Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2023, **14**, 1844

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 25th November 2022
Accepted 11th January 2023

DOI: 10.1039/d2sc06490a

rsc.li/chemical-science

Asymmetric synthesis of complex tricyclo[3.2.2.0] nonenes from racemic norcaradienes: kinetic resolution *via* Diels–Alder reaction†

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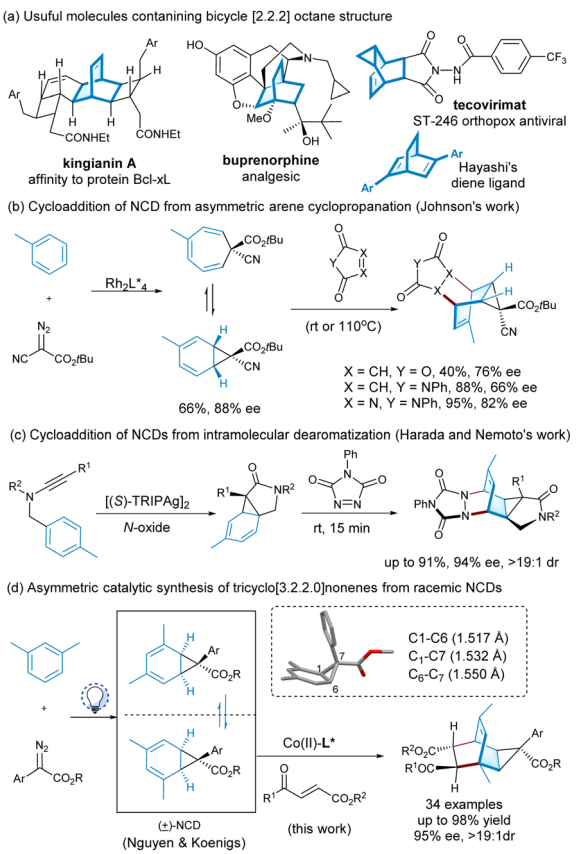
Herein, the enantioselective synthesis of complex tricyclo[3.2.2.0]nonenes through the Diels–Alder reaction is reported. Utilizing racemic norcaradienes prepared from the visible-light-mediated dearomative cyclopropanation of *m*-xylene as dienes and enone derivatives as dienophiles, the overall process represents a kinetic asymmetric transformation in the presence of a chiral cobalt(II) complex of chiral *N*,*N*′-dioxide. High diastereo- and enantioselectivity could be obtained in most cycloaddition processes and part racemization of norcaradiene is observed. The topographic steric maps of the catalysts were collected to rationalize the relationship between reactivity and enantioselectivity with the catalysts.

Introduction

Bridged bicyclo[2,2,2]octane structure represents an important class of polycyclic hydrocarbon scaffolds, and their rigidity allows functional groups encompassing three-dimensional shapes precisely.[1] Such structure exists in numerous natural products and drugs, such as kingianin A[2] and buprenorphine[3] (Scheme 1a). Tecovirimat, the class of ST-246 orthodox antivirals, contains the tricyclo[3.2.2.0]nonene backbone as a variation.[4] Additionally, chiral bicyclo[2,2,2]octene-based diene has been discovered as a class of privileged ligands for transition metal-catalyzed asymmetric reactions (Scheme 1a).[5] The Diels–Alder reaction of 1,3-cyclohexadiene with dienophile is a straightforward route for synthesizing bicyclo[2.2.2] ring system with a bridgehead olefin,[6] but the cyclic diene system exhibits more flexibility and competing aromatization to arene.[7] Norcaradienes (NCDs) are useful diene partners bearing a cyclopropane bridge, rendering enhanced rigidity and predictable topographical selectivity[8] accessible *via* arene cyclopropanation.[8e,f,9] However, the existence of norcaradiene (NCD)-cycloheptatriene (CHT) equilibrating *via* ring opening and closure has an uncertain effect on the functionalization process.[10]



Scheme 1 Importance of the bicyclo[2.2.2]octane core and [4 + 2] cycloadditions accessing tricyclic varieties from NCDs.

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† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H} NMR, HPLC spectra (PDF). X-ray crystallographic data for **1a**, **3aa**, **5ab** and Co(OTf)$_2$/**L$_3$-PePr$_2$** complex. CCDC 2070991, 2155946, 2212551 and 2212550. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2sc06490a

Chiral transition metal complex-catalyzed arene cyclopropanations enable the *in situ* generation of enantiomerically enriched NCDs and their valence tautomers,[11] which have been employed for rapid conversion to an array of complex bridge tricyclic structures and other cyclohexane building blocks. For instance, the Johnson group took advantage of chiral dirhodium complex-mediated regio- and stereoselective arene cyclopropanation using α-cyanodiazoacetate as a carbene procedure to affordd optically enriched NCDs, serving as tunable templates for the synthesis of complex cyclohexanes (Scheme 1b).[12] The azo-Diels–Alder reaction with 1,2,4-triazole-3,5-dione performed well, but the cycloaddition of maleic anhydride or *N*-phenyl maleimide required high reaction temperature with the slight erosion of enantioselectivity. Very recently, Johnson's group also used enantioenriched cycloheptatriene from anisole and aryl-substituted α-diazoester for diastereoselective [4 + 2] cycloaddition with nitroethylene, enabling the preparation of chiral tricycle[2.2.2]nonene for late-stage functionalization into diene ligands.[13] Harada *et al.* developed a method for the diazo-free generation of silver-carbene species from an ynamide to transiently generate chiral norcaradiene, which can be further decorated to complex molecules upon cycloaddition (Scheme 1c).[14]

We are interested in developing an asymmetric catalytic Diels–Alder reaction to construct the chiral tricyclo[3.2.2.0] nonenes, similar to the tecovirimat structure, which might be useful for bioactivity evaluation.[4] In addition to typical transition-metal-mediated arene cyclopropanation, Nguyen and coworkers investigated the metal-free visible-light photolysis of aryl diazoacetates in aromatic solvents for NCD synthesis (Scheme 1d).[8e] We envision an alternative pathway to achieve complex tricyclononenes from racemic NCDs *via* Diels–Alder reaction with dienophile (Scheme 1d). As chiral NCD could locate the facial approach of the dienophile,[12–15] three issues need to be considered for the process: (1) the discriminate enantiomers of the diene with a chiral catalyst in the cycloaddition; (2) diastereoselectivity controlled by chiral substrate or chiral catalyst; (3) tautomerization and racemization of the NCDs in the presence of Lewis acids. In this context, the choice of chiral Lewis acid catalyst is critical, and our endeavor in developing chiral Lewis acids of *N*,*N*′-dioxides[16] now allows for the asymmetric catalytic Diels–Alder reaction of racemic norcaradienes with enones. Herein, we describe the enantioselective construction of tricyclo[3.2.2.0]nonenes with seven stereocenters from racemic NCDs based on the visible-light-mediated dearomative cyclopropanation of *m*-xylene.[8e] Kinetic resolution process in connection with diastereo- and enantioselective cycloaddition performs well with chiral cobalt(II) complex under mild reaction conditions.

The racemic norcaradiene synthesis followed the method reported by Nguyen and Koenigs *via* the visible-light-mediated cyclopropanation reaction of arenes.[8e] Considering the regioselectivity of the cyclopropanation and the optical property of the norcaradienes, the racemic *exo*-norcaradiene **1a** from *m*-xylene and methyl 2-diazo-2-phenylacetate is prepared for the Diels–Alder reaction (Scheme 1d). In contrast to norcaradiene from cyanodiazoacetate,[12,17] the related *exo*-ester norcaradiene **1a** of *m*-xylene is stable and a favourable tautomer. From the X-ray crystallographic data of norcaradiene **1a**,[10c,18] it is found that the C_1–C_6 bond is shorter than the C_1–C_7 and C_6–C_7 bonds. This agrees with the molecular orbital explanation of the stabilization of norcaradiene bearing an electron-withdrawing group at the C_7-position.[19] This implies that the *anti*-bonding character of the C_1–C_6 bond is weakened and the electron density is drawn away from the cyclopropane into the vicinal π-system, benefiting the normal electron-demanding Diels–Alder reaction.

Electron-deficient ethyl (*E*)-4-oxo-4-phenylbutenoate **2a** is selected as the dienophile. We investigate the feasibility of the reaction by identifying chiral Lewis acid catalysts using *N*,*N*′-dioxide **L_3-PiPr$_2$** as the ligand (Fig. 1). Initially, the reaction is carried out by mixing an equal amount of norcaradiene **1a** and ethyl (*E*)-4-oxo-4-phenylbutenoate **2a** in CH_2Cl_2 at 30 °C (Table 1). Several metal salts were subjected to the reaction system, but only a minority of them could accelerate the cycloaddition to an extent, and representative results are listed in entry 1–4 in Table 1. Although $Yb(OTf)_3$ could afford comparable reactivity and enantioselectivity, but diastereoselectivity is poor (entry 2). The use of $Co(OTf)_2$ leads to the sole generation of one diastereoisomer **3aa** with moderate results (entry 4). The next modification of the ring structure of the *N*,*N*′-dioxides yield gradually improved enantioselectivity (entries 4–7), orderly from **L_3-PiPr$_2$**, **L_3-PrPr$_2$**, **L_3-RaPr$_2$**, to octahedron-1*H*-indole-based **L_3-PePr$_2$**. The five-substituted tricyclo[3.2.2.0]nonene product **3aa** could be isolated in a 35% yield, >19 : 1 dr and 89% ee in the presence of **L_3-PePr$_2$** and $Co(OTf)_2$ (entry 7). Further exploration of the reaction solvents reveals that 1,1,1,2-tetrachloroethane (TCE) increases enantioselectivity to 92% ee (Table 1, entry 7–9). Polar halohydrocarbons, which are good solvents for the solution of the chiral cobalt(II) complex of chiral *N*,*N*′-dioxides, were critical to the yield and enantioselectivity (see the ESI† for details). When the amount of norcaradiene increases into two equivalents, the yield of the product doubles (entry 10), with up to a 92% yield, >19 : 1 dr and 91% ee are afforded after the reaction time is prolonged (entry 11). The absolute configuration of product **3aa** was determined to be (1*R*, 2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 7*S*) by X-ray crystallography analysis.[18]

With the optimized set of conditions in hand, we evaluate the generality of this reaction. As illustrated in Table 2, first, various 4-oxo-4-arylbutenoates undergo cycloaddition with

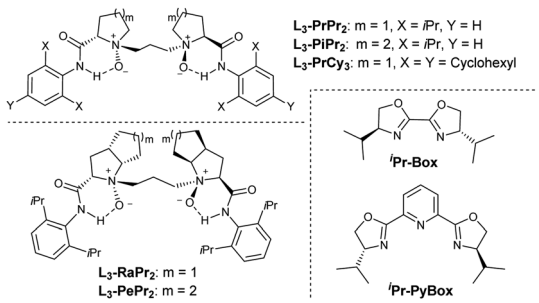
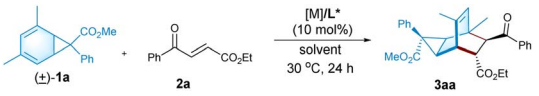


Fig. 1 Chiral ligands used for the reaction.

Table 1 Optimization of the reaction conditions[a]



Entry	Metal salt/ligand	Solvent	Yield[b] (%)	dr[c]	ee[d]
1	$Sc(OTf)_3$/**L_3-PiPr$_2$**	DCM	27	>19 : 1	27
2	$Yb(OTf)_3$/**L_3-PiPr$_2$**	DCM	30	1 : 3	30
3	$Zn(OTf)_2$/**L_3-PiPr$_2$**	DCM	38	>19 : 1	17
4	$Co(OTf)_2$/**L_3-PiPr$_2$**	DCM	26	>19 : 1	35
5	$Co(OTf)_2$/**L_3-PrPr$_2$**	DCM	28	>19 : 1	65
6	$Co(OTf)_2$/**L_3-RaPr$_2$**	DCM	34	>19 : 1	77
7	$Co(OTf)_2$/**L_3-PePr$_2$**	DCM	35	>19 : 1	89
8	$Co(OTf)_2$/**L_3-PePr$_2$**	DCE	8	>19 : 1	73
9	$Co(OTf)_2$/**L_3-PePr$_2$**	TCE	32	>19 : 1	92
10[e]	$Co(OTf)_2$/**L_3-PePr$_2$**	TCE	67	>19 : 1	91
11[e,f]	$Co(OTf)_2$/**L_3-PePr$_2$**	TCE	92	>19 : 1	91
12[e,f]	$Co(OTf)_2$/**L_3-TQPr$_2$**	TCE	20	3 : 1	0/12
13[e,f]	$Co(OTf)_2$/**^{i}PrPyBox**	TCE	Trace	—	—
14[e,f]	$Co(OTf)_2$/**^{i}Pr-Box**	TCE	Trace	—	—

[a] Unless otherwise noted, all reactions were carried out with metal salt/ligand (1:1, 10 mol%), **1a** (1.0 equiv.), **2a** (0.10 mmol) in DCM (1.0 mL) at 30 °C for 24 h. [b] Isolated yield of **3aa**. [c] Determined by ^{1}H NMR. [d] Determined by HPLC on a chiral stationary phase. [e] **1a** (2.0 equiv.). [f] 48 h. DCE = 1,2-dichloroethane; TCE = 1,1,1,2-tetrachloethane.

norcaradiene **1a** to afford the desired products (**3aa–3ar**) as nearly one diastereomer (>19 : 1 dr) with good enantioselectivity (81–93% ee). In general, higher yields are observed with electron-withdrawing substitution at the benzoyl group than alkyl-substituted ones (**3ak–3an**), but *para*-nitro-bearing **3aj** is an exception owing to the decomposition of the related substrate. Notably, the alkynyl group is tolerable in the reaction, and the desired product **3ao** is isolated in 97% yield and 87% ee. In addition, the reaction is amenable to 2-naphthoyl-containing dienophile, affording the corresponding product **3as** in a 90% yield with 87% ee. The ester group of 4-oxo-4-benzylbutenoates could be changed from ethyl to methyl, *n*-butyl, isopropyl and benzyl groups; the enantioselectivity could basically be maintained (**3at**−**3aw**, 79–92% yields, 88–94% ee).

Norcaradienes synthesized from different aryl α-diazoestres are also suitable for this process. The reaction of 7-aryl norcaradienes bearing *para*-substitution as halo, methyl, methoxyl, or Bpin, under the standard conditions, performs well to provide the related tricyclo[3.2.2.0]nonenes (**3ba–3ga**) in good to excellent yields (65–98%), with up to 19 : 1 dr with satisfied enantioselectivity (85–95% ee). The reaction of norcaradienes with a 2-chlorophenyl or a 2-methoxyphenyl at the C_7-position is clearly different from the other transformations in terms of diastereoselectivity. The related adducts (**3ha** and **3ia**) are obtained in poor diastereoselectivity but comparable good enantioselectivity for both isomers. This might be due to the decreased split rate of the norcaradiene, as a result of steric hindrance, which led to the two enantioisomers of the norcaradienes having similar reaction rates. Low diastereoselectivity is also observed when 3-halophenyl-substituted norcaradienes are subjected to standard conditions (see the ESI† for details). In addition, the 7-ester group of norcaradienes could be changed from methyl to ethyl, *iso*-propyl or benzyl group, and all of the corresponding products (**3ja–3la**) could obtain good results (81–90% yields, >19 : 1 dr, 85–90% ee).

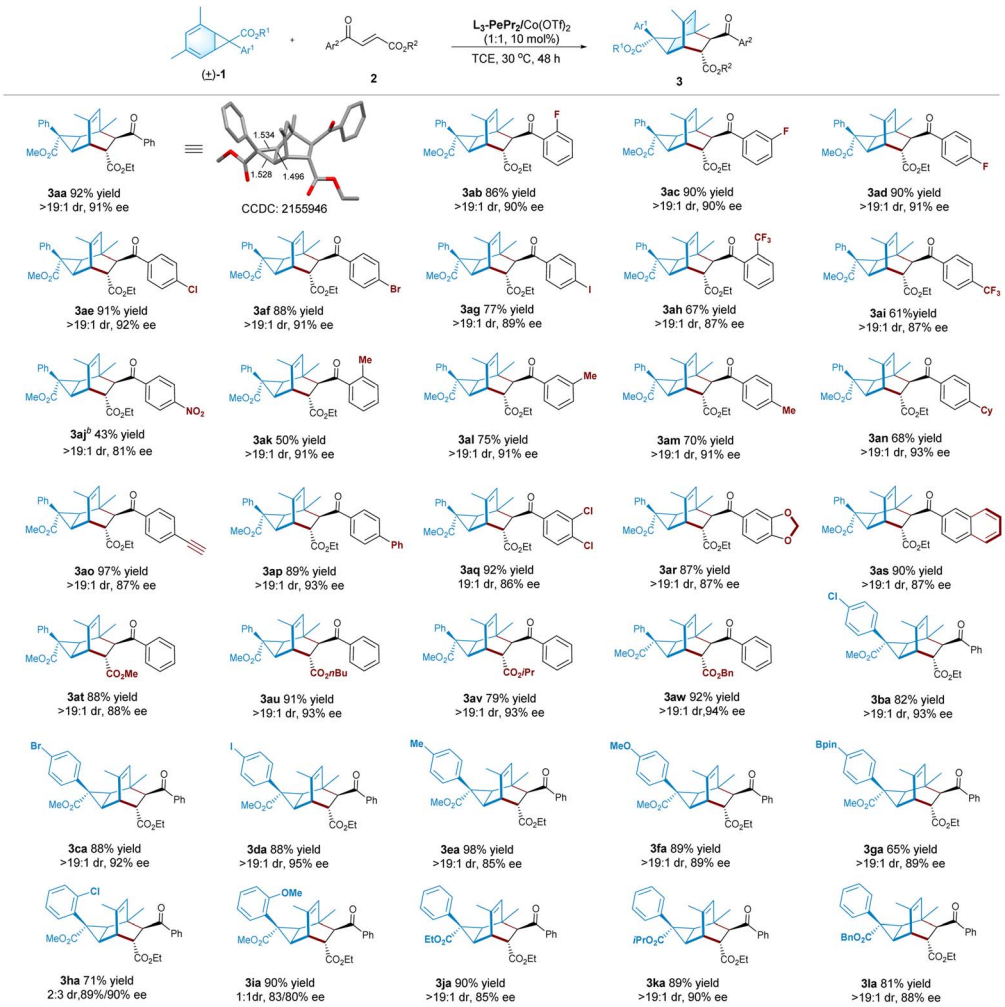
We next ivestigated 3-nitrophenylpropenones as the dienophiles to synthesize bicyclo[2,2,2]octene-based dienes that represent a type of interesting chiral ligands.[5] As shown in Table 3, the reaction between racemic norcaradiene **1a** and β-nitroenone **4a** in the presence of the cobalt(II) complex of *N*,*N*′-dioxide **L_3-PrCy$_3$**, following the treatment with DBU, led to the formation of the corresponding diene **5aa** in 84% yield, >19 : 1 dr, and 80% ee. Noteworthily, there is a reversed regioselectivity using β-nitroenone compared with 4-oxo-4-arylbutenoate as a dissymmetrical pull–pull olefin for cyclo-addition[20] mainly because of the natural bond polarizations. Other β-nitroenones **4** bearing-substituted benzoyl groups, 2-naphthoyl group, or thiophene-3-carbonyl group, were tolerable to afford the desired dienes (**5ab–5ag**) in moderate to good yield and enantioselectivity. The absolute configuration of product **5ab** was determined to be (1*R*, 2*S*, 3*R*, 4*S*, 5*S*) by X-ray crystallography analysis.[18] This indicates that there is an antilogous preference for the enantiomer of norcaradiene and the activation of the electron-withdrawing group of dienophile.

To illustrate the potential synthetic utility of the current catalytic system, a gram-scale synthesis was carried out with racemic norcaradiene **1a** (5.0 mmol) and enone **2a** (2.5 mmol) under the optimal catalytic system, which afforded the corresponding tricyclo[3.2.2.0]nonene **3aa** in 80% yield with 19 : 1 dr and 91% ee (Scheme 2a). Sequential reduction by $LiAlH_4$ led to the formation of the tri-hydroxyl-substituted derivative **6** in 71% yield, 19 : 1 dr and 90% ee (Scheme 2b).

To probe into the stereocontrol of the process, we detected the enantioselectivity of product **3aa** and unreacted norcaradiene **1a** at various timescales. As shown in Scheme 2c, high enantioselectivity was detected during the whole process although it slightly dropped after around 40 hours. Simultaneously, the optical activity of norcaradiene gradually increased but did not exceed 60% ee at the end. From the absolute configuration of product **3aa**, we can rationalize that (7*S*)-**1a** reacts more readily with **2a** than (7*R*)-**1a** in the presence of the chiral catalyst of Co(II)/**L_3-PePr$_2$**. Given the high diastereoselectivity and enantioselectivity of **3aa** but the moderate ee of the recovered NCD, it is proposed that the kinetic resolution and racemization of NCD might occur along with the cycloaddition.

To probe into the stereo–selective profile of the cycloaddition, control experiments were performed using enantioenriched norcaradiene **1a** (Scheme 3), which exhibited disparate reactivity and stereoselectivity. When the recovered norcaradiene (rationalized as 7*R*-configuration) with moderate ee value (53% ee) was put into the chiral catalyst system, the desired product was afforded a good yield after a long reaction time with moderate diastereo- and enantioselectivity (Scheme 3a, condition i). If there is no catalyst, the spontaneous process is weak, and only a trace amount of tricyclononene is detected in 1 : 1 dr and decreases enantioselectivity (condition ii).

Table 2 Substrate scope of the asymmetric Diels–Alder reaction of 4-oxo-4-arylbutenoates[a]



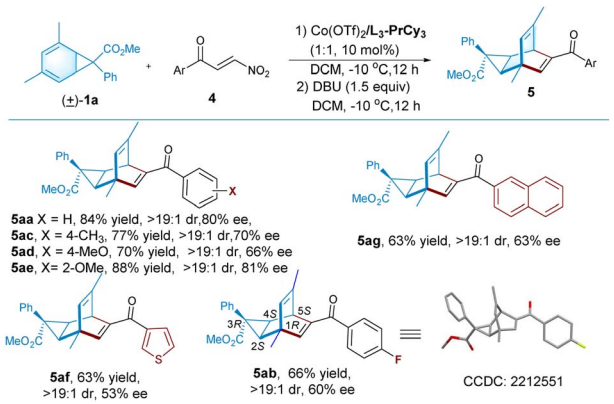
[a] All reactions were carried out with **1** (2.0 equiv.), **2** (0.10 mmol), $Co(OTf)_2$/**L_3-PePr$_2$** (1 : 1, 10 mol%), in TCE (1.0 mL) at 30 °C for 48 h. Isolated yield. dr was determined by ^{1}H NMR, and ee was determined by HPLC on a chiral stationary phase. [b] Under N_2 atmosphere for 72 h.

However, the reaction with (7*S*)-enriched norcaradiene **1a** performed well in the standard reaction condition, with a 95% yield >19 : 1 dr and 94% ee (condition iii), confirming that the (7*S*)-isomer of **1a** participates in the cycloaddition in priority. Equally, only trace adduct is detected with a poor dr value and reduced enantioselectivity without a catalyst after a two-day reaction time (condition iv).

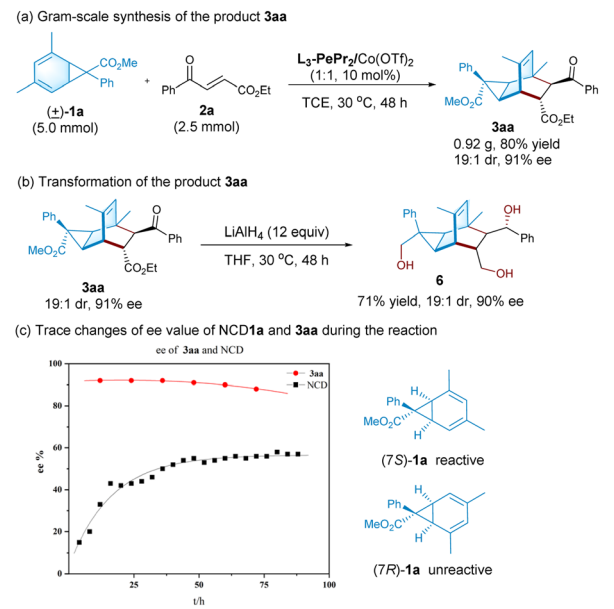
The erosion of the optical activity of norcaradiene in the presence of a chiral Lewis acid catalyst was observed (Scheme 3b). The stability of *exo*- and *endo*-**1a**, as well as its valence tautomer CHTs, was evaluated by applying the Gaussian 09 D.01 package at the level of M06-2X-D3/def-SVP//M06-2X-D3/def2-TZVP with the SMD solvent model of dichloromethane (see ESI† for more details).[21] *Exo*-**1a** exhibits the lowest Gibbs free energy compared to that of *endo*-**1a** (3.7 kcal mol^{-1}), CHT-**a** (6.9 kcal mol^{-1}) and CHT-**b** (6.2 kcal mol^{-1}), and this reveals that *exo*-ester **1a** is more stable than the others, which agrees with the experimental results. Next, the possible decreased enantioselectivity was rationalized *via* C_6–C_7 heterolysis, which is the longest bond of cyclopropane, assisted by Lewis acid to form dimethyl-cyclohex-2,4-dienylium ions (Scheme 3b). Neither the rearomatization byproduct nor other types of norcaradiene isomers are tracked two days after the reaction. As shown in Scheme 3b, the occurrence of the 1,2*H* shift of the zwitterionic intermediates between the C_1 and C_6 positions leads to the loss of stereochemistry at the C_1-carbon center, and C_6–C_7 rebound may yield *exo*-ester norcaradiene with the opposite configuration.

To understand the steric effects on the enantioselectivity of the ligand, we choose Cavallo's SambVca 2 Web tool[22,23] to construct topographical steric maps (Scheme 4) based on the general structures of the metal complex of chiral *N*,*N*′-dioxide ligands.[24] It is found that the percent buried volumes of the catalysts varied dramatically with the ring structure of the amino acid backbone of the ligands, following **L_3-PrPr$_2$** < **L_3-PePr$_2$** < **L_3-PiPr$_2$** ≅ **L_3-RaPr$_2$** < **L_3-PePr$_3$** < **L_3-TQPr$_2$**. The

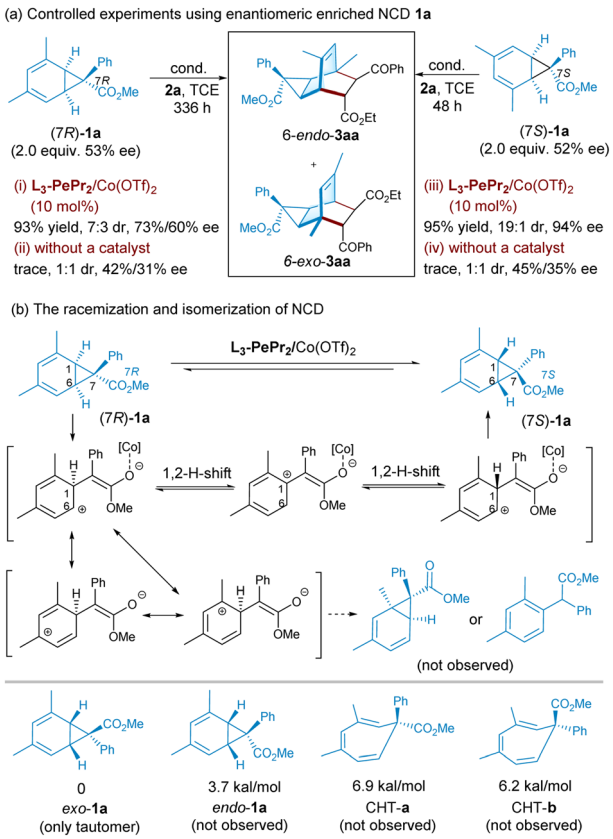
Table 3 Asymmetric catalytic synthesis of bicyclo[2,2,2]octene-based dienes from 3-nitro-phenylpropenones[a]



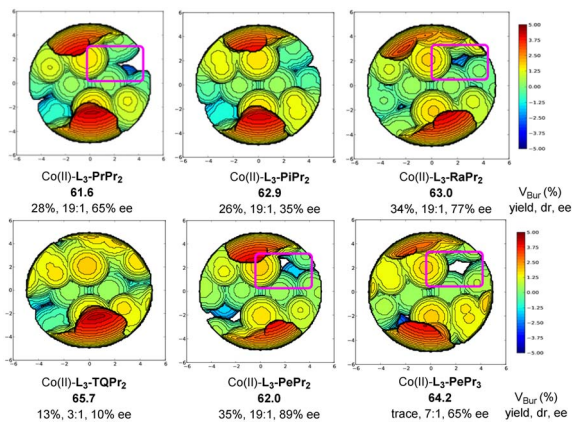
[a] Unless otherwise noted, all reactions were carried out with **1a** (0.20 mmol), **4** (0.1 mmol), and $Co(OTf)_2$/**L_3-PrCy$_3$** (1 : 1, 10 mol%) in DCM (1.0 mL) under nitrogen at −10 °C. After 12 hours, DBU (0.15 mmol) was added, and the mixture continued stirring for another 12 hours. Isolated yield. dr was determined by ^{1}H NMR, and ee was determined by HPLC on a chiral stationary phase.



Scheme 2 Other experiments.



Scheme 3 The control experiments and identification of the racemization of NCD.



Scheme 4 Steric map of cobalt(II) complexes of various ligands.

significantly increased buried volume of **L_3-TQPr$_2$** might arise from its distorted trigonal bipyramidal arrangement[25] after coordination with cobalt salt, differing from the majority of the structures of the others in an octahedron configuration. In connection with the observed yield and enantioselectivity, it seems that if a crowded space exists around the metal center with a larger buried volume (**L_3-TQPr$_2$** and **L_3-PePr$_3$**), the reactivity drops. However, if there are obvious grooves inside the pink box (less steric hindrance), the enantioselectivity of the reaction is higher.

The four transition states shown in Fig. 2 are rationalized to account for the generation of possible isomers of tricyclononene products. Albeit there are seven stereocenters in the adduct, due to the conformation-limitation of NCD **1a** with steric encumbrance by the three-membered bridge, as well as the cycloaddition process dictated by Woodward-Hoffmann rules, four isomers of tricyclononene would generate, in which the cyclopropane ring and the unsaturated bridge locate at *syn*-position, and the benzoyl and ester group from the

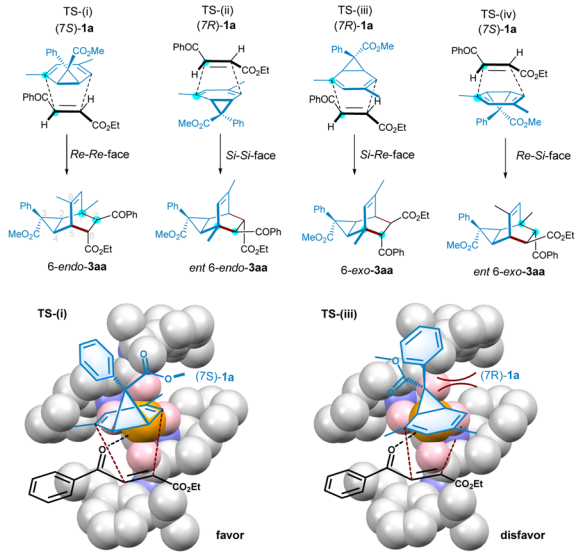


Fig. 2 Possible transition states for the Diels–Alder reaction.

dienophile adopt *anti*-position. Based on the absolute configuration of product **3aa** determined by X-ray crystallography analysis, it is proposed that the transition state TS-(i) is the favorable one to yield the adduct 6-*endo*-**3aa** from(7*S*)-**1a** using the Re–Re-facial approach. The ability of the antipode to afford *ent*-6-*endo*-**3aa** from (7*R*)-**1a** *via* TS-(ii) is disfavored. The other two transition states (iii) and (iv) to form 6-*exo*-**3aa** were nearly inhibited in the presence of the optimal chiral catalyst.

Based on the X-ray crystal structure of $Co(OTf)_2$/**L_3-PePr$_2$** complex,[18,26] and the activation manner of enone in cycloaddition, we rationalized the favorable enantioselective version of the Diels–Alder reaction and the kinetic resolution of norcaradiene (Fig. 2, below). As shown in the full view of TS-(i), the coordination of 4-oxo-4-arylbutenoate to the cobalt(II) center decreases the LUMO energy of the dieneophile, benefiting the cycloaddition. The Si-face of the enone is well shielded by the downward amide unit of the ligand. Thus, norcaradiene prefers to approach from the upper opening area. It is easy to see how to distinguish between the two enantiomers of norcaradiene, as shown in TS-(i) and TS-(iii). (7*S*)-**1a** could undergo [4 + 2]-cycloaddition with less steric hindrance, but the reaction of its enantiomer seems to be unfavorable owing to the steric hindrance of the inward cyclopropane-unit. Consequently, the facial selective addition in connection with the kinetic resolution yields the (1*R*, 2*R*, 3*S*, 4*R*, 5*S*, 6*R*, 7*S*)-**3aa** as the major adduct.

Conclusions

In summary, we have developed an enantioselective Diels–Alder reaction of norcaradienes with (*E*)-4-oxo-4-phenylbutenoates and β-nitroenones. The reactions catalyzed by a *N*,*N*′-dioxide/Co(II) complex use racemic norcaradienes prepared *via* visible-light-mediated dearomative cyclopropanation of *m*-xylene and α-diazoesters as the dienes and proceed *via* kinetic asymmetric transformation. Under otherwise identical reaction conditions, a series of complicated bridged tricyclo[3.2.2.0]nonene systems bearing seven contiguous stereocenters were accomplished under mild reaction conditions. Mechanism experiments also revealed the origin of the enantioselectivity and resolution of the isomers of norcaradienes. Further exploration of the catalyst system for other asymmetric reactions is under investigation.

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 **1a**, **3aa**, **5ab** and $Co(OTf)_2$/**L_3-PePr$_2$** complex are available in the ESI.†

Author contributions

S. Y. W. performed the experiments and prepared the ESI† and paper. Y. Q. Z. analyzed the X-ray diffraction crystal data and completed the theoretical calculation. W. L. X. and Z. G. L. 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.

Acknowledgements

We thank the National Natural Science Foundation of China (no. 22188101), Sichuan Science and Technology Program (no. 2021YJ0561) and Sichuan University (2020SCUNL204) for financial support.

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