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# Copper(I)-Catalyzed Kinetic Resolution of *exo*-3-Oxodicyclopentadienes and *endo*-3-Oxodicyclopentadiene

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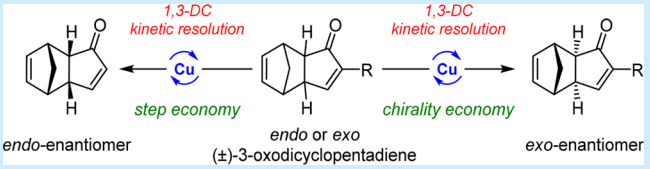
Supporting Information

**ABSTRACT:** The first example of highly efficient kinetic resolution of *exo*-3-oxodicyclopentadienes and *endo*-3-oxodicyclopentadiene has been developed by means of Cu(I)-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylide. Compared with the existing methodologies for those synthetically important optically active convex molecules, the current protocol provides an alternative but more practical approach from the readily available racemic starting materials, which is free from the repetitive reduction/oxidation steps in the enzymatic resolution or the indispensable stoichiometric amount of chirality-induction reagents.






Exploitation of efficient and practical methods toward synthetically useful and enantiomerically enriched molecules from readily available starting materials has always been a formidable challenge yet a primary goal in modern synthetic chemistry.[1] Optically active *endo*-3-oxodicyclopentadiene is a well-known convex molecule that has been widely applied as the chiral building block in the asymmetric synthesis of a variety of naturally occurring cyclopentanoids,[2,3] compounds of pharmaceutical interest,[4] and also a class of important chiral diene ligands.[5] Enzymatic resolution is regarded as the key step in the preparation of enantiomerically enriched *endo*-3-oxodicyclopentadiene as shown in Scheme 1a.[6] Racemic *endo*-3-oxodicyclopentadiene was obtained through two sequential oxidation steps with cyclopentadiene dimer as the starting material or one-pot allylic oxidation catalyzed by tetraphenylporphyrin (TPP).[7] Both enantiomers of *endo*-3-oxodicyclopentadiene were obtained in enantiopure form from the racemic compound through sequential *exo*-selective reduction, enzyme-mediated kinetic ester-exchange reaction, and reoxidation of the resolved *exo*-alcohol.[6] However, optically active *exo*-3-oxodicyclopentadienes have been used as the pivotal building block in the enantioselective construction of biologically important Brefeldin A, prostanes dPPJ1, and carbanucleosides Carbovir and Abacavir.[8] The intermolecular Pauson−Khand reaction (PKR) of norbornadiene and alkynes is particularly suitable for the preparation of racemic *exo*-3-oxodicyclopentadienes.[9] Although the stereochemistry of the intermolecular PKR can be controlled via chiral auxiliaries or stoichiometric amount of chiral ligands,[2] only one successful example of Co-catalyzed asymmetric PKR of norbornadiene and alkynes was reported with moderate yields and enantioselectivities ranging from 2 to 97% ee[10a] (Scheme 1b).

In view of the ready-availability of racemic *exo*-3-oxodicyclopentadienes and *endo*-3-oxodicyclopentadiene, it occurred to us the strategy of chemical kinetic resolution[11,12] could be utilized to differentiate both enantiomers of *exo*-3-oxodicyclopentadienes and *endo*-3-oxodicyclopentadiene through direct functionalization of the incorporated enone moiety. The success of this protocol would provide an alternative but more practical approach to both of the enantioenriched *exo*-3-oxodicyclopentadienes and *endo*-3-oxodicyclopentadiene, free from the repetitive reduction/oxidation steps in the enzymatic resolution[6] or the indispensable stoichiometric amount of chirality-induction reagents.[2] As a continuation of our research interest in azomethine ylide-involved catalytic asymmetric reactions,[13] we envisioned that catalytic asymmetric 1,3-dipolar cycloaddition reaction[14] could preferentially consume one enantiomer of racemic *exo*-3-oxodicyclopentadienes and *endo*-3-oxodicyclopentadiene as the dipolarophiles to form fused tetracyclic heterocycles[15] bearing biologically and synthetically important pyrrolidine[16] and norbornene[17] moieties, and thus leave the other enantiomer as the recovered enones. However, the intricate stereochemical interactions caused by the inherent *exo*- or *endo*-fused convex norbornene skeleton is a challenge to the above design. Herein, we reported our preliminary results on the first kinetic resolution of racemic *exo*-3-oxodicyclopentadienes and *endo*-3-oxodicyclopentadiene via a highly efficient Cu(I)-catalyzed 1,3-dipolar cycloaddition.

Initially, the reaction of racemic *exo*-3-oxodicyclopentadiene **8a** (readily accessible by the intermolecular PKR[18]) and aldimine ester **9** were employed as the model substrates to examine the feasibility of our design. Several metal salts coordinated by chiral ligand TF-BiphamPhos were tested in $CH_2Cl_2$ at room temperature with $Et_3N$ as the base (Table 1, entries 1−4). Although no reaction occurred with silver(I) salts, the cycloaddition reaction did proceed smoothly in the presence

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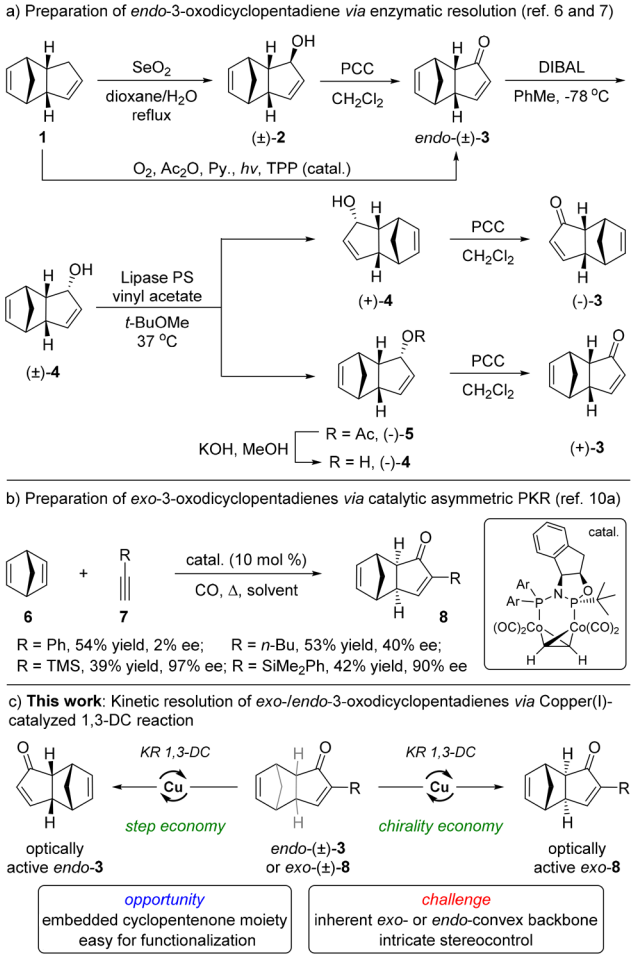
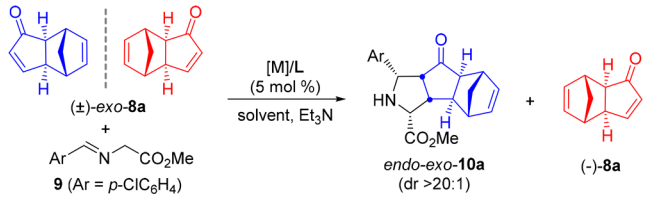
**Scheme 1. Asymmetric Construction of Enantioenriched *exo*- and *endo*-3-Oxodicyclopentadienes (Previous Work and This Work)**



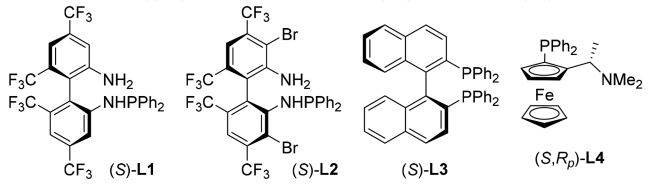

of $Cu(MeCN)_4BF_4$, affording the adduct **10a** with exclusive *endo*-selectivity and the recovered (−)-**8a** albeit with unsatisfying enantioselectivities (entries 2 and 4). Next, chiral ligands (*S*)-BINAP **L3** and ($S,R_p$)-PPFA **L4** were further tested. A significant improvement in enantioselectivity for both *endo*/*exo*-**10a** (93% ee) and the recovered (−)-**8a** (90% ee) was observed when ($S,R_p$)-**L4** was employed as the chiral ligand ($S$ = 85; entry 6). To further optimize the stereoselectivity, we then conducted this reaction to evaluate the effect of solvent and temperature (entries 7−10). Solvent screening revealed that 1,2-dichloroethane is the best choice, and the recovered (−)-**8a** was obtained in 46% yield with 93% ee ($S$ = 94; entry 7). Reducing the reaction temperature to −30 °C led to the best outcome, affording the recovered (−)-**8a** in 40% yield with 98% ee without compromising the yield and ee value of **10a** ($S$ = 127; entry 11). The absolute configuration of **10a** was determined as (1*S*,3*R*,3a*S*,3b*S*,4*R*,7*S*,7a*S*,8a*R*) with *endo*/*exo*-geometry by X-ray diffraction analysis. Compared with the reported optical rotation,[19] the absolute configuration of the recovered **8a** was assigned as (3a*S*,4*S*,7*R*,7a*R*).

With the optimized reaction condition in hand, we next investigated the scope of *exo*-3-oxodicyclopentadienes **8** that participate in the cycloaddition of **9**, with a focus on kinetic resolution[20] (Figure 1). 2-Substituted *exo*-3-oxodicyclopentadienes could be readily synthesized by the intermolecular PKR of norbornadiene with terminal alkynes.[21] Although the

**Table 1. Reaction Optimization**[a]




| entry | L | [M] | solvent | $t$ (°C) | 10a yield(ee) (%)[b] | 8a yield(ee) (%)[b] | $S$[c] |
|---|---|---|---|---|---|---|---|
| 1 | **L1** | Ag(I) | $CH_2Cl_2$ | rt | - | - | - |
| 2 | **L1** | Cu(I) | $CH_2Cl_2$ | rt | 42(30) | 51(35) | 3 |
| 3 | **L2** | Ag(I) | $CH_2Cl_2$ | rt | - | - | - |
| 4 | **L2** | Cu(I) | $CH_2Cl_2$ | rt | 40(39) | 52(26) | 3 |
| 5 | **L3** | Cu(I) | $CH_2Cl_2$ | rt | 38(27) | 51(13) | 2 |
| 6 | **L4** | Cu(I) | $CH_2Cl_2$ | rt | 43(93) | 44(90) | 85 |
| 7 | **L4** | Cu(I) | $(CH_2Cl)_2$ | rt | 42(93) | 46(93) | 94 |
| 8 | **L4** | Cu(I) | THF | rt | 42(92) | 42(92) | 79 |
| 9 | **L4** | Cu(I) | PhMe | rt | 53(89) | 40(96) | 67 |
| 10 | **L4** | Cu(I) | $Et_2O$ | rt | 50(92) | 42(93) | 82 |
| 11 | **L4** | Cu(I) | $(CH_2Cl)_2$ | -30 | 43(93) | 40(98) | 127 |




[a]All reactions were carried out with *rac*-*exo*-**8a** (0.40 mmol), **9** (0.24 mmol), and $Et_3N$ (15 mol %) in 2 mL of solvent. [b]Isolated yields based on *rac*-*exo*-**8a**, >20:1 dr was determined by the crude $^1H$ NMR, and ee value of the cycloadduct **10a** and the recovered *exo*-**8a** were determined by HPLC and GC analysis, respectively. [c]$S = \ln[(1 - C)(1 - ee_{8a})]/\ln[(1 - C)(1 + ee_{8a})]$; $C = ee_{8a}/(ee_{8a} + ee_{10a})$.

corresponding cycloadducts contain one quaternary stereocenter adjacent to two tertiary stereocenters, to our surprise, the additional steric congestion caused by the substituent group at the 2-position brings no detrimental effect to this kinetic resolution protocol. The substrates **8b** and **8c** containing primary *n*-alkyl substituent were well tolerated, affording the recovered substrates with high selectivity factors (Figure 1, entries 1 and 2). Branched *iso*-pentyl group could be incorporated, delivering a 44% yield of **8d** with 94% ee accompanied by a 43% yield of **10d** with 95% ee ($S$ = 139, entry 3). To further check the effect of varying the alkyl group on this kinetic resolution protocol, *exo*-**8e** and *exo*-**8f** with sterically congested alkyl groups (cyclopropyl and cyclohexyl) were employed, and the reaction proceeded smoothly to recover the unreacted *exo*-(−)-**8e** and *exo*-(−)-**8f** in good yields with excellent enantioselectivities (entries 4 and 5). 2-Phenyl substituted *exo*-**8g**, which is one of the challenging products in Co-catalyzed asymmetric PKR,[10a] was also allowed in this protocol, affording the recovered *exo*-(+)-**8g** in 42% yield and 86% ee, and the ee value could be easily improved to 99% through single recrystallization (entry 6). Furthermore, functional groups such as hydroxyl, ether, and amide are also allowed to be incorporated (entries 7−11). Notably, bulky silyl substituted groups such as TMS and TES were well tolerated, and *exo*-**8m** and *exo*-**8n** could be efficiently resolved with *S* factor of 170 and 74, respectively (entries 12 and 13). The current protocol was compatible with halogen substituents, and unreacted *exo*-**8o** incorporating an iodine atom could be recovered in 40% yield and 99% ee with excellent selective



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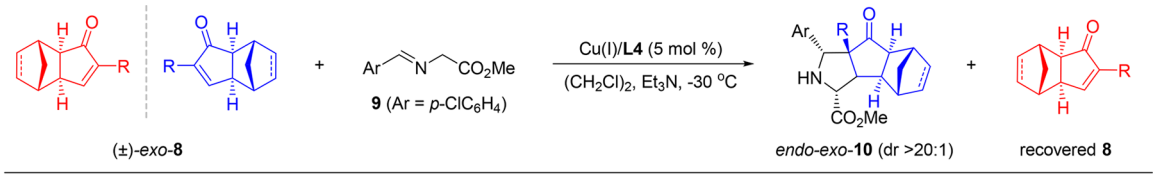


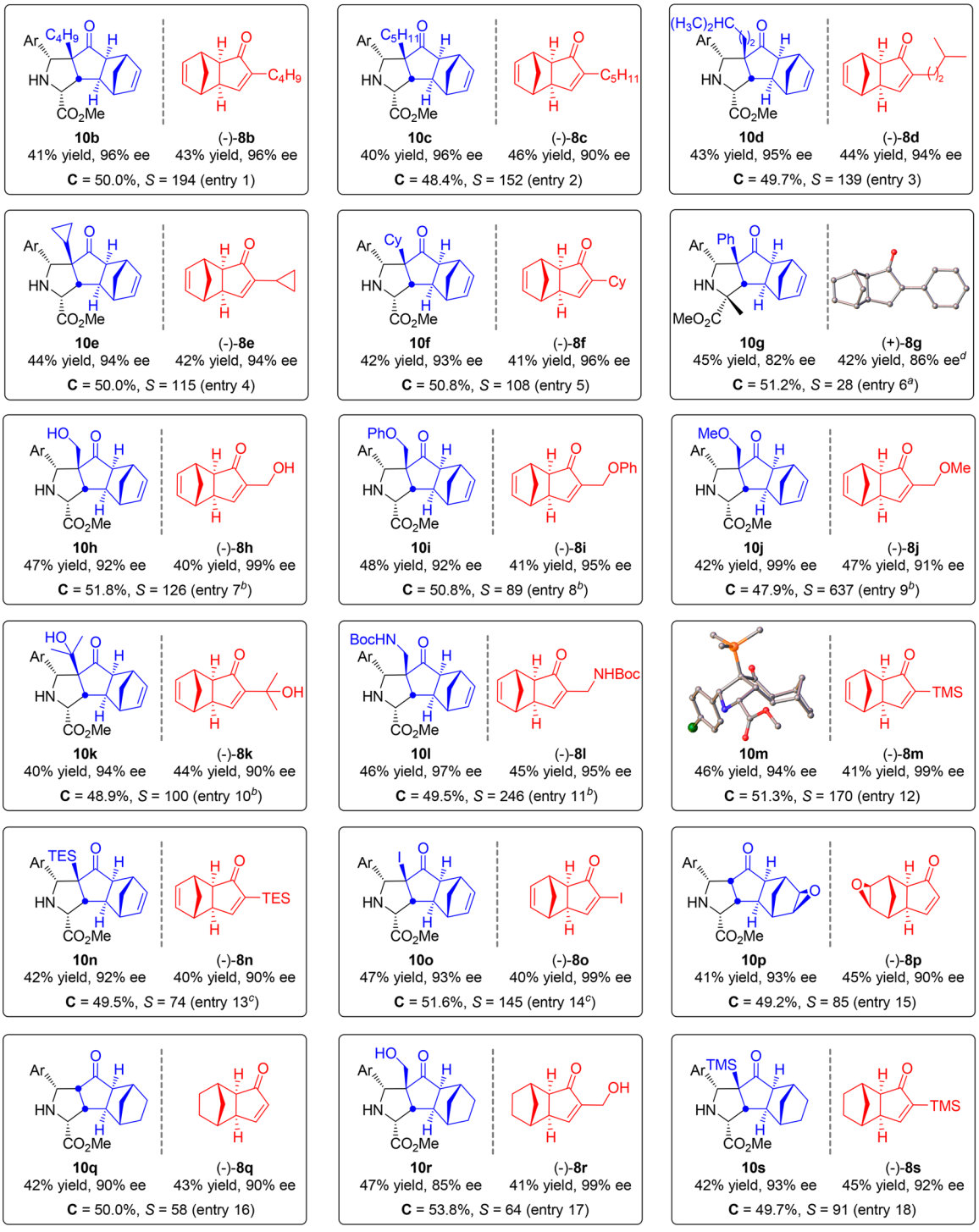


**Figure 1.** Kinetic resolution of racemic *exo*-3-oxodicyclopentadienes **8**. Unless otherwise noted, all reactions carried on with Cu(I)/**L4** (5 mol %), 0.4 mmol of *rac-exo*-**8**, and 0.24 mmol of **9** in 2 mL of $(CH_2Cl)_2$. Isolated yield based on *rac-exo*-**8**, >20:1 dr was determined by the crude $^1$H NMR, and ee values of **10** and recovered **8** were determined by HPLC analysis or GC analysis, respectively. $S = \ln[(1 - C)(1 - ee_8)]/\ln[(1 - C)(1 + ee_8)]$; $C = ee_8/(ee_8 + ee_{10})$. [a]$Cs_2CO_3$ was used as the base at −50 °C with $CH_2Cl_2$ as the solvent. [b]Reaction runs at −50 °C with $CH_2Cl_2$ as the solvent. [c]Reaction runs at −78 °C with $CH_2Cl_2$ as the solvent. [d]The ee value could be easily improved to 99% through single recrystallization.



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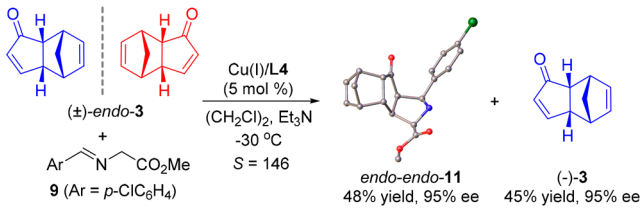
factor (145) (entry 14). Substrate *exo*-**8p**, in which the C=C bond of norbornene backbone was functionalized into oxirane moiety, worked well in this resolution (entry 15). In addition, several substrates *exo*-**8q**−**8s** derived from norbornene could be efficiently resolved through this protocol with accepted selectivity factors ($S$ = 58−91) (entries 16−18).

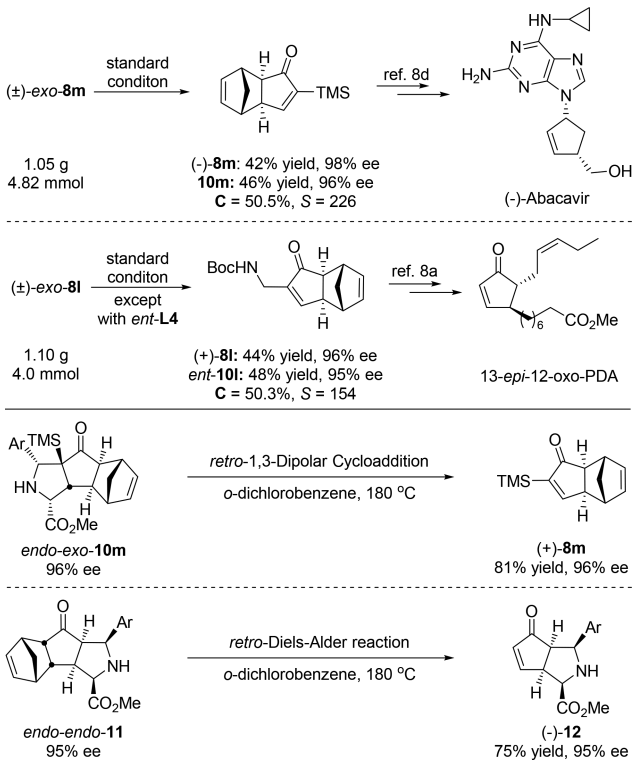
Encouraged by the successful kinetic resolution of *exo*-3-oxodicyclopentadienes, we further investigate the compatibility of this protocol with respect to racemic *endo*-3-oxodicyclopentadiene **3**. Pleasingly, racemic *endo*-**3** performed well in the current catalytic system, and *endo*-(−)-**3** was recovered in 45% yield with 95% ee accompanied by the cycloadduct **11** in 48% yield with 95% ee ($S$ = 146; Scheme 2), which indicates that the geometry of the fused norbornene backbone has a negligible effect on the efficiency of this kinetic resolution protocol.

**Scheme 2. Kinetic Resolution of Racemic *endo*-Oxodicyclopentadiene 3**




To further evaluate the synthetic potential of this kinetic resolution protocol, a gram-scale reaction of *rac-exo*-**8m** was then carried out, and the yields and enantioselectivities for both cycloadduct **10m** and the recovered *exo*-(−)-**8m** were achieved with the maintained high selectivity factor (Scheme 3, upside).

**Scheme 3. Gram-scale Reaction for the Synthesis of the Key Intermediates of Bioactive Compounds, Pyrolytic *retro*-1,3-Dipolar Cycloaddition, and *retro*-Diels Alder Reaction**




Optically active *exo*-(−)-**8m** is the key intermediate for the asymmetric synthesis of (−)-Abacavir and (−)-Carbovir,[8d] which have shown major antiviral and anticancer activities. Employing Cu(I)/($R$,$S_p$)-PPFA(*ent*-**L4**) complex as the catalyst, *exo*-(+)-**8l**, the pivotal building block for the enantioselective synthesis of 13-*epi*-12-oxo-PDA,[8a] could be readily achieved in good yield with 96% ee and up to 154 selective factor under the optimized reaction condition. Both *exo*-(−)-**8m**[8d] and *exo*-(+)-**8l**[8a] were previously obtained with a stoichiometric amount of chiral Co-complex. By comparison, the current kinetic resolution protocol is realized with a catalytic amount of chiral catalyst. Notably, (+)-**8m** and (−)-**12** could be readily achieved in good yields without loss of enantiopurity through pyrolytic *retro*-1,3-dipolar cycloaddition and *retro*-Diels−Alder reaction of the corresponding cycloadduct *endo*/*exo*-**10m** and *endo*/*endo*-**11**, respectively (Scheme 3, bottom).

In summary, we have developed the first example of kinetic resolution of racemic *exo*-3-oxodicyclopentadienes and *endo*-3-oxodicyclopentadiene through Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylide under mild reaction conditions, thus achieving excellent enantioselectivity (up to 99% ee) and high selectivity factors (up to 637). The current protocol provides an alternative but more practical approach to both of the optically active *exo*-3-oxodicyclopentadienes and *endo*-3-oxodicyclopentadiene. The easy-availability of the racemic starting materials and the synthetic importance of the enantioenriched enones make this methodology particularly interesting in synthetic chemistry. Further investigations on the reaction mechanism and applications of this methodology are under way.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00136.

Experimental procedures and compound characterization data (PDF)

### Accession Codes

CCDC 1864127−1864128, 1865669, and 1867702 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.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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