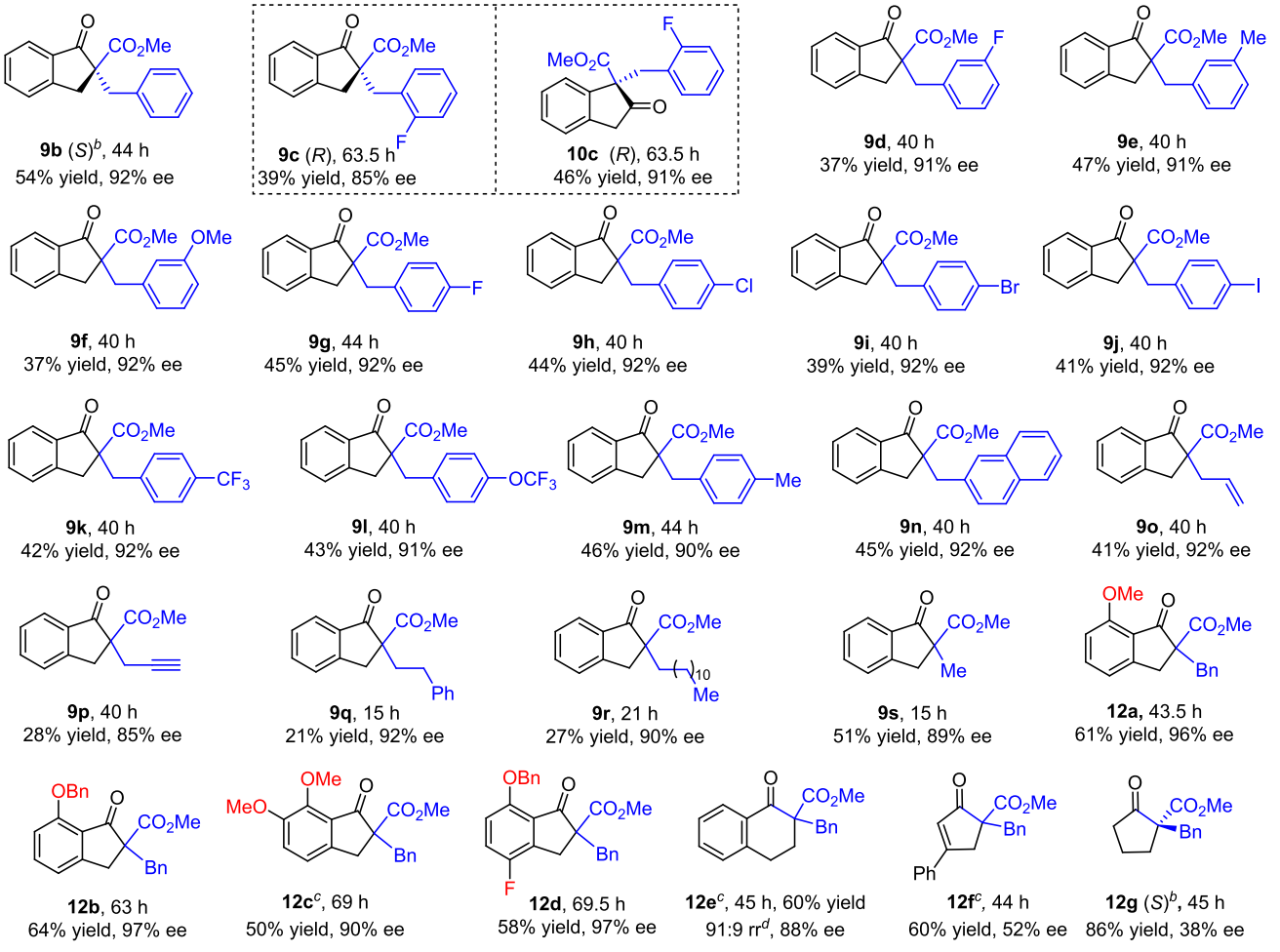
Second, α-diazo ester nucleophilically adds to **Add** and **Add′**. Diverse intermediates were formed via the corresponding transition states **TS1** (Figure 3 and the Supporting Information). Finally, the carbon−nitrogen bond of the intermediates is cleaved (**TS2**), leading to the simultaneous release of N_2 and alkyl migration for the resulting products. This step is shown to be the rate-determining step (Figure 3). This is in agreement with the influence of the electronic nature of the substituents on acetophenone, where an electron-withdrawing substituent did not accelerate the reaction due to the instability of the corresponding intermediates, although the nucleophilic addition step might be easier.

The main product **3a** is given by the transition state $TS2_R$, in which the leaving N_2 is antiperiplanar to a migrating alkyl (or aryl) group of diazo for a concerted process, and steric repulsion between the bulky $-CO_2Me$ and $-N_2$ of α-diazo

https://dx.doi.org/10.1021/jacs.0c12683
J. Am. Chem. Soc. 2021, 143, 2394−2402

Table 5. Scope of α-Diazo Esters 2 with Cyclic Ketones[a]





[a]Unless otherwise noted, all reactions were performed with $Sc(OTf)_3$ (11 mol %), L_4-**PiPr**$_3$ (10 mol %), **8a** or **11** (0.15 mmol), and **2** (0.10 mmol) in CH_2Cl_2 (0.5 mL) at 30 °C for the indicated time. Isolated yields are given. The ee values were determined by HPLC analysis on a chiral stationary phase. [b]The absolute configuration was determined by a comparison of the optical rotation with the corresponding literature value.[48,49] [c]L_2-**PiPr**$_3$ (10 mol %) was used. [d]The rr was determined by a ^{1}H NMR analysis.

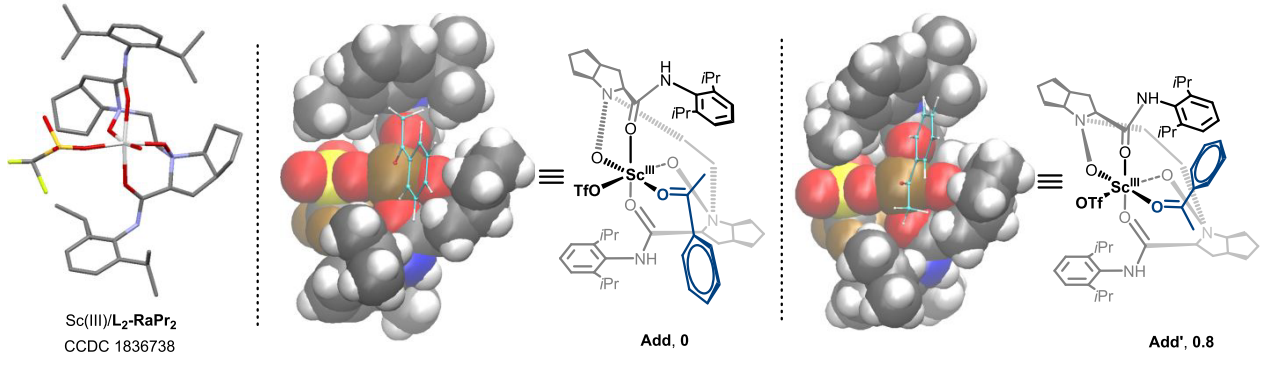


Figure 2. Two binding modes of ketone to Sc(III).

https://dx.doi.org/10.1021/jacs.0c12683
J. Am. Chem. Soc. 2021, 143, 2394−2402

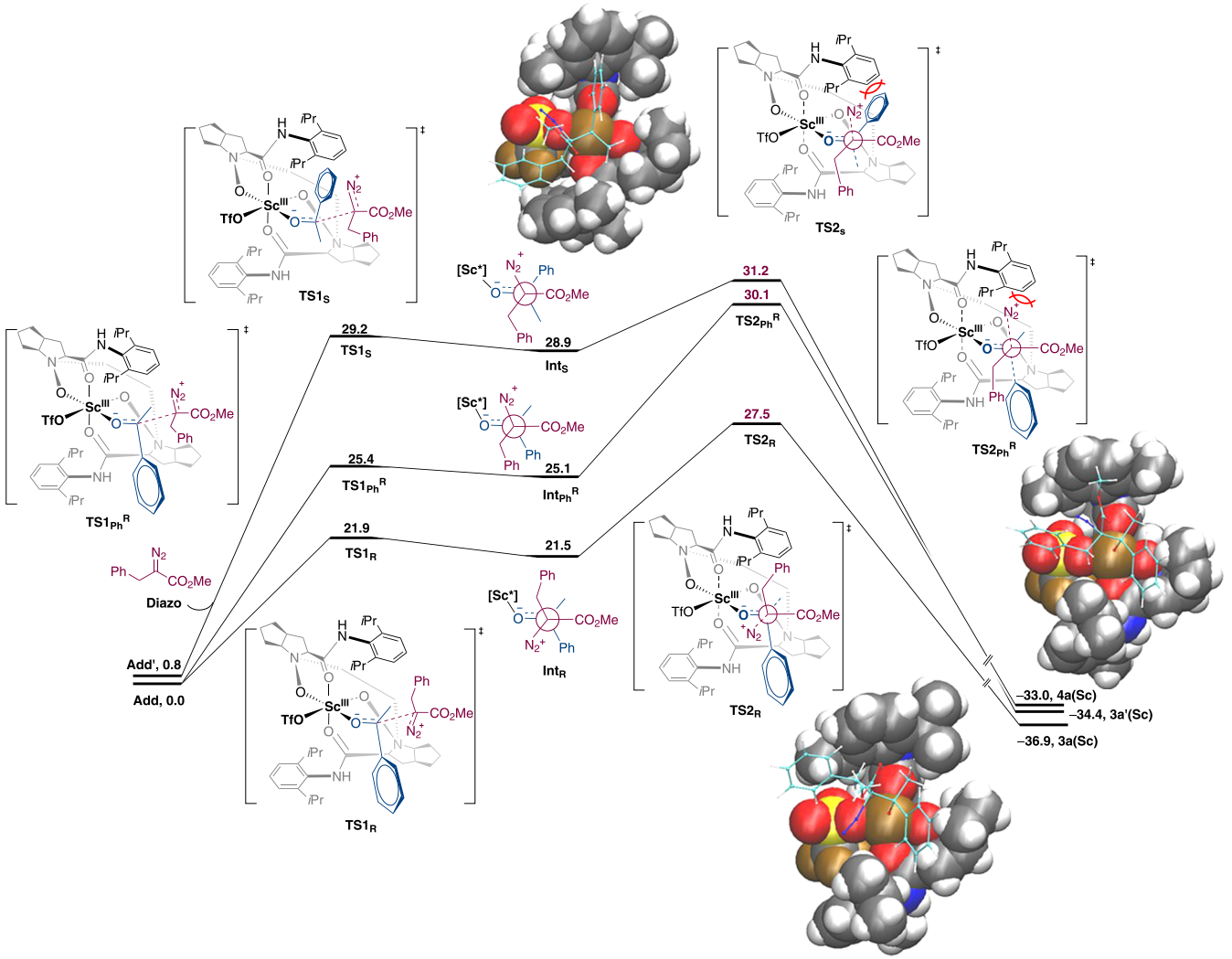


Figure 3. Free energy profile for *R*-**3a**, *R*-**4a**, and *S*-**3a** (**3a′**) calculated using CPCM (dichloromethane) at the M06L/Def2-TZVP//B3LYP-D3/6-31G(d,p), SDD(Sc) level of theory.

ester with the aryl on the chiral *N*,*N*′-dioxide ligand is prevented. Also, the phenyl migration product (*R*)-**4a** is generated via $\mathbf{TS2_{Ph}}^{R}$, in which the N_2 extrusion directionality points toward the metal−ligand complex and steric repulsion between $-CO_2Me$ and the aryl of the dioxide ligand is present (2.6 kcal/mol higher in energy than $\mathbf{TS2_R}$). However, **3a′** with an *S* configuration as a minor product is given by the transition state $\mathbf{TS2_S}$ derived from **Add′**. Moreover, other high energy transition states for N_2-release/methyl (or phenyl)-migration processes are shown in the Supporting Information as well.

3. CONCLUSION

In summary, the efficient catalytic asymmetric intermolecular homologation of acetophenone derivatives with α-diazo esters was accomplished under mild conditions. The key to success is the use of a chiral *N*,*N*′-dioxide−$Sc(OTf)_3$ complex as the chiral Lewis catalyst, which enabled the activation of acetophenone derivatives and precisely controlled the stereoselectivity of the addition/rearrangement process. This protocol provided a rapid and facile route to chiral acyclic β-keto esters with a quaternary carbon center in high yield with excellent regioselectivity and enantioselectivity. This transformation could be scaled up to gram scale without erosion of reactivity and enantioselectivity. Moreover, the ring expansion of benzocyclobutenone derivatives with α-diazo esters to deliver various cyclic β-keto esters was compatible under slightly modified conditions, and a number of enantioenriched cyclic β-keto esters were readily afforded. In addition, DFT calculations were conducted to understand the activation mode and the origin of regioselectivity and enantioselectivity. Further application of this reaction in organic synthesis and the exploration of other reactions with α-diazo esters are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12683.

Detailed experimental procedures, characterization data for all new compounds, ^{1}H, $^{19}F\{^{1}H\}$, and $^{13}C\{^{1}H\}$ NMR and HPLC spectra, and computational studies (PDF)

Accession Codes

CCDC 1951827, 1951831, and 1959085 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.

https://dx.doi.org/10.1021/jacs.0c12683
J. Am. Chem. Soc. 2021, 143, 2394−2402

uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

Xiaohua Liu − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China;* orcid.org/0000-0001-9555-0555; Email: liuxh@scu.edu.cn

Yun-Dong Wu − *Shenzhen Bay Laboratory, Shenzhen 518055, People's Republic of China; Lab of Computational Chemistry and Drug Design, State Key Laboratory of Chemical Oncogenomics, Peking University Shenzhen Graduate School, Shenzhen 518055, People's Republic of China;* orcid.org/0000-0003-4477-7332; Email: wuyd@pkusz.edu.cn

Xiaoming Feng − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China;* orcid.org/0000-0003-4507-0478; Email: xmfeng@scu.edu.cn

Authors

Fei Tan − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China*

Maoping Pu − *Shenzhen Bay Laboratory, Shenzhen 518055, People's Republic of China;* orcid.org/0000-0002-0745-9549

Jun He − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China*

Jinzhao Li − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China*

Jian Yang − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China*

Shunxi Dong − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China;* orcid.org/0000-0002-3018-3085

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c12683

Author Contributions

‖F.T. and M.P. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge financial support from the National Natural Science Foundation of China (grant nos. 21890723 and 21625205). We thank Dr. Yuqiao Zhou (Sichuan University) for help in X-ray single-crystal analysis.

REFERENCES

(1) Ye, T.; McKervey, M. A. Organic synthesis with α-diazocarbonyl compounds. *Chem. Rev.* **1994**, *94*, 1091−1160.

(2) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*. Wiley: New York, 1998.

(3) Zhang, Z.; Wang, J. Recent studies on the reactions of α-diazocarbonyl compounds. *Tetrahedron* **2008**, *64*, 6577−6605.

(4) Zhang, Y.; Wang, J. Recent development of reactions with α-diazocarbonyl compounds as nucleophiles. *Chem. Commun.* **2009**, 5350−5361.

(5) Moebius, D. C.; Rendina, V. L.; Kingsbury, J. S. Catalysis of Diazoalkane−Carbonyl Homologation. How New Developments in Hydrazone Oxidation Enable a Carbon Insertion Strategy for Synthesis. *Top. Curr. Chem.* **2014**, *346*, 111−162.

(6) Candeias, N. R.; Paterna, R.; Gois, P. M. P. Homologation reaction of ketones with diazo compounds. *Chem. Rev.* **2016**, *116*, 2937−2981.

(7) Guttenberger, N.; Breinbauer, R. C−H and C−C bond insertion reactions of diazo compounds into aldehydes. *Tetrahedron* **2017**, *73*, 6815−6829.

(8) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. Selective homologation of ketones and aldehydes with diazoalkanes promoted by organoaluminum reagents. *Synthesis* **1994**, *1994*, 1283−1290.

(9) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. Diverse alkanones by catalytic carbon insertion into the formyl C−H bond. Concise access to the natural precursor of achyrofuran. *Org. Lett.* **2009**, *11*, 3202−3205.

(10) Moebius, D. C.; Kingsbury, J. S. Catalytic homologation of cycloalkanones with substituted diazomethanes. Mild and efficient single-step access to α-tertiary and α-quaternary carbonyl compounds. *J. Am. Chem. Soc.* **2009**, *131*, 878−879.

(11) Greene, A. E.; Luche, M. J.; Serra, A. A. An efficient, enantioconvergent total synthesis of natural hirsutic acid C. *J. Org. Chem.* **1985**, *50*, 3957−3962.

(12) Ahmad, Z.; Goswami, P.; Venkateswaran, R. V. A formal stereocontrolled synthesis of (±) isoclovene. *Tetrahedron* **1989**, *45*, 6833−6840.

(13) Honda, T.; Ishige, H.; Nagase, H. Chiral synthesis of a trinorguaiane sesquiterpene, clavukerin A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3305−3310.

(14) Hamelin, O.; Deprés, J. P.; Greene, A. E. Highly stereoselective first synthesis of an A-ring-functionalized bakkane: Novel free-radical approach to 9-acetoxyfukinanolide. *J. Am. Chem. Soc.* **1996**, *118*, 9992−9993.

(15) Yamashita, M.; Ohta, N.; Shimizu, T.; Matsumoto, K.; Matsuura, Y.; Kawasaki, I.; Tanaka, T.; Maezaki, N.; Ohta, S. First total synthesis of (±)-Linderol A, a tricyclic hexahydrodibenzofuran constituent of Lindera umbellata bark, with potent inhibitory activity on melanin biosynthesis of cultured B-16 melanoma cells. *J. Org. Chem.* **2003**, *68*, 1216−1224.

(16) Hashimoto, T.; Naganawa, Y.; Maruoka, K. Brønsted acid-catalyzed insertion of aryldiazoacetates to sp^2 carbon−CHO bond: Facile construction of chiral all-carbon quaternary center. *J. Am. Chem. Soc.* **2008**, *130*, 2434−2435.

(17) Li, W.; Wang, J.; Hu, X. L.; Shen, K.; Wang, W. T.; Chu, Y. Y.; Lin, L. L.; Liu, X. H.; Feng, X. M. Catalytic asymmetric Roskamp reaction of α-alkyl-α-diazoesters with aromatic aldehydes: Highly enantioselective synthesis of α-alkyl-β-keto esters. *J. Am. Chem. Soc.* **2010**, *132*, 8532−8533.

(18) Hassner, A.; Namboothiri, I. In *Organic Syntheses Based on Name Reactions*, 3rd ed.; Elsevier: Oxford, 2011; p 408.

(19) Gao, L.; Kang, B. C.; Hwang, G.-S.; Ryu, D. H. Enantioselective synthesis of α-alkyl-β-ketoesters: Asymmetric Roskamp reaction catalyzed by an oxazaborolidinium ion. *Angew. Chem., Int. Ed.* **2012**, *51*, 8322−8325.

(20) Gao, L.; Kang, B. C.; Ryu, D. H. Catalytic asymmetric insertion of diazoesters into aryl−CHO bonds: Highly enantioselective

construction of chiral all-carbon quaternary centers. *J. Am. Chem. Soc.* **2013**, *135*, 14556−14559.
(21) Kim, J. Y.; Kang, B. C.; Ryu, D. H. Catalytic asymmetric Roskamp reaction of silyl diazoalkane: Synthesis of enantioenriched α-silyl ketone. *Org. Lett.* **2017**, *19*, 5936−5939.
(22) Hashimoto, T.; Naganawa, Y.; Maruoka, K. Desymmetrizing asymmetric ring expansion: stereoselective synthesis of 7-membered cyclic β-keto carbonyl compounds with an α-hydrogen. *Chem. Commun.* **2010**, *46*, 6810−6812.
(23) Hashimoto, T.; Naganawa, Y.; Maruoka, K. Desymmetrizing asymmetric ring expansion of cyclohexanones with α-diazoacetates catalyzed by chiral aluminum Lewis acid. *J. Am. Chem. Soc.* **2011**, *133*, 8834−8837.
(24) Rendina, V. L.; Moebius, D. C.; Kingsbury, J. S. An enantioselective synthesis of 2-aryl cycloalkanones by Sc-catalyzed carbon insertion. *Org. Lett.* **2011**, *13*, 2004−2007.
(25) Li, W.; Liu, X. H.; Hao, X. Y.; Cai, Y. F.; Lin, L. L.; Feng, X. M. A catalytic asymmetric ring-expansion reaction of isatins and α-alkyl-α-diazoesters: Highly efficient synthesis of functionalized 2-quinolone derivatives. *Angew. Chem., Int. Ed.* **2012**, *51*, 8644−8647.
(26) Li, W.; Liu, X. H.; Tan, F.; Hao, X. Y.; Zheng, J. F.; Lin, L. L.; Feng, X. M. Catalytic asymmetric homologation of α-ketoesters with α-diazoesters: Synthesis of succinate derivatives with chiral quaternary centers. *Angew. Chem., Int. Ed.* **2013**, *52*, 10883−10886.
(27) Li, W.; Tan, F.; Hao, X. Y.; Wang, G.; Tang, Y.; Liu, X. H.; Lin, L. L.; Feng, X. M. Catalytic asymmetric intramolecular homologation of ketones with α-diazoesters: Synthesis of cyclic α-aryl/alkyl β-ketoesters. *Angew. Chem., Int. Ed.* **2015**, *54*, 1608−1611.
(28) Gutsche, C. D. The reaction of diazomethane and its derivatives with aldehydes and ketones. *Org. React.* **2011**, *8*, 364−430.
(29) Tan, F.; Liu, X. H.; Wang, Y.; Dong, S. X.; Yu, H.; Feng, X. M. Chiral Lewis acid catalyzed reactions of α-diazoester derivatives: Construction of dimeric polycyclic compounds. *Angew. Chem., Int. Ed.* **2018**, *57*, 16176−16179.
(30) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. Stereoselective cyclopropanation reactions. *Chem. Rev.* **2003**, *103*, 977−1050.
(31) Desimoni, G.; Faita, G.; Jørgensen, K. A. C_2-Symmetric chiral bis(oxazoline) ligands in asymmetric catalysis. *Chem. Rev.* **2006**, *106*, 3561−3651.
(32) Garcia, J. I.; Jimenez-Oses, G.; Lopez-Sanchez, B.; Mayoral, J. A.; Velez, A. Stereoselectivity induced by support confinement effects. Aza-pyridinoxazolines: A new family of C_1-symmetric ligands for copper-catalyzed enantioselective cyclopropanation reactions. *Dalton Trans.* **2010**, *39*, 2098−2107.
(33) Davies, H. M. L.; Morton, D. Guiding principles for site selective and stereoselective intermolecular C−H functionalization by donor/acceptor rhodium carbenes. *Chem. Soc. Rev.* **2011**, *40*, 1857−1869.
(34) Pan, X. L.; Bao, X. H. The effects of confinement inside carbon nanotubes on catalysis. *Acc. Chem. Res.* **2011**, *44* (8), 553−562.
(35) Contreras, C. B.; Azzaroni, O.; Soler-Illia, G. J. A. A. 1.16 Use of confinement effects in mesoporous materials to build tailored nanoarchitectures. In *Comprehensive Nanoscience and Nanotechnology*, 2nd ed.; Elsevier: 2019; pp 331−348.
(36) Feng, X. M.; Liu, X. H. In *Scandium: Compounds, Productions and Applications*; Nova Science: 2011; pp 1−47.
(37) Liu, X. H.; Lin, L. L.; Feng, X. M. Chiral *N,N′*-dioxides: New ligands and organocatalysts for catalytic asymmetric reactions. *Acc. Chem. Res.* **2011**, *44*, 574−587.
(38) Liu, X. H.; Lin, L. L.; Feng, X. M. Chiral *N,N′*-dioxides: Synthesis, coordination chemistry and asymmetric catalysis. *Org. Chem. Front.* **2014**, *1*, 298−302.
(39) Liu, X. H.; Zheng, H. F.; Xia, Y.; Lin, L. L.; Feng, X. M. Asymmetric cycloaddition and cyclization reactions catalyzed by chiral *N,N′*-dioxide−metal complexes. *Acc. Chem. Res.* **2017**, *50*, 2621−2631.
(40) Liu, X. H.; Dong, S. X.; Lin, L. L.; Feng, X. M. Chiral amino acids-derived catalysts and ligands. *Chin. J. Chem.* **2018**, *36*, 791−797.
(41) Wang, Z.; Liu, X. H.; Feng, X. M. Asymmetric catalysis enabled by chiral *N,N′*-dioxide−nickel(II) complexes. *Aldrichim. Acta* **2020**, *53*, 3−10.
(42) Lin, X. B.; Tan, Z.; Yang, W. K.; Yang, W.; Liu, X. H.; Feng, X. M. Chiral cobalt(II) complex catalyzed asymmetric [2,3]-sigmatropic rearrangement of allylic selenides with α-diazo pyrazoleamides. *CCS Chem.* **2020**, *2*, 1423−1433.
(43) An *N,N′*-dioxide with a shorter tether can provide a smaller chiral pocket, which probably increases the interaction of substrates, thus improving the reactivity and results.
(44) Zhou, L.; Liu, X. H.; Ji, J.; Zhang, Y. H.; Hu, X. L.; Lin, L. L.; Feng, X. M. Enantioselective Baeyer-Villiger oxidation: Desymmetrization of meso cyclic ketones and kinetic resolution of racemic 2-arylcyclohexanones. *J. Am. Chem. Soc.* **2012**, *134*, 17023−17026.
(45) Hu, H. P.; Xu, J. X.; Wang, F.; Dong, S. X.; Liu, X. H.; Feng, X. M. Chiral Sc^{III}-*N,N′*-dioxide-catalyzed 1,3-dipolar cycloaddition of diaziridines with chalcones. *Org. Lett.* **2020**, *22*, 93−97.
(46) The Hammett plot of the relationship between the substituents and reactivity showed a nonlinear relationship, indicating a complicated reaction process. For a detailed analysis, see pages S27−S32 in the Supporting Information.
(47) Zhao, P.; Zeng, Z.; Feng, X. M.; Liu, X. H. Multisubstituted pyrazole synthesis via [3 + 2] cycloaddition/rearrangement/N−H insertion cascade reaction of α-diazoesters and ynones. *Chin. Chem. Lett.* **2021**, *32*, 132−135.
(48) Falk, H.; Fröstl, W.; Schlögl, K. Darstellung und absolute konfiguration von optisch aktivem 2,2′-spiro-biindanon-1. *Tetrahedron Lett.* **1974**, *15*, 217−220.
(49) Wang, Y.; Li, Y.; Lian, M.; Zhang, J.; Liu, Z.; Tang, X.; Yin, H.; Meng, Q. Asymmetric α-alkylation of cyclic β-keto esters and β-keto amides by phase-transfer catalysis. *Org. Biomol. Chem.* **2019**, *17*, 573−584.
(50) The ^{1}H NMR spectrum of the crude reaction mixture indicated that the ratio of alkyl-migration product **9b** to aryl-migration product **10b** was ca. 1:1, and the ratio of **9a** to **10a** was around 0.74:1. For more details, see page S24 in the Supporting Information.
(51) The reactivity of cyclic ketones follows the general order of rings with 3 > 4 > 6 > 7 ≥ 5 members; see: Wovkulich, P. M. 3.3 Skeletal Reorganizations: Chain Extension and Ring Expansion. In *Comprehensive Organic Synthesis*; Fleming, B. M. T., Ed.; Pergamon: Oxford, 1991; pp 844−861.
(52) Li, W.; Liu, X. H.; Hao, X. Y.; Hu, X. L.; Chu, Y. Y.; Cao, W. D.; Qin, S.; Hu, C. W.; Lin, L. L.; Feng, X. M. New electrophilic addition of α-diazoesters with ketones for enantioselective C−N bond formation. *J. Am. Chem. Soc.* **2011**, *133*, 15268−15271.
(53) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, M. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Rev. D.01*; Gaussian, Inc.: Wallingford, CT, 2009.

https://dx.doi.org/10.1021/jacs.0c12683
J. Am. Chem. Soc. 2021, 143, 2394−2402