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# Asymmetric Baeyer–Villiger oxidation: classical and parallel kinetic resolution of 3-substituted cyclohexanones and desymmetrization of *meso*-disubstituted cycloketones†

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Regioselectivity is a crucial issue in Baeyer–Villiger (BV) oxidation. To date, few reports have addressed asymmetric BV oxidation of 3-substituted cycloketones due to the high difficulty of controlling regio- and stereoselectivity. Herein, we report the asymmetric BV oxidation of 3-substituted and *meso*-disubstituted cycloketones with chiral *N*,*N*′-dioxide/Sc(III) catalysts performed in three ways: classical kinetic resolution, parallel kinetic resolution and desymmetrization. The methodology was applied in the total and formal synthesis of bioactive compounds and natural products. Control experiments and calculations demonstrated that flexible and adjustable catalysts played a significant role in the chiral recognition of substrates.

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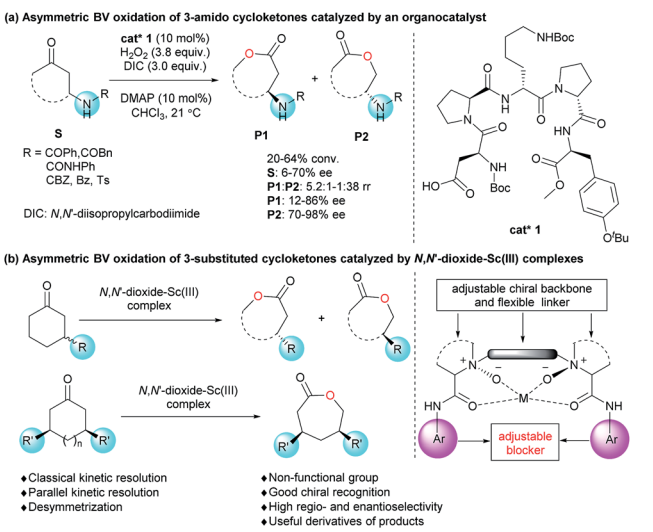
## Introduction

Asymmetric Baeyer–Villiger oxidation provides direct, efficient access to chiral lactones from cycloketones,[1–3] including kinetic resolution of racemic cycloketones and desymmetrization of mesomeric cycloketones. Classical kinetic resolution (CKR) and parallel kinetic resolution (PKR) are two main sub-categories in kinetic resolution reactions. Impressive developments have been made in the CKR of highly ring-strained 2-substituted monocyclic ketones and bicyclic cyclobutanones *via* BV oxidation.[4] PKR enabled the generation of two regioisomers of lactones. Several examples related to bicyclic cyclobutanones were realized, yet high ee values could not be obtained for both regioisomers simultaneously.[5] Previously reported desymmetrization of cycloketones *via* BV oxidation mainly focused on 3-substituted cyclobutanones and 4-substituted cyclohexanones.[6,7] Systematic studies on mesomeric disubstituted cycloketones are scarce; only 3,5-*cis*-dimethyl cyclohexanone was discussed in biocatalytic cases.[7d,f] To sum up, despite remarkable advancements in asymmetric BV oxidation, the scope of substrates is still limited. Meanwhile, to develop an efficient catalytic system that can promote all three above-mentioned types of Baeyer–Villiger oxidation reactions is also highly meaningful.[4b,6b,7e]

On the other hand, regioselectivity has long been a "camphor mystery" in BV oxidation.[2c,8] In comparison with 2-substituted cyclic ketones, asymmetric BV oxidation of 3-substituted cyclic ketones (cyclopentanones and cyclohexanones) was less discussed owing to the high difficulty to control regio- and stereoselectivity.[9] Several biocatalyst-promoted reactions have been reported with moderate stereoselectivity[9c] or regioselectivity.[9a,b,d] In 2014, Miller's group developed the asymmetric BV




Scheme 1 Asymmetric Baeyer–Villiger oxidation of 3-substituted cycloketones.

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† Electronic supplementary information (ESI) available: $^{1}$H, $^{13}$C, $^{19}$F NMR, and HPLC spectra (PDF). X-ray crystallographic data for **5a**, **L-RaPr$_2$-*t*Bu**/Sc(OTf)$_3$ (CIF). CCDC 1848335 and 1856535. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc01563a

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oxidation of 3-substituted cycloketones with a peptide-based organocatalyst, where hydrogen bonding between the catalyst and the functional groups of the substrates resulted in moderate to good regio- and stereoselectivities (Scheme 1a).[9f]

The induced-fit model of BV oxidation in biocatalysis provides such a sight of view for molecular catalysts that a conformationally flexible structure can streamline the adjustment of catalysts toward cycloketones with different configurations and conformations, leading to high regio- and stereo-selectivity.[4d,4f,7c,10] The privileged chiral *N*,*N*′-dioxide, bearing a catenulate alkyl linker as well as two backbones and aniline groups bound to Lewis acids, is by nature a flexible structure,[11] which forms an adjustable blocker for chiral recognition. Herein, we describe novel CKR, PKR and desymmetrization of 3-substituted cycloketones (non-functional group) with a single chiral *N*,*N*′-dioxide/Sc(III) catalytic system (Scheme 1b).

## Results and discussion

Our investigation began with the CKR of racemic 3-phenyl cyclohexanone (**1a**) by using *m*-chloro peroxobenzoic acid (*m*-CPBA, 0.5 equiv.) as an oxidant in the presence of 5 mol% **L-PrPr$_2$**/Sc(OTf)$_3$ complex in EtOAc at 30 °C (Table 1, entry 1). The corresponding mixture of lactones **2a** and **3a** was obtained in moderate yield with poor regio- and stereoselectivity, while racemic **1a** was recovered. Next, the backbones of the chiral *N*,*N*′-dioxide ligands were evaluated and found to have an important effect on the regio- and stereoselectivity (Fig. 1). **L-RaPr$_2$** derived from L-ramipril was superior to L-proline-derived **L-PrPr$_2$** and L-pipecolic acid derived **L-PiPr$_2$** (Table 1, entry 3 *vs.* 1–2). Both regio- and stereoselectivity of the reaction were improved by introducing a bulky group into the para-position of the phenyl group in the ligand (Table 1, entries 4 and 5). For instance, the ligand **L-RaPr$_2$-*t*Bu** bearing *tert*-butyl groups, coordinated with Sc(OTf)$_3$, catalyzed the reaction and gave a mixture of **2a** and **3a** in an 83 : 17 ratio with 81% ee of **2a** (Table 1, entry 5). Upon lowering the temperature to 0 °C, the ratio of **2a** to **3a** could be improved to 85 : 15 and the ee value of **2a** was increased to 85% in 12 h (Table 1, entry 6). However, upon further decreasing the temperature to −20 °C, no better result was achieved (Table 1, entry 7). To our delight, the regio- and stereoselectivity had a significant improvement with the addition of Al(Oi-Pr)$_3$[4e,6f] (**2a** : **3a** = 91 : 9, 93% ee of **2a**, and 81% ee of recovered **1a**), albeit with prolonged reaction time (72 h) (Table 1, entry 8). It was found that when Al(Oi-Pr)$_3$ and 3 Å MS were both used as additives, optimal reaction results could be obtained within 48 h (Table 1, entry 9, 48% yield of the mixture of **2a** and **3a**, **2a**:**3a** = 92 : 8, 93% ee of **2a**, 48% yield of **1a**, and 82% ee of **1a**).

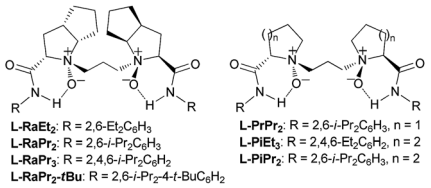
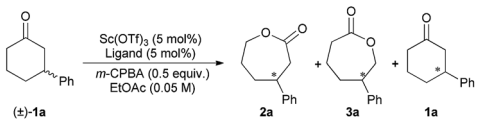



Fig. 1 Chiral *N*,*N*′-dioxide ligands used in this work.

The substrate scope of CKR was then explored. A range of racemic 3-aryl cyclohexanones were transformed into the corresponding lactones smoothly under the optimized reaction conditions. Regardless of the presence of electron donating or withdrawing groups on the 3-phenyl group, excellent yields and moderate to good regioselectivities with good ee values of **2a**–**2g** were obtained (Table 2, entries 1–7, 45–49% yields, 85–93% ee of **2**, and up to 95 : 5 rr). For the condensed-ring substrate **1h**

Table 1 Condition optimization for the CKR of racemic 3-phenyl cyclohexanones




| Entry[a] | Ligand | *T* (°C) | Additives | Yield[b] (%) 1a | 2a + 3a | 2a : 3a[c] | ee[c] (%) 1a | 2a | 3a |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **L-PrPr$_2$** | 30 | — | 61 | 33 | 50 : 50 | 1 | 9 | 5 |
| 2 | **L-PiPr$_2$** | 30 | — | 49 | 50 | 51 : 49 | 2 | 23 | 17 |
| 3 | **L-RaPr$_2$** | 30 | — | 47 | 43 | 75 : 25 | 13 | 69 | 84 |
| 4 | **L-RaPr$_3$** | 30 | — | 49 | 51 | 82 : 18 | 42 | 77 | 72 |
| 5 | **L-RaPr$_2$-*t*Bu** | 30 | — | 48 | 48 | 83 : 17 | 54 | 81 | 78 |
| 6[d] | **L-RaPr$_2$-*t*Bu** | 0 | — | 53 | 44 | 85 : 15 | 62 | 85 | 68 |
| 7[e] | **L-RaPr$_2$-*t*Bu** | −20 | — | 73 | 25 | 89 : 11 | 24 | 73 | 89 |
| 8[ef] | **L-RaPr$_2$-*t*Bu** | −20 | Al(Oi-Pr)$_3$ | 49 | 50 | 91 : 9 | 81 | 93 | 96 |
| 9[g] | **L-RaPr$_2$-*t*Bu** | −20 | 3 Å MS | 48 | 48 | 92 : 8 | 82 | 93 | 91 |

[a] Unless otherwise specified, the reaction was performed with Sc(OTf)$_3$ (5 mol%), ligand (5 mol%), **1a** (0.20 mmol) and *m*-CPBA (0.5 equiv.) in EtOAc (0.05 M) at 30 °C for 12 h under an air atmosphere. [b] Yields of the isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] At 0 °C. [e] At −20 °C for 72 h. [f] Al(Oi-Pr)$_3$ (50 mol%) was added. [g] At −20 °C for 48 h, Al(Oi-Pr)$_3$ (50 mol%) and 3 Å MS (50 mg) were added.

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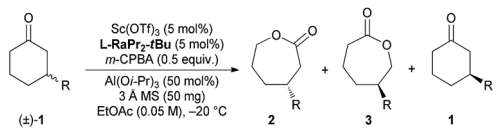
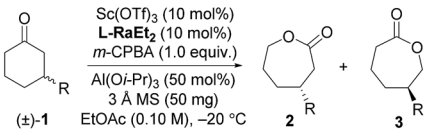
Table 2 Substrate scope for the CKR of racemic 3-substituted cyclohexanones




| | | Yield[b] (%) | | | ee[c] ([b]) | | |
|---|---|---|---|---|---|---|---|
| Entry[a] | R | 1 | 2 + 3 | 2 : 3[c] | 1 | 2 | 3 |
| 1 | Ph (**1a**) | 48 | 48 | 92 : 8 | 82 | 93 | 91 |
| 2 | 2-Me$C_6H_4$ (**1b**) | 48 | 48 | 90 : 10 | 72 | 88 | 73 |
| 3 | 3-Me$C_6H_4$ (**1c**) | 46 | 49 | 82 : 18 | 67 | 91 | 61 |
| 4 | 4-Me$C_6H_4$ (**1d**) | 49 | 47 | 88 : 12 | 67 | 85 | 90 |
| 5 | 4-*n*-Bu$C_6H_4$ (**1e**) | 42 | 45 | 88 : 12 | 79 | 90 | 96 |
| 6 | 3-Cl$C_6H_4$ (**1f**) | 49 | 49 | 90 : 10 | 74 | 90 | 75 |
| 7 | 4-$F_3C$$C_6H_4$ (**1g**) | 43 | 45 | 95 : 5 | 88 | 91 | 73 |
| 8 | 2-Naphthyl (**1h**) | 49 | 50 | 95 : 5 | 62 | 87 | 98 |
| 9 | Bn (**1i**) | 43 | 48 | 70 : 30 | 40 | 82 | 97 |
| 10 | Me (**1j**) | 43 | 44 | 74 : 26 | 55 | 90 | 95 |

[a] Unless otherwise specified, the reaction was performed with $Sc(OTf)_3$ (5 mol%), **L-RaPr$_2$-*t*Bu** (5 mol%), **1a** (0.20 mmol), *m*-CPBA (0.5 equiv.), Al(Oi-Pr)$_3$ (50 mol%) and 3 Å MS (50 mg) in EtOAc (0.05 M) under an air atmosphere. [b] Yields of the isolated products. [c] Determined by HPLC or SFC analysis using a chiral stationary phase. For the absolute configuration of the products, see the ESI for more details.

Table 3 Substrate scope for the PKR of racemic 3-substituted cyclohexanones




| | | Yield[b] (%) | | ee[c] (%) | |
|---|---|---|---|---|---|
| Entry[a] | R | 2 + 3 | 2 : 3[c] | 2 | 3 |
| 1 | Ph (**1a**) | 98 | 55 : 45 | 81 | 97 |
| 2 | 2-Me$C_6H_4$ (**1b**) | 94 | 56 : 44 | 80 | 93 |
| 3 | 3-Me$C_6H_4$ (**1c**) | 97 | 53 : 47 | 82 | 91 |
| 4 | 4-Me$C_6H_4$ (**1d**) | 97 | 55 : 45 | 80 | 96 |
| 5 | 4-*n*-Bu$C_6H_4$ (**1e**) | 98 | 55 : 45 | 83 | 95 |
| 6 | 4-MeO$C_6H_4$ (**1k**) | 92 | 52 : 48 | 83 | 97 |
| 7 | 2-Naphthyl (**1h**) | 94 | 55 : 45 | 81 | 96 |
| 8 | *n*-Bu (**1l**) | 84 | 62 : 38 | 87 | 97 |

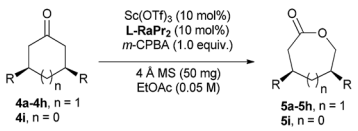
[a] Unless otherwise specified, the reaction was performed with $Sc(OTf)_3$ (10 mol%), **L-RaEt$_2$** (10 mol%), **1** (0.10 mmol), *m*-CPBA (1.0 equiv.), Al(Oi-Pr)$_3$ (50 mol%) and 3 Å MS (50 mg) in EtOAc (0.10 M) at −20 °C under an air atmosphere. [b] Yields of the isolated products. [c] Determined by HPLC or SFC analysis using a chiral stationary phase. For the absolute configuration of the products, see the ESI for more details.

(Table 2, entry 8), the desired products were obtained in 50% yield and 87% ee of **2h** with 95 : 5 rr. 3-Alkyl substituted cyclohexanones **1i** (Bn) and **1j** (Me) were also tolerated in this catalytic system, providing the corresponding lactones in 48% yield, 82% ee of **2i** with 70 : 30 rr and 44% yield, and 90% ee of **2j** with 74 : 26 rr, respectively (Table 2, entries 9 and 10). The ee values of the minor isomers **3i** and **3j** were excellent (97% ee and 95% ee). All the unreacted 3-aryl cyclohexanones **1** were recovered in excellent yields with moderate to good ee values.

Then, we turned our attention to the PKR of racemic 3-substituted cyclohexanones. After a slight modification of the reaction conditions (see Table S1 in the ESI for details†), by altering the ligand **L-RaPr$_2$-*t*Bu** to **L-RaEt$_2$** as well as increasing the catalyst loading to 10 mol% and the reaction concentration to 0.10 M, **2a** and **3a** were obtained with 81% ee and 97% ee (Table 3, entry 1). The PKR of other 3-aryl substituted cyclohexanones proceeded well to give both lactone isomers with good to excellent enantioselectivities (Table 3, entries 2–7, 80–83% ee of **2** and 91–97% ee of **3**). Substrate **1l** bearing a *n*-butyl group was converted into the desired oxidation products in 84% mixed yield and 62 : 38 rr with 87% ee of **2l** and 97% ee of **3l**.

Inspired by the CKR and PKR of 3-substituted cyclohexanones, we then focused on the desymmetrization of *cis*-3,5-diphenyl cyclohexanones. Upon further survey of the reaction parameters, the optimal conditions were found to be **4** (0.10 mmol), *m*-CPBA (0.10 mmol), **L-RaPr$_2$**/$Sc(OTf)_3$ complex (1 : 1, 10 mol%) and 3 Å MS (50 mg) in EtOAc at 0 °C for 48 h (see Table S4 in the ESI for details†). The substituents on the phenyl group of the cyclohexanones were proven to have little effect on this reaction, and a series of desymmetrization products **5a–5g** were obtained in excellent yields and enantioselectivities (Table 4, entries 1–7, 96–99% yields, and 93–97% ee). The absolute configuration of **5a** was determined to be (4*R*,6*R*) by X-ray crystallographic analysis.[12a] Dimethyl substituted **4h** could

Table 4 Substrate scope for the desymmetrization of *meso*-disubstituted cycloketones




| Entry[a] | R | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | Ph (**4a**) | 97 | 96 |
| 2 | 3-Me$C_6H_4$ (**4b**) | 98 | 97 |
| 3 | 4-OMe$C_6H_4$ (**4c**) | 96 | 93 |
| 4 | 4-F$C_6H_4$ (**4d**) | 98 | 94 |
| 5 | 3-Cl$C_6H_4$ (**4e**) | 99 | 93 |
| 6 | 4-Cl$C_6H_4$ (**4f**) | 98 | 94 |
| 7 | 4-Br$C_6H_4$ (**4g**) | 99 | 94 |
| 8 | Me (**4h**) | 99 | 91 |
| 9[d] | Ph (**4i**) | 99 | 96 |

[a] Unless otherwise specified, the reaction was performed with $Sc(OTf)_3$ (10 mol%), **L-RaPr$_2$** (10 mol%), **4** (0.10 mmol), *m*-CPBA (1.0 equiv.), and 4 Å MS (50 mg) in EtOAc (0.05 M) at −20 °C for 48 h under an air atmosphere. [b] Yields of the isolated products. [c] Determined by HPLC or SFC analysis using a chiral stationary phase. For the absolute configuration of the products, see the ESI for more details. [d] For **4i**, *n* = 0; **L-PiEt$_3$** was used instead of **L-RaPr$_2$** at 0 °C for 24 h.

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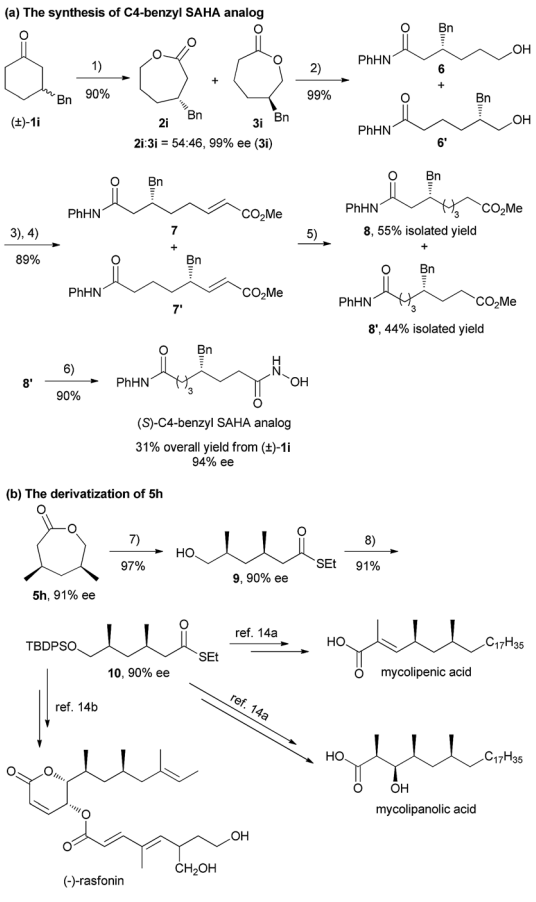
undergo transformation as well and gave the target lactone **5h** in 99% yield with 91% ee (Table 4, entry 8). In addition, 3,4-diphenyl cyclopentanone **4i** was also tolerated in this desymmetrization reaction (Table 4, entry 9, 99% yield, 96% ee).

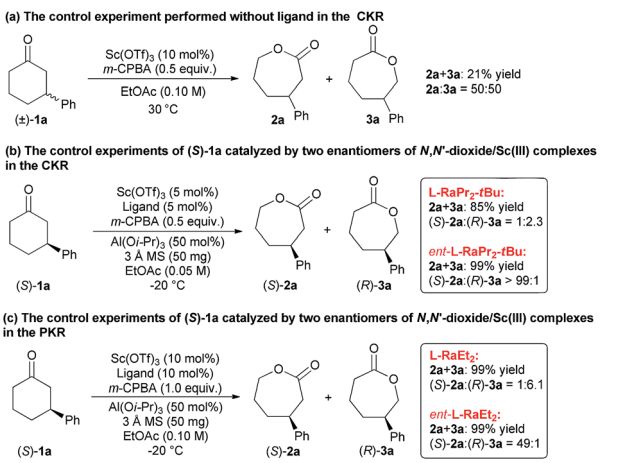
(*S*)-C4-benzyl suberoylanilide hydroxamic acid (SAHA) exhibits high selectivity for histone deacetylases (HDAC) 6 and 8, which can regulate gene expression *via* deacetylation of nucleosomal histones. Recently, Pflum's group realized the synthesis of the (*S*)-C4-benzyl SAHA analog in 9 steps (6.3% overall yield) from (*R*)-4-benzyloxazolidin-2-one.[13] In contrast, as shown in Scheme 2a, the (*S*)-C4-benzyl SAHA analog could be obtained in 31% overall yield with 94% ee in 6 steps from racemic **1i**, involving the key step of asymmetric BV oxidation of **1i** to a mixture of **2i** and **3i**. The *Syn*-1,3-dimethyl moiety served as a core chiral skeleton in various natural products,[14] such as mycolipenic acid, mycolipanolic acid and (−)-rasfonin. Manipulating the desymmetrization product **5h** with a two-step transformation, *syn*-1,3-dimethyl thioester **10** was obtained, which could be easily transformed into the aforementioned natural products (Scheme 2b, see the ESI for details†).

To elucidate the regioselectivity in both CKR and PKR, several control experiments were conducted. First, when $Sc(OTf)_3$ was used to promote the CKR of **1a** without a ligand, only 21% mixed yield of **2a** and **3a** with 50 : 50 rr was obtained (Scheme 3a). Furthermore, when the enantiopure substrate (*S*)-**1a** was tested under the standard conditions of CKR type of BV oxidation with the ligand *ent*-**L-RaPr$_2$-*t*Bu** derived from D-ramipril, a mixture of **2a** and **3a** was obtained in quantitative yield. However, when **L-RaPr$_2$-*t*Bu** was used, the reactivity was diminished and lower regioselectivity was obtained (Scheme 3b). These results suggest that (*S*)-**1a** matched with *ent*-**L-RaPr$_2$-*t*Bu** and gave the major product (*S*)-**2a**; however, (*S*)-**1a** mismatched with **L-RaPr$_2$-*t*Bu** and revealed poorer reactivity to give (*R*)-**3a**. A similar phenomenon was also observed in the PKR type of BV oxidation with **L-RaEt$_2$** and *ent*-**L-RaEt$_2$** as the ligands (Scheme 3c).

As discussed above, the migratory aptitude of **1a** contributed little to the regioselectivity in the formation of lactones (Scheme 3a). We proposed that the stereoelectronic effect in the Criegee intermediate, a notion that the migrating group needs to be antiperiplanar to the leaving group in peroxide acids before the migration of the alkyl group in the Criegee intermediate, could be essential for the recognition of **1a** (Fig. 2a).[3d,e] Since different aniline groups in **L-RaPr$_2$-*t*Bu**[12b] and **L-RaEt$_2$** resulted in different steric hindrances between **1a** and catalysts, the energy difference in the alkyl migration step in the formation of **2a** and **3a** with different configurations would result in the difference of regioselectivity. To provide further evidence for the above conjecture, ONIOM (M06/6-31G*: HF/STO-3G) calculations were performed (see the ESI for details†). Based on previous theoretical studies of BV oxidation with chiral *N*,*N*′-dioxide/Sc(III) catalysts,[15] the transition states in the alkyl group migration step in CKR and PKR were optimized and their Gibbs free energies were calculated (Fig. 2b, c). In **L-RaPr$_2$-*t*Bu**-TS-(*R*)-**2a** and **L-RaEt$_2$**-TS-(*R*)-**2a**, **1a** was placed away from the aniline groups, while in **L-RaPr$_2$-*t*Bu**-TS-(*R*)-**3a** and **L-RaEt$_2$**-TS-(*R*)-**3a**, **1a** was placed between the aniline group and the bicyclic ring




Scheme 2 The synthesis of the (*S*)-C4-benzyl SAHA analog and the derivatization of **5h**. (1) *m*-CPBA (1.0 equiv.), **L-RaPr$_2$-*t*Bu**/$Sc(OTf)_3$ (1 : 1, 10 mol%), $Al(Oi\text{-}Pr)_3$ (50 mol%), 3 Å MS (50 mg), EtOAc (0.05 M), −20 °C for 48 h. (2) $PhNH_2$ (2.0 equiv.), $AlMe_3$ (2.0 equiv.), THF, 0 °C to rt. (3) PCC (2.0 equiv.), celite, $N_2$, DCM. (4) $(OMe)_2(O)PCH_2COOMe$ (1.4 equiv.), NaH (1.5 equiv.), THF. (5) Pd/C, $H_2$, MeOH. (6) $H_2NOH{\cdot}HCl$, KOH, MeOH, 0 °C. (7) EtSH, $AlMe_3$, THF, 0 °C to rt. (8) TBDPSCl, NaH, EtOAc.




Scheme 3 Control experiments.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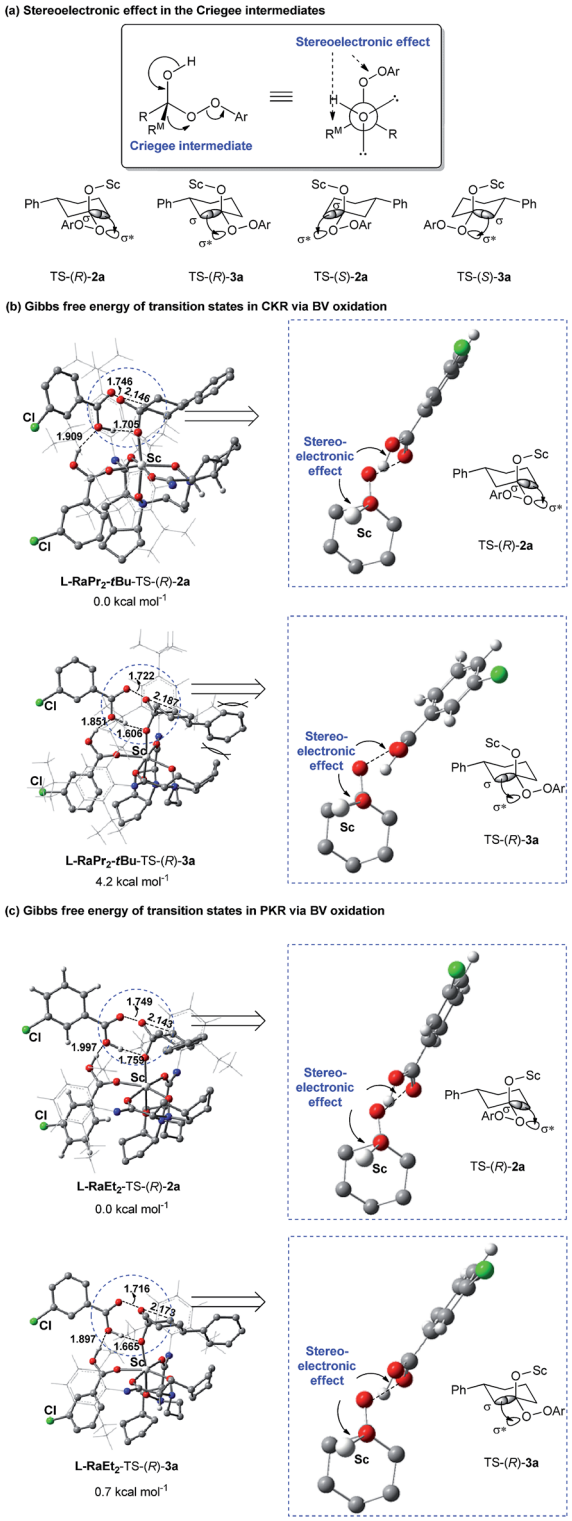


Fig. 2 Gibbs free energy diagram of the optimized transition states of (±)-**1a** and *m*-CPBA catalyzed by *N*,*N*′-dioxide/Sc(III) complexes.

backbone of the ligand. For **L-RaPr$_2$-*t*Bu** with bulky iso-propyl and *tert*-butyl groups on the aniline group, the larger steric hindrance between the ligand and **1a** resulted in a larger energy difference between **L-RaPr$_2$-*t*Bu**-TS-(*R*)-**3a** and **L-RaPr$_2$-*t*Bu**-TS-(*R*)-**2a** (Fig. 2b, $\Delta G = 4.2$ kcal mol$^{-1}$), and so the former is the favored transition state while the latter is the disfavored one. Meanwhile, owing to a less bulky aniline group and the flexible catalyst structure, the energy difference between **L-RaEt$_2$**-TS-(*R*)-**3a** and **L-RaEt$_2$**-TS-(*R*)-**2a** was significantly smaller (Fig. 2c, $\Delta G =$ 0.7 kcal mol$^{-1}$), and both transition states are favored. Such a revelation is consistent with the control experiments in Scheme 3. The theoretical study shows that the adjustable aniline groups and flexible catalyst structure proved to be powerful for the regioselectivity and enantioselectivity in the BV oxidation of **1a** with *N*,*N*′-dioxide/Sc(III) catalysts through the recognition of the 3-position of the cyclohexanones in BV oxidation.

## Conclusions

We realized the catalytic asymmetric CKR and PKR of 3-substituted cyclohexanones and desymmetrization of *meso*-disubstituted cycloketones through BV oxidation with a single catalytic system. The pending problem of regio- and stereoselectivity in BV oxidation was solved by the modulation of the structure of chiral *N*,*N*′-dioxide/Sc(III) complexes. The experimental studies and theoretical calculations showed that flexible and adjustable catalysts can influence the migratory aptitude of the substrate *via* stereoelectronic control and chiral recognition. Besides, this methodology has been proven to be efficient in synthesizing useful bioactive compounds and natural products.

## Conflicts of interest

There are no conflicts to declare.

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