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HIGHLIGHTS
- Kinetic resolution of racemic alkylidene norcamphors
- Spiro architectures incorporating norbornane and pyrrolidine scaffolds
- Unique ligand-enabled umpolung-type 1,3-dipolar cycloaddition

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Kinetic Resolution of Alkylidene Norcamphors via a Ligand-Controlled Umpolung-Type 1,3-Dipolar Cycloaddition

Chong Shen,1,2,5 Yuhong Yang,4,3,5 Liang Wei,1 Wu-Wei Dong,1 Lung Wa Chung,3,* and Chun-Jiang Wang1,2,6,*

SUMMARY
Development of a general catalytic and highly efficient method utilizing readily available precursors for the regio- and stereoselective construction of bioactive natural-product-inspired spiro architectures remains a formidable challenge in chemical research. Transition metal-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides produces numerous N-heterocycles, but reaction control with the regioselectivity opposite to the conventional fashion has rarely been demonstrated. Herein, we report a unique ligand-controlled Cu(I)-catalyzed umpolung-type 1,3-dipolar cycloaddition of azomethine ylide to realize efficient kinetic resolution of racemic alkylidene norcamphors with the concomitant construction of previously inaccessible spiro N-heterocycles with high levels of regio- and stereoselectivity. The success of this methodology relies on the strategy of kinetic resolution, and the serendipitous discovery of a unique ligand-enabled regiospecific cycloaddition, which not only provides evidence for the existence of the minor zwitterionic resonance form in metallated azomethine ylide but also diversifies the existing chemistry of azomethine ylide-involved 1,3-dipolar cycloadditions with rare polarity inversion.

INTRODUCTION
1,3-Dipolar cycloaddition reaction is one of the fundamental processes in organic chemistry (Huisgen, 1963; Padwa, 1984; Padwa and Pearson, 2003). In particular, catalytic asymmetric 1,3-dipolar cycloaddition of in situ-formed metallated azomethine ylides (dipoles) from readily available imino esters (Figure 1A) offers the most powerful and diversity-oriented synthesis (Schreiber, 2000) (DOS) for the convergent construction of numerous enantioenriched five- or six-membered nitrogen-containing heterocycles in stereocontrolled fashion (Hashimoto and Maruoka, 2015; Adro and Carretero, 2011, 2014; Stanley and Sibi, 2008; Álvarez-Corrall et al., 2008; Najera and Sansano, 2005; Pelissier, 2007; Pandey et al., 2006; Coldham and Hufton, 2005), which are very important pharmaceuticals, natural alkaloids, and building blocks in organic synthesis. Metallated azomethine ylide has four π electrons spread over a C-N-C unit, which can be presented by the two most common zwitterionic resonance forms as shown in Figure 1B: the coordinated central N atom is positively charged, and the negative charge is distributed over the two adjacent carbon atoms (Pandey et al., 2006; Coldham and Hufton, 2005). In general, the major zwitterionic resonance form I makes greater contribution to the resonance hybrid structure because the negative charge of the intermediate is delocalized by the neighboring electron-withdrawing ester group, which accounts for the observed regioselectivity of the well-explored 1,3-dipolar cycloaddition controlled by the highest occupied molecular orbital (HOMO) of the azomethine ylide interacting with the lowest unoccupied molecular orbital of the electron-deficient dipolarophiles (Pandey et al., 2006; Coldham and Hufton, 2005; Houk, 1975; Houk et al., 1973). Although the umpolung-type 1,3-dipolar cycloaddition related with the minor zwitterionic resonance form II would give rise to the opposite regioselectivity and thus greatly enhance the diversity of product accessible from azomethine ylide, such polarity inversion reactivity remains elusive so far and was sporadically reported in limited examples (Barr et al., 1989; Kanemasa et al., 1990; Chen et al., 2009; Xu et al., 2018; Feng et al., 2018) or the intramolecular cycloaddition caused by conformational ring constrain (Stohler et al., 2005).

Kinetic resolution (Kagan and Fiaud, 1988; Vedejs and Jure, 2005; Pelissier, 2011) is one of the commonly used strategies to obtain the optically active compounds from racemic starting materials, which was recently also employed in cycloaddition reactions (Cardona et al., 2001; Yu et al., 2010; Takayama et al., 2013; Xu et al., 2016; Yuan et al., 2018). As part of our ongoing research interest in asymmetric 1,3-dipolar cycloaddition (Wang et al., 2008, 2012; He et al., 2013; Li et al., 2014), we considered employing kinetic

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resolution strategy to develop a new cycloaddition process with readily accessible racemic alkylidene norcamphors as dipolarophiles (Figure 1C). This methodology would not only provide a simple and efficient access to synthetically important chiral building block alkylidene norcamphors but also efficiently assemble complex natural-product-inspired polycyclic spiro architectures incorporating norbornane and pyrrolidine scaffolds, both of which are the core structures embedded ubiquitously in natural products and pharmaceuticals, and therefore much attention has been paid to synthetic and biological studies (Reinhard et al., 1992; Suchocki et al., 1991; Demole et al., 1976; Odds, 2001; Chen and Lipton, 2006; Iqbal et al., 2013) (Figure 1D). However, several significant challenges are associated with this design and differentiate it from the majority of azomethine ylide-involved cycloadditions described previously including (1) the lower reactivity of alkylidene norcamphors with the inherent convex skeleton as dipolarophiles because both the upper and lower sides of C=C bond are sterically hindered from a facial recognition standpoint, which would impede the approach of the dipole, and (2) a formidably challenging spiro quaternary stereogenic carbon center (Christoffers and Baro, 2005) is generated on the sterically congested pyrrolidines ring (having up to five substituents) with stereoselectivity control. The paucity of synthetic methodologies available in the literature for the efficient construction of enantioenriched alkylidene norcamphors and spiro[norbornane-pyrrolidines] encouraged us to launch this project. Herein, we report for the first time the highly efficient kinetic resolution of readily available racemic alkylidene norcamphors via Cu(I)-catalyzed 1,3-dipolar cycloaddition with concomitant construction of previously inaccessible spiroheterocycles. Notably, this rationally designed 1,3-dipolar cycloaddition is endowed with the serendipity of realizing the potential polarity inversion of metallated azomethine ylide (Figure 1C), which provides direct and convincing experimental evidence for the existence of the minor zwitterionic resonance form in metallated azomethine ylide.

RESULTS AND DISCUSSION

To test the feasibility of racemic alkylidene norcamphors as dipolarophiles, in preliminary experiments we examined the reaction of commercially available 3-methylene norcamphor 1a and N-(4-chlorobenzylidene)-glycine methyl ester 2a with Et$_3$N as the base in the presence of Cu(I)/rac-(±)-TF-BiphamPhos
complex (Wang et al., 2008) as the catalyst (Scheme 1). In view of steric hindrance, terminal alkene moiety connected to the bulky norcamphor scaffold is believed to possess higher reactivity and therefore facilitate the potential cycloaddition process. Racemic TF-BiphamPhos \((\text{L}1)\) was employed as the ligand to simplify the stereochemical analysis of the cycloadduct because only diastereoselectivity was considered in this case. TF-BiphamPhos, as one of the privileged ligands in 1,3-dipolar cycloaddition (Adrio and Carretero, 2014), exhibited exclusive endo-selectivity for a variety of pyrrolidine synthesis, which is the foundation of the hypothetic kinetic resolution of racemic alkylidene norcamphors. Initial experimental results were far from encouraging; full conversions of methylene norcamphor were observed at 5 mol % catalyst loading, but resulted in cycloadducts as two inseparable isomers in 3:1 ratio on silica gel column according to crude \(^1\text{H}\) nuclear magnetic resonance, which at first was regarded as the diastereoselective ratio of the endo-adduct to the exo-adduct. This assumed diastereoselectivity is contradactible with the perfect endo-selectivity control exhibited by TF-BiphamPhos in our previous work. Therefore some verification experiments must be carried out to provide the irrefutable evidence on the stereochemical configurations of the two original isomers. Subsequent N-tosylation of the cycloadducts successfully converted the two isomers into separable and crystallizable compounds. To our surprise, X-ray diffraction analysis of the tosylated \(3\alpha\) and \(5\alpha\) revealed that both the cycloadducts are regiosomers rather than the assumed diastereomers (see Supplemental Information for the details). It is generally believed that the approach of the azomethine ylide to the methylene norcamphor would occur specifically from the EXO-direction due to the "picket fence effect" exhibited by norbornane (Mangan et al., 2016; Corey et al., 1962) (Scheme 2). The major isomer was formed through the endo-selective 1,3-dipolar cycloaddition related with the major zwitterionic resonance form I, but the minor one with the opposite regioselectivity was formed via the umpolung-type endo-selective 1,3-dipolar cycloaddition related with the minor zwitterionic resonance form II (Scheme 1). Notably, this serendipitous finding regarding the minor isomer \(5\alpha\) offers direct experimental
evidence on the two zwitterionic resonance structures of a metallated azomethine ylide. Inspired by these promising results, we further investigated the potential regioselectivity and enantioselectivity control to realize the asymmetric variant of this umpolung-type cycloaddition with a series of chiral TF-BiphamPhos ligands, and the results are tabulated in Table 1. With Cu(I)/((S)-L1 complex as the catalyst, cycloadducts (3a + 5a) were separated in 96% yield with moderate regioselective ratio (rr) (3:1), and 73% enantiomeric excess (ee) for 3a and 20% ee for 5a (Table 1, entry 1). When the phenyl group on the phosphorus atom of ligand L1 was replaced by bulky electron-donating 3,5-bis(methyl)phenyl (L2), or electron-withdrawing 3,5-bis(trifluoromethyl)phenyl group (L3), however, the conventional cycloadduct endo-3a was formed predominantly in high yields with good to excellent rr and good ee (Table 1, entries 2 and 3). Chiral ligand L4 containing cyclohexyl groups on the phosphorus atom also displayed normal regioselectivity control with a detrimental effect on the enantioselectivity. To our delight, further ligand screening revealed that ligand L5 incorporating two bromine atoms at the 3,3'-positions of the biphenyl scaffold completely reversed the regioselectivity, affording endo-5a in 90% yield with exclusive diastereoselectivity and 92% ee (Table 1, entry 5). A subsequent solvent survey indicated that dichloromethane was the best solvent of choice in terms of regioselectivity and diastereo-/enantioselectivity (Table 1, entries 5–10). Lowering the reaction temperature was beneficial for enantioselectivity control, and high yield with 94% ee was achieved for endo-5a when the reaction was performed at −40°C (Table 1, entry 11).

Having the optimized reaction conditions in hand, we examined the substrate scope of the 1,3-dipolar cycloaddition by treating methylene norcamphor (rac-1a) with various imine esters 2 (Table 2). The representative results are tabulated in Table 2. A variety of glycine ester imines are compatible with this umpoling-type 1,3-dipolar cycloaddition reaction, providing the desired cycloadducts in excellent regio- and stereoselectivities. Aryl aldimine esters incorporating different substitution patterns on the phenyl ring were well tolerated in this reaction, and the corresponding cycloadducts 5 were obtained in acceptable yield (59%–94%) with exclusive regioselectivity (>20:1 rr), perfect diastereoselectivity (>20:1 dr) and

Scheme 2. Computed Overall Free-Energy Barrier of the Formation of Several Products from the Reaction of (1R,4S)-1a and 2a Catalyzed by Cu(I)-LI in Dichloromethane (DCM) Solution by the Polarizable Continuum Model (PCM)-B3LYP//B3LYP Method

The two coordination modes of Ph in the Cu-azomethine ylides (L1D and L1U) were considered for the most important intermediates (D: Ar downward; U: Ar upward). The computed NBO charge for the two reacting carbon atoms is also given in an italic form.
excellent enantioselectivity (93%–97%) (Table 2, entries 1–14). It is worth mentioning that perfect regioselectivity and excellent stereoselectivity could be still achieved with the sterically hindered ortho-chloro (2e), ortho-methyl (2l), and 1-naphthyl (2m) imino esters (entries 5, 12, and 13). The electronic property of the substituent group on the aryl ring slightly affected the reactivity of this cycloaddition. The cycloaddition reaction furnished quickly with aldimine ester containing strong electron-deficient \( p \)-NO\(_2\) or \( p \)-CN substitution on the phenyl ring (entries 6 and 7). Extended reaction time was needed for electron-rich aldimine esters, but the regioselectivity and stereoselectivity still maintained at the excellent level (Table 2, entries 9–12). Aliphatic aldimine esters were not compatible in this reaction, probably due to the reduced reactivity. Notably, \( \alpha \)-methyl- or benzyl-substituted aldimine esters were tested to further investigate the

| Entry | Ligand | Solvent | \( rr \) | Yield (%) | ee (%) |
|-------|--------|---------|---------|-----------|--------|
| 1     | L1     | CH\(_2\)Cl\(_2\) | 1:3     | 96        | 73 (3a) |
| 2     | L2     | CH\(_2\)Cl\(_2\) | 1:14    | 94        | 84 (3a) |
| 3     | L3     | CH\(_2\)Cl\(_2\) | <1:20   | 96        | 89 (3a) |
| 4     | L4     | CH\(_2\)Cl\(_2\) | <1:20   | 83        | 46 (3a) |
| 5     | L5     | CH\(_2\)Cl\(_2\) | >20:1   | 90        | 92 (5a) |
| 6     | L5     | THF     | 8:1     | 92        | 86 (5a) |
| 7     | L5     | EtOAc   | 4:1     | 94        | 86 (5a) |
| 8     | L5     | CH\(_3\)CN | 10:1    | 78        | 93 (5a) |
| 9     | L5     | PhMe    | 18:1    | 93        | 88 (5a) |
| 10    | L5     | CHCl\(_3\) | 6:1     | 88        | 90 (5a) |
| 11    | L5     | CH\(_2\)Cl\(_2\) | >20:1   | 91        | 94 (5a) |

Table 1. Optimization of 1,3-Dipolar Cycloaddition of Azomethine Ylide with 3-Methylene-2-Norbornanone 1a

\(^{a}\) All reactions were carried out with 0.20 mmol of 2a and 0.40 mmol of 1a in 2 mL solvent, 48–60 hr CuBF\(_4\) = Cu(MeCN)\(_4\)BF\(_4\).

\(^{b}\) \( rr \) was determined by crude \(^1\)H nuclear magnetic resonance, and ee was determined by high-performance liquid chromatography.

\(^{c}\) Isolated yield of 3a and 5a based on 2a.

\(^{d}\) Carried out at \(-40°C\).
The cycloaddition proceeded very well, affording the corresponding spiro[3.3]norbornane-pyrrolidines decorated with one all-carbon and one N-containing quaternary stereogenic center in synthetically useful yields (57%–70%) with exclusive regioselectivity (>20:1 dr) and excellent stereo-selectivities (>20:1 dr; 96%–99% ee) (Table 2, entries 15–18).

The fact that enantioenriched spirocycloadduct 5a could be formed regiospecifically in an exclusive diastereoselective fashion from racemic methylene norcamphor 1a (Table 1, entry 11) shows that the two enantiomers of methylene norcamphor have significantly different reactivity in this catalytic system. Therefore kinetic resolution of alkylidene norcamphors employing Cu(I)/(S)-L5-catalyzed cycloaddition should be worthy of our further investigation. In the early study of treating 0.4 mmol of racemic methylene norcamphor 1a with 0.2 mmol of glycine imino ester 2a (Table 1, entry 11), when the spirocycloadduct 5a was

| Entry | R   | R’  | S   | Yield (%) | ee (%) |
|-------|-----|-----|-----|-----------|--------|
| 1     | p-Cl-C6H4 | H   | 5a  | 91        | 94     |
| 2     | m-Cl-C6H4 | H   | 5b  | 88        | 95     |
| 3     | p-Br-C6H4 | H   | 5c  | 84        | 95     |
| 4     | m-Br-C6H4 | H   | 5d  | 85        | 94     |
| 5     | o-Cl-C6H4 | H   | 5e  | 94        | 94     |
| 6     | p-NO2-C6H4 | H   | 5f  | 72        | 98     |
| 7     | p-CN-C6H4 | H   | 5g  | 83        | 94     |
| 8d    | Ph   | H   | 5h  | 86        | 93     |
| 9d    | p-MeO-C6H4 | H   | 5i  | 59        | 95     |
| 10d   | p-Me-C6H4 | H   | 5j  | 74        | 93     |
| 11d   | m-Me-C6H4 | H   | 5k  | 66        | 94     |
| 12d   | o-Me-C6H4 | H   | 5l  | 64        | 97     |
| 13d   | 1-Naphthyl | H   | 5m  | 73        | 95     |
| 14d   | 2-Naphthyl | H   | 5n  | 88        | 93     |
| 15    | p-Cl-C6H4 | Me  | 5o  | 70        | 97     |
| 16d   | p-MeO-C6H4 | Me  | 5p  | 57        | >99    |
| 17d   | 2-Thienyl | Me  | 5q  | 64        | 96     |
| 18d-f | p-Cl-C6H4 | Bn  | 5r  | 68        | >99    |

Table 2. Scope of Azomethine Ylides for Cu(I)-Catalyzed 1,3-Dipolar Cycloaddition with 3-Methylene-2-Norbornanone 1a

*All reactions were carried out with 0.2 mmol of 2 and 0.4 mmol of 1a in 2 mL CH2Cl2 in 8–12 hr.

1Isolated yield based on 2.

dr was determined by crude 1H nuclear magnetic resonance, and ee was determined by high-performance liquid chromatography.

carried out at –20°C in 36 hr.

*Inorganic base Cs2CO3 was used.

Carried out at –0°C in 48 hr.
Table 3. Kinetic Resolution of Various rac-Alkylidene Norcamphors 1

(Continued on next page)
Table 3. Continued

*Reaction conditions: rac-1 (0.4 mmol), 2 (0.6 mmol), Et<sub>3</sub>N (0.01 mmol), Cu(I)/(S)-L<sub>5</sub> (0.02 mmol) in 2 mL CH<sub>2</sub>Cl<sub>2</sub> in 48 hr. Isolated yield was based on 1, and the maximum possible yield of (1S,4R)-1 is 50%. >20:1 dr of 3 was determined by crude <sup>1</sup>H nuclear magnetic resonance. ee of 4 and (1S,4R)-4 was determined by high-performance liquid chromatography, and ee of (1S,4R)-4 and (1S,4R)-1 was determined by gas chromatography.

*Carried out at −60°C.

*Conversion of (rac)-1 = ee<sub>1</sub>/([ee<sub>1</sub> + ee<sub>3</sub>]).

*S-factor = ln([1 - conv],[1 - conv]/ln([1 - conv],[1 + conv]).

*Carried out at −40°C.

*The crystal of (±)-5a for X-ray analysis was obtained from the corresponding cycloadduct with (±)-TF-BiphamPhosL<sub>5</sub> as the ligand.
separated in 91% yield (isolated yield based on imino ester 2a) with >20:1 dr and 94% ee, methylene nor
camphor 1a was also recovered in 45% yield (isolated yield based on 1a initially used) and 91% ee with high
selectivity factor ($S = 103$) albeit within longer reaction time of up to 48 hr. In consideration of the fact that
enantioenriched norcamphors are synthetically useful building blocks, we further re-optimized the reaction
conditions to develop more efficient kinetic resolution protocol in terms of both the selectivity factor and
reaction time. In short, by increasing the feed ratio of imino ester to alkylidene norcamphor and adjusting
the reaction temperature (see Supplemental Information for the details), a variety of racemic alkylidene
norcamphors could be resolved more reproducibly with high selectivity factors ($S = 38–303$) within reduced
reaction time (18–24 hr) (Table 3). Under the re-optimized reaction conditions, terminal methylene norca-
mphor ($\text{rac}-1a$) was resolved efficiently via asymmetric Cu-catalyzed cycloaddition of different aldimine esters
with selectivity factors of up to 136 and good yields (Table 3, entries 1–4). Notably, excellent ee values for
both spiroaduct 5o and recovered 1a were achieved with high selectivity factors when alanine-derived
imino esters 2o were employed as the reaction partner. To better define the substrate scope and limitation
with respect to the dipolarophiles, an array of more challenging trisubstituted alkylidene norcamphors
were further investigated. (E)-benzylidene norcamphors containing various substituents at para- or
meta-position of the phenyl ring were tolerated well, regardless of the electron properties (e.g., electron
deficient, electron neutral, or electron rich), affording the desired spirocycloadducts with 93%–97% ee and
the recovered norcamphors with 94–99% ee, corresponding to selectivity factors ($S$) of 98–188. Probably
due to disfavored steric hindrance, ortho-fluoro-substituted benzylidene norcamphor has detrimental ef-
ficacy on the regioselectivity of the cycloadducts, but still furnishes the recovered norcamphor 1f with an ee
value of 99%. Heteroarylidene norcamphors were also well tolerated in this catalytic system (Table 3, entries
14 and 15). Remarkably, 3-pyridin-2-ylidene norcamphor 1l could be resolved efficiently, producing the ex-
pected cycloadduct 5c with 97% ee and recovered product 1l with 98% ee, with the highest selectivity fac-
tor of 303. Alkyl-substituted alkylidene norcamphors were not viable substrates in this reaction, probably
due to the pretty low reactivity. All the racemic trisubstituted alkylidene norcamphors tested in this work were obtained exclusively with more than 99% (E)-geometry via base-promoted condensation between norcamphor and the corresponding aldehyde. Considering that the geometry of C=C double bond has an important influence on the reactivity or stereoselectivity in alkene-involved asymmetric reactions, we further studied the performance of (Z)-benzylidene norcamphor 1b, which could be obtained with 99% configurational purity upon UV light irradiation (Berthelette et al., 1997) of (E)-1b. Under the same reaction conditions, no reaction took place when racemic (Z)-benzylidene norcamphor was tested. No reaction occurred with the racemic methylene camphor as the dipolarophile presumably because the disfavored steric repulsion caused by the bridged 7,7-dimethyl group impedes the approach of the azomethine ylide from the EXO-direction. Both racemic methylene exo- and endo-tricycle[5.2.1.02,6]decan-8-one, containing a fused cyclopentane moiety on the norcamphor skeleton, were well tolerated and resolved to afford the corresponding spiroadducts containing seven stereogenic centers and the recovered fused norcamphors with selectivity factors of 156 and 38, respectively (Table 3, entries 16 and 17). Exo-1m displayed higher reactivity, furnishing the chiral spiro polycyclic adduct with better ee value. Racemic methylene 2-benzonorbornanone 1o bearing a fused benzene ring was also a viable substrate for this kinetic resolution protocol, providing the cycloadduct 5F and the recovered 1o with high enantioselectivity and a selectivity factor of 74 (Table 3, entry 18). The absolute configuration of spirocycloadduct 5b from methylene norcamphor and 5u from para-bromobenzylidene norcamphor was unambiguously determined by X-ray diffraction crystallography as (1S,2S,20S,4R,50R) and (1S,2R,20S,4R,50R), respectively (see Supplemental Information for the details). The absolute configuration of the recovered methylene norcamphors was assigned as (1S,4R), which was deduced from the stereochemistry result of kinetic resolution and further confirmed by comparing the optical rotation of 1a with the data reported in the literature (Krotz and Helmchen, 1994). Those of other spiroadducts and recovered alkylidene norcamphors were deduced based on these results.

To understand the mechanism of the unusual ligand-controlled regioselectivity and kinetic resolution of the cycloaddition reaction, density functional theory (DFT) (B3LYP/6-31G(d)+SDD method) (Wang et al., 2012) calculations were carried out by using Cu(I), substrates 1a and 2a, as well as L1 ligand (or L5 for the most important cases) as our system (See Supplemental Information for the details). As shown in Schemes 2 and 3 and Figure 2, the reacting C2 atom of two Cu-azomethine ylide intermediates L1D and L5D had a more negative charge (−0.24) and contributed to slightly larger HOMO than the other reacting C4. This result supported the major resonance form I (Scheme 1). For the reaction with (1R,4S)-1a, our computational results showed that intermediate L1D (using L1 ligand) generally had lower barriers for the cycloaddition toward the EXO-direction to the methylene norcamphor than the ENDO-direction, owing to the above-mentioned “picket fence effect” (Scheme 2). Moreover, the most kinetically favorable pathway preferred the formation of the normal and major endo-selective cycloaddition product P3a other than the exo-selective P4a via the rate-determining Michael-addition-type transition state 3a-L1D-TS1endo (Scheme 2 and Figure 3), which had a lower barrier than that for the umpolung-type and minor endo-selective cycloaddition product P5a via 5a-L1D-TS1endo (Michael-addition type) by roughly 3.0 kcal/mol. The norcamphor approached the amine side of L1 ligand and formed a strong hydrogen bond (NH−O: 1.78 Å) in 3a-L1D-TS1endo. However, when the norcamphor approached the phosphorus side of L1 ligand to form P5a
in 5a-L1D-TS1endo, the amine nitrogen of L1 ligand was found to dissociate from the Cu center and the carbonyl oxygen of the norcamphor coordinated to the metal (Cu–O: 2.14 Å). As the norcamphor was required to approach the phosphorus side of the ligand to afford \( P_{5a} \), increasing steric repulsion between norcamphor and the more bulky phosphine ligand (L2, L3 or L4) should further disfavor the umpolung-type regioselectivity (Table 1). In addition, the reaction of intermediate L1D with (1S,4R)-1a was computed to have a higher barrier to form \( P_{3a} \) by about 2.1 kcal/mol, which demonstrated a lower reactivity of (1S,4R)-1a and explained the observed kinetic resolution.

Interestingly, when replacing L1 ligand by L5 ligand, the most favorable pathway switched to the umpolung regiochemistry to give endo-selective 5a via 5a-L5D-TS1end, which is lower in free energy than the normal regiochemistry to form endo-selective 3a via 3a-L5D-TS1end by ~0.9 kcal/mol (Scheme 3). An electrostatic repulsion between the carbonyl oxygen of the norcamphor and one bromine (Br1) atom of the biphenyl ligand (O–Br: 3.23 Å in 3a-L5D-TS1end, shorter than the sum of their van der Waals radii [3.37 Å]; see Figure 3) was found to weaken the hydrogen bond between the substrate and ligand and, thus, should play a key role in inverting regiocontrol of the cycloaddition. Moreover, the natural bond orbital (NBO) charge of the reacting C2 and C4 atoms were found to become less negatively charged and more negatively charged, respectively, in the key umpolung-type transition states 5a-L1D-TS1endo and 5a-L5D-TS1endo, showing more contribution of the minor resonance form II (Scheme 1). Furthermore, the reaction of L5D with (1S,4R)-1a leading to \( P_{5a} \) had to overcome a higher barrier height by 1.2 kcal/mol relative to the formation of \( P_{5a} \) from (1R,4S)-1a. Overall, these computational results were

**Figure 3. DFT Calculations**

The computed most critical transition states with NBO charge for the two reacting carbon atoms (in an italic form), key bond lengths (in angstrom), and relative free energy (in kcal/mol) for the reactions with 2a, (1R,4S)-1a, or (1S,4R)-1a catalyzed by Cu(I)-L1 or Cu(I)-L5 in Dichloromethane (DCM) solution by the polarizable continuum model (PCM)-B3LYP/B3LYP method.
qualitatively consistent with the observed ligand-controlled regioselectivity and kinetic resolution, and also showed the key role of the bromine atoms.

To demonstrate the scalability of this methodology, we carried out the gram-scale kinetic resolution of methylene norcamphor rac-1a (9.0 mmol, 1.10 g) with imino ester 2a in the presence of as low as 1 mol % of Cu(I)/L5 catalyst, which furnished (1S,4R)-1a (44% yield, 96% ee) and the spirocycloduct 5a (48% yield, 97% ee) with a selectivity factor of 260 at 50% conversion (Scheme 4A). In a similar fashion, benzylidene norcamphor rac-1b (5.3 mmol, 1.05 g) could also be efficiently resolved with a selectivity factor of 121 at 50% conversion. The synthetic transformations of the resolved benzylidene norcamphor were then evaluated. Luche reduction of the carbonyl group in (1S,4R)-1b with NaBH4/Ca(OTf)2 in a highly diastereo- selective fashion led to compound endo-6 in 88% yield with the maintained enantioselectivity. Direct hydrogenation of 1b in the presence of catalytic amount of Pd/C in methanol gave compound endo-7 in 81% yield with exclusive diastereoselectivity control. Subsequent Baeyer-Villiger oxidation of 7 with meta-chloroperbenzoic acid (m-CPBA) in CH2Cl2 at room temperature afforded the previously inaccessible bridged lactone 8 in 98% yield without loss of enantiomeric excesses (Scheme 4B). To further demonstrate the potential utility of this methodology, the Cu(I)-catalyzed kinetic resolution of alkylidene norcamphor was successfully applied to the facile synthesis of the key intermediate of (Z) and (E)-β-santalol (Krotz and Helmchen, 1994) (Scheme 4C). A concise synthetic route was designed to those chiral odorants, which

Scheme 4. Synthetic Versatility of the Present Catalytic System
(A) Scale-up of the kinetic resolution process with as low as 1 mol % catalyst loading.
(B) Derivatization of recovered optically active alkylidene norbornanone (1S,4R)-1b.
(C) Facile access to the key intermediate of chiral odorants (Z) and (E)-β-santalol.
relies on the highly efficient kinetic resolution of racemic methyldiene norcamphor with Cu(I)/(R)-L5 complex, leading to (1R,4S)-1a (40% yield, >99% ee) with excellent efficiency at 54% conversion. (1R,4S)-1a could be readily hydrogenated with Pd/C to deliver compound endo-9 in 99% yield with the maintained enantioselectivity in an excellent diastereoselective manner (>20:1 dr). Treatment of compound 9 with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by the addition of Stowell iodide (Stowell et al., 1983) exclusively afforded the exo-alkylation product 11, the key intermediate for (−)-2 and (E)-β-santalol.

Conclusion
We have developed an expedient kinetic resolution of synthetically important racemic alkylidene norcamphors by Cu(I)-catalyzed umpolung-type 1,3-dipolar cycloaddition of azomethine ylide with the DOS of natural-product-inspired spiro[norbornane-pyrrolidines] containing multiple stereogenic centers. The success of this methodology relies heavily on the rational design, which led to implement the strategy of kinetic resolution, and serendipity, which led to the discovery of a unique ligand-controlled regiospecific cycloaddition, which is especially notable and provides direct experimental evidence for the existence of two zwitterionic resonance forms in metallated azomethine ylide. Beyond the broad utility in organic synthesis, this protocol diversifies the existing chemistry of transition metal-catalyzed 1,3-dipolar cycloadditions of azomethine ylide with rare polarity inversion.

METHODS
All methods can be found in the accompanying Transparent Methods supplemental file.

DATA AND SOFTWARE AVAILABILITY
Crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC) as CCDC 1592399 (tosylated(±)-endo-3a), 1592400 (tosylated endo’-5a), 1562402 (5b), 1562404 (5s), 1562405 (±-5u), and 1562406 (±-1d), which can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/getstructures.

SUPPLEMENTAL INFORMATION
Supplemental Information includes Transparent Methods, 183 figures, 10 tables, and 6 data files and can be found with this article online at https://doi.org/10.1016/j.isci.2018.12.010.

ACKNOWLEDGMENTS
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AUTHOR CONTRIBUTIONS
C.-J.W. and C.S. conceived and designed the research. C.S., L.W., and W.-W.D. performed the research. Y.Y. and L.W.C. performed the DFT calculations. C.J.W., L.W.C., and C.S. co-wrote the paper. All authors analyzed the data, discussed the results, and commented on the manuscript.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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Berthelette, C., McCooye, C., Leblanc, Y., and Trimble, L.A. (1997). Studies on the dimerization of 2-benzylidene-1-indanone. J. Org. Chem. 62, 4339–4342.
Supplemental Information

Kinetic Resolution of Alkyldene Norcamphors via a Ligand-Controlled Umpolung-Type 1,3-Dipolar Cycloaddition

Chong Shen, Yuhong Yang, Liang Wei, Wu-Wei Dong, Lung Wa Chung, and Chun-Jiang Wang
Supplemental Figures for $^1$H, $^{13}$C and NOESY NMR Spectra and HPLC Spectra

Figure S1. $^1$H NMR spectrum of 5a, related to Table 2.

Figure S2. $^{13}$C NMR spectrum of 5a, related to Table 2.
### Area Percent Report

Sort By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

**Signal 1:** DA1, Sig=220, Ref=363,100

| Peak RetTime Type | Width | Area   | Height | Area |
|------------------|-------|--------|--------|------|
|                  | [min] | [min]  | [pmAU] | [pmAU] |
|                  |       |        |        |      |
| 1                | 12.328 BB | 0.4035 | 2,696,183 | 975.1151 | 49.3298 |
| 2                | 21.726 BB | 0.8053 | 2,714,693 | 493.86307 | 50.1710 |

Totals: 5,410,766 | 1465.97450

---

Data File E:\\DATA\\Sc-2-51Rac\Sc-2-51RAC 2016-10-28 21-24-25\Sc-2-51RAC.0
Sample Name: Sc-2-51RAC

Acc. Operator: SYSTEM
Acc. Instrument: i260
Injection Date: 10/29/2016 12:25:40 PM
Inj Volume: 5.000 µL
Inj: 1
Location: 91

Acq. Method: E:\\DATA\\sc-2-51Rac\Sc-2-51RAC 2016-10-28 21-24-25\Sc-2-51RAC.0 (Sequence Method)

Last changed: 10/29/2016 12:24:25 PM by SYSTEM

Analysis Method: E:\\DATA\\Sc-2-51Rac\Sc-2-51RAC 2016-10-28 21-24-25\Sc-2-51RAC.0 (Sequence Method)

(modified after loading)

Additional Info: Peak[2] manually integrated

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Figure S3. HPLC spectrum of 5a, related to Table 2.
Figure S4. $^1$H NMR spectrum of 5b, related to Table 2.

Figure S5. $^{13}$C NMR spectrum of 5b, related to Table 2.
Data File E:\DATA\2C-2-56A\2C-2-56A-ASH-95-5 2016-11-11 10-10-39\2C-2-56A.D
Sample Name: 2C-2-56A-ASH-95-5

Acq. Operator: SYSTEM
Seq. Line: 1
Acq. Instrument: 1360
Inj: 1
Injection Date: 11/12/2016 2:12:01 AM
Injection Volume: 8.000 µl

Acq. Method: E:\DATA\2C-2-56A\2C-2-56A-ASH-95-5 2016-11-11 10-10-39\2C-2-ASH-95-5-220M-LL.L
Last changed: 11/12/2016 2:10:39 AM by SYSTEM

Analysis Method: E:\DATA\2C-2-56A\2C-2-56A-ASH-95-5 2016-11-11 10-10-39\2C-2-ASH-95-5-220M-LL.L (Sequence Method)
Last changed: 6/3/2017 8:25:05 PM by SYSTEM
(modified after loading)

Additional Info: Peaks manually integrated

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factors with ISTDs

Signal 1: DA01 A, S1p=220, S Ref=360,100

Peak RetTime Type Width Area Height Area
F [min] [min] [nAµs] [nA] [ µs]
------------------------|------------------------|------------------------|------------------------|
1 15.293 BD 0.7806 7586.30518 140.11862 50.0122
2 25.164 MN 1.1196 7884.61230 113.41533 49.9878

Totals: 1.51729ed 256.55395

1,260 6/3/2017 8:25:17 PM SYSTEM
Figure S6. HPLC spectrum of 5b, related to Table 2.
Figure S7. $^1$H NMR spectrum of 5c, related to Table 2.

Figure S8. $^{13}$C NMR spectrum of 5c, related to Table 2.
Data File E:\DATA\SC\SC-2-55A\SC-2-55A-AD 2016-11-11 08-17-41\SC-2-55A-AD.3
Sample Name: SC-2-55A-AD

Additional Info: Peak(s) manually integrated

Area Percent Report

Signal 1: DAU1 A, Stg-229, 4 Ref-369,100

Peak RetTime Type Width Area Height Area
|  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
| 1 | 13.052 | BB | 0.354 | 1.059 | 75e4 | 459.02 | 25 | 49.90 | 2 |
| 2 | 24.706 | BB | 0.863 | 1.086 | 298e4 | 238.45 | 700 | 80.09 | 5 |

Totals: 2.12174e4 697.48325

1260 6/3/2017 8:28:43 PM SYSTEM
Figure S9. HPLC spectrum of 5c, related to Table 2.
Figure S10. $^1$H NMR spectrum of 5d, related to Table 2.

Figure S11. $^{13}$C NMR spectrum of 5d, related to Table 2.
Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAUL A, Stg-220,4 Ref=369,100

Peak RecLine Type Width Area Height Area
| # | T [min] | W [min] | H [a.u.] | H/A |
|---|--------|--------|--------|-----|
| 1 | 14.365 | 1.0263 | 9953.1839 | 137.53425 | 50.0191 |
| 2 | 32.578 | 1.6737 | 9945.56934 | 99.03499 | 49.9099 |
Totals: 1.989884e+08 236.56915
Figure S12. HPLC spectrum of 5d, related to Table 2.
Figure S13. $^1$H NMR spectrum of 5e, related to Table 2.

Figure S14. $^{13}$C NMR spectrum of 5e, related to Table 2.
Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISSTDs

Signal 1: DAD A, Sig=220,4 Ref=365,100

| Peak RetTime | Type    | Width (min) | Area (mAU*min) | Height (mAU) | Area (%) |
|--------------|---------|-------------|----------------|--------------|----------|
| 1            | 5.669   | 0.570       | 8799.78115     | 435.71069    | 49.9074  |
| 2            | 17.142  | 0.9290      | 9836.15318     | 176.46739    | 20.9036  |

Totals: 1.96359e+4 613.17809
Figure S15. HPLC spectrum of 5e, related to Table 2.
Figure S16. $^1$H NMR spectrum of 5f, related to Table 2.

Figure S17. $^{13}$C NMR spectrum of 5f, related to Table 2.
**Area Percent Report**

---

**Signal**

*Signal has been modified after loading from rawdata file!*

**Peak Peak**

| # | Width | Height | Area | Area |
|---|-------|--------|------|------|
| 1 | 10.357 | 0.3339 | 306.08394 | 148.89696 |
| 2 | 17.650 | 0.7481 | 389.04370 | 75.50265 |

**Totals:**

6795.12964 224.39761
Figure S18. HPLC spectrum of 5f, related to Table 2.
Figure S19. $^1$H NMR spectrum of 5g, related to Table 2.

Figure S20. $^{13}$C NMR spectrum of 5g, related to Table 2.
Area Percent Report

Signal 1: DAD1 A, Sig=220,4 Ref=350,100

| Peak RetTime | Type Width | Area  | Height | Area |
|--------------|------------|-------|--------|------|
|              | [min]      | [nm]  | [mAU*sec] | [mAU] | %    |
| 1            | 8.753      | 0.2534| 3888.39844 | 200.38562 | 50.1301 |
| 2            | 15.817     | 0.5381| 3858.21405 | 100.48194 | 49.8699 |

Totals: 7756.60869 300.66755
Figure S21. HPLC spectrum of 5g, related to Table 2.
Figure S22. $^1$H NMR spectrum of 5h, related to Table 2.

Figure S23. $^{13}$C NMR spectrum of 5h, related to Table 2.
Figure S24. HPLC spectrum of 5h, related to Table 2.
Figure S25. $^1$H NMR spectrum of 5i, related to Table 2.

Figure S26. $^{13}$C NMR spectrum of 5i, related to Table 2.
Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000

Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAK1 A, Sig=220,4 Ref=369,100

| Peak RefType | Width | Area | Height | Area |
|--------------|-------|------|--------|------|
|              | [min] | [min] | [nmol/L] | [nmol] |
| 1            | 17.307 | 0.0313 | 7958.63318 | 155.54708 | 50.9598 |
| 2            | 22.552 | 1.3893 | 7740.37256 | 106.47124 | 49.9411 |
| Totals       |       |       | 1.54990e+4 | 264.01992 |

1260 6/3/2017 0:56:05 PM SYSTEM
Figure S27. HPLC spectrum of 5i, related to Table 2.
Figure S28. $^1$H NMR spectrum of 5j, related to Table 2.

Figure S29. $^{13}$C NMR spectrum of 5j, related to Table 2.
**Signal 1:** DAD A, Sig=220,4 Ref=360,100

**Peak Ret/Time Type** | **Width** | **Area** | **Height** | **Area%**
---|---|---|---|---
1 | 11.520 | 0.4417 | 7197.94727 | 247.20704 | 50.1603
2 | 19.059 | 0.8527 | 7145.23304 | 139.65513 | 49.8162

**Totals:**

1.4343264 386.66252
Figure S30. HPLC spectrum of 5j, related to Table 2.
Figure S31. $^1$H NMR spectrum of 5k, related to Table 2.

Figure S32. $^{13}$C NMR spectrum of 5k, related to Table 2.
Area Percent Report

| Signal  | Peak Type | Width | Area | Height | Area |
|---------|-----------|-------|------|--------|------|
| 12.471  | 1         | 0.428 | 2676.323 | 105.332 | 49.951 |
| 15.314  | 2         | 0.483 | 2683.549 | 61.797 | 50.048 |
| Totals  | 5962.072 | 107.130 |

Data File E:\DATA\SC\SC-170605-BU\SC-170605-BU 2017-06-05 16-44-53\SC-170605-BU4.D
Sample Name: SC-170605-BU

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Location : 73
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Injection Volume : 5.000 µl

Acq. Method : E:\DATA\SC\SC-170605-BU\SC-170605-BU 2017-06-05 16-44-53\SC-2-ADH-90-10-220M-30M-4LNX
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Analysis Method : E:\DATA\SC\SC-170605-BU\SC-170605-BU 2017-06-05 16-44-53\SC-2-ADH-90-10-220M-30M-4LNX (Sequence Method)
Last changed : 6/5/2017 8:36:55 PM by SYSTEM (modified after loading)

Additional Info : Peak(s) manually integrated

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1260 6/5/2017 8:37:02 PM SYSTEM
Figure S33. HPLC spectrum of 5k, related to Table 2.
**Figure S34.** $^1$H NMR spectrum of 5l, related to Table 2.

**Figure S35.** $^{13}$C NMR spectrum of 5l, related to Table 2.
### Area Percent Report

Sorted by: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

**Signal 1: TAD1 A, Sup=220,4 Ref=360,100**

|     | m/z [min] | m/z [min] | m/z [min] | m/z [min] |
|-----|-----------|-----------|-----------|-----------|
| 1   | 8.875     | 0.3205    | 3499.00317| 181.22896  |
| 2   | 11.314    | 0.4006    | 3479.15088| 134.67351  |

Totals: 6598.15405 316.60246

6/3/2017 11:44:00 PM SYSTEM
Figure S36. HPLC spectrum of 5l, related to Table 2.
Figure S37. $^1$H NMR spectrum of 5m, related to Table 2.

Figure S38. $^{13}$C NMR spectrum of 5m, related to Table 2.
Signal 1: DAP1 A, Sig=220,4 Ref=360,100

| Peak RetTime | Width | Area | Height | Area |
|-------------|-------|------|--------|------|
|             | [min] | [min] | [NPU]  | [NPU] % |
| 1           | 10.986 | 0.6069 | 2.2799354 | 625.56201 | 49.8603 |
| 2           | 15.460 | 0.7776 | 2.2807564  | 490.99962 | 50.1397 |

Totals: 4.56073e4 1116.55341

1200 6/4/2017 3:13:26 AM SYSTEM
Figure S39. HPLC spectrum of 5m, related to Table 2.
Figure S40. $^1$H NMR spectrum of 5n, related to Table 2.

Figure S41. $^{13}$C NMR spectrum of 5n, related to Table 2.
Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISIDs

Signal 1: DA44 L, Sig=2204, Def=363.100

| Peak RetTime | Type | Width | Height | Area | Area % |
|-------------|------|-------|--------|------|--------|
| 15.079 min  |      | 1.4168| 3.99655e4| 470.13996| 50.0011 |
| 23.722 min  |      | 1.7954| 3.99655e4| 371.00281| 49.9999 |

Totals: 7.99312e4 641.14257
Figure S42. HPLC spectrum of 5n, related to Table 2.
Figure S43. $^1$H NMR spectrum of 5o, related to Table 2.

Figure S44. $^{13}$C NMR spectrum of 5o, related to Table 2.
Figure S45. HPLC spectrum of 5o, related to Table 2.
**Figure S46.** $^1$H NMR spectrum of 5p, related to Table 2.

**Figure S47.** $^{13}$C NMR spectrum of 5p, related to Table 2.
Acq. Operator : SYSTEM
Seq. Line : 1
Acq. Instrument : 1250
Location : 79
Injection Date : 12/5/2016 8:34:34 AM
Inj. : 1
Inj. Volume : 5.000 μL
Acq. Method : \( \text{X:\(DATA\SC\SC-2-111B\SC-2-111B-AD-70 2016-12-05 08-33-07\SC-2-111B.D} \)
Last Changed : 12/5/2016 8:33:07 AM by SYSTEM
Analysis Method : \( \text{X:\(DATA\SC\SC-2-111B\SC-2-111B-AD-70 2016-12-05 08-33-07\SC-2-ADH-70-30-DAD} \)
Last Changed : 12/5/2016 8:33:07 AM by SYSTEM
\( \text{-1XL.N} \) (Sequence Method)
Last changed : 12/5/2016 8:33:07 AM by SYSTEM
\( \text{(modified after loading)} \)
Additional Info : Peak(s) manually integrated
Figure S48. HPLC spectrum of 5p, related to Table 2.
Figure S49. $^1$H NMR spectrum of 5q, related to Table 2.

Figure S50. $^{13}$C NMR spectrum of 5q, related to Table 2.
### Area Percent Report

#### Sorted By: Signal

| Multiplier | Dilution Factor |
|------------|-----------------|
| 1.0000     | 1.0000          |

Do not use Multiplier & Dilution Factor with ISTDs

#### Signal: DAB 1 A, Spec-229, 4 Ref-369,100

**Peak RetTime** | **Type** | **Width** | **Area** | **Height** | **Area** | **%**
--- | --- | --- | --- | --- | --- | ---
1 | 31.139 | BB | 0.8509 | 3906.25781 | 65.39045 | 50.0133 |
2 | 34.720 | BB | 0.9147 | 3994.18262 | 58.79794 | 49.9867 |

**Totals:** 7810.44043 124.18829

---

1200 6/5/2017 8:49:54 PM SYSTEM
Figure S51. HPLC spectrum of 5q, related to Table 2.
Figure S52. $^1$H NMR spectrum of 5r, related to Table 2.

Figure S53. $^{13}$C NMR spectrum of 5r, related to Table 2.
Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISSTDs

Signal 1: DAD1 A, Sig=220, 4 Ref=365, 100

| Peak RetTime Type | Width | Area | Height | Area % |
|------------------|-------|------|--------|--------|
| #1               | 0.3040| 0.0084| 403.7357| 50.0362|
| #2               | 0.3335| 0.0068| 400.2638| 49.9638|

Totals: 1.00043=4 883.02005
Figure S54. HPLC spectrum of 5r, related to Table 2.
Figure S55. $^1$H NMR spectrum of 1a, related to Table 3.

Figure S56. $^{13}$C NMR spectrum of 1a, related to Table 3.
Figure S57. HPLC spectrum of 1a, related to Table 3.
Figure S58. HPLC spectrum of 5a, related to Table 3.
Figure S59. HPLC spectrum of 1a, related to Table 3.
Figure S60. HPLC spectrum of 5b, related to Table 3.
Figure S61. HPLC spectrum of 1a, related to Table 3.
Figure S62. HPLC spectrum of 5h, related to Table 3.
Figure S63. HPLC spectrum of 1a, related to Table 3.
Figure S64. HPLC spectrum of 5o, related to Table 3.
Figure S65. $^1$H NMR spectrum of 1b, related to Table 3.

Figure S66. $^{13}$C NMR spectrum of 1b, related to Table 3.
Area Percent Report

Sorted By: Signal
Multiplier: 1.0930
Dilution: 1.0930
The Multiplier & Dilution factor used is 1.0000

Signal is P10 A.

Peak Retime Type Width Area Height Area %
# [min] [min] [pA^2] [pA] [pA]
-------- --- --- --- --- ---
1 29.137 HR 0.2520 2382.23936 621.25971 59.65051
2 30.719 HR 0.3962 884.9322 114.49104 49.94599
Totals: 4100.25798 232.75971

--- End of Report ---
Figure S67. HPLC spectrum of 2b, related to Table 3.
Figure S68. $^1$H NMR spectrum of 5s, related to Table 3.

Figure S69. $^{13}$C NMR spectrum of 5s, related to Table 3.
Area Percent Report

Signal 1: 5AK, Sig=220,4 Ref=955,90, ECT
Signal has been modified after loading from rawdata file!

| Peak Ref | Type | Width | Area | Height | Area |
|---------|------|-------|------|--------|------|
|         |      |       |      |        |      |
| 1       | 93.69 | 0.293 | 2.53203 | 1101.39020 | 49.9714 |
| 2       | 16.817 | 1.1469 | 2.857224 | 366.49433 | 50.0388 |

Totals: 5.066855e4 1549.32452

1260 6/3/2017 9:21:06 AM SYSTEM
Figure S70. HPLC spectrum of 5s, related to Table 3.
Figure S71. $^1$H NMR spectrum of 1c, related to Table 3.

Figure S72. $^{13}$C NMR spectrum of 1c, related to Table 3.
Figure S73. HPLC spectrum of $1c$, related to Table 3.
Figure S74. $^1$H NMR spectrum of 5t, related to Table 3.

Figure S75. $^{13}$C NMR spectrum of 5t, related to Table 3.
Area Percent Report

Signal 1: DAD 1, Sng=229,4 Per=369,100

| Peak ParmType | Width | Area   | Height | Area   |
|---------------|-------|--------|--------|--------|
|               | [min] | [nm]   | [nAmps]| [nA]   |
| 1             | 6.470 | 0.3717 | 1.8407e4| 956.95520| 49.9355 |
| 2             | 17.446 | 1.7170 | 1.8455e4| 179.13693| 50.0645 |

Totals: 9.6862e4 996.09213
Figure S76. HPLC spectrum of 5t, related to Table 3.
Figure S77. $^1$H NMR spectrum of 1d, related to Table 3.

Figure S78. $^{13}$C NMR spectrum of 1d, related to Table 3.
Data File: \DATA|SC\2-13C\SC-2-13C-03-98 2016-11-20 20-02-24\SC-2-13C.D
Sample Name: SC-2-13C-03-98

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Injection Date : 11/29/2016 12:03:47 PM  
Inj. : 1  
Inj. Volume : 5.000 µL  
Acq. Method : ?\DATA\SC-2-13C\SC-2-13C-03-98 2016-11-20 20-02-24\SC-5-00R-96-2-DAD-1ML.M  
Last changed : 11/29/2016 12:02:24 PM by SYSTEM  
Analysis Method : ?\DATA\SC\SC-2-13C\SC-2-13C-03-98 2016-11-28 20-02-24\SC-5-00R-98-2-DAD-1ML.M (Sequence Method)  
Last changed : 6/4/2017 4:22:41 AM by SYSTEM  
(modified after loading)  
Additional Info : Peak(s) manually integrated  
TMDT: HP-22544B INSTRUMENT DATE: 02/19/2016 20-02-24/SC-2-13C.D

About the Area Percent Report

Gradient: Signal  
Multiplier: 1.0000  
Injection: 1.0000  
Do not use Multiplier & Dilution Factor with ISSTDs

Signal 1: DAPI A, Sig=220,4 Ref=360,100

| Peak Ret.Time Type Width Area Height Area % |
|---|-------|-------|-------|-------|
| 1 | 15.126 BR | 0.3062 | 425,048 | 249,293 | 49.9044 |
| 2 | 15.850 | 0.3186 | 495,127 | 234,185 | 50.0856 |
| Totals | 9897.17480 | 474.41059 |

1260 6/4/2017 4:22:52 AM SYSTEM
Figure S79. HPLC spectrum of 1d, related to Table 3.
Figure S80. $^1$H NMR spectrum of $5u$, related to Table 3.

Figure S81. $^{13}$C NMR spectrum of $5u$, related to Table 3.
Data File E:\DATA\SC\SC-2-42B\SC-2-42B-ASH-90-10 2016-11-13 21-24-00\SC-2-42B.D
Sample Name: SC-2-42B-ASH-90-10

Acq. Operator : SYSTEM  Seq. Line : 1
Acq. Instrument : 1260  Location : 83
Injection Date : 11/24/2016 1:25:33 PM  Inj : 1
Inj Volume : 5.000 µL

Acq. Method : E:\DATA\SC\SC-2-42B\SC-2-42B-ASH-90-10 2016-11-13 21-24-00\SC-1-ASH-90-10-DAD-1NL.B
Last changed : 11/14/2016 11:24:00 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-42B\SC-2-42B-ASH-90-10 2016-11-13 21-24-00\SC-1-ASH-90-10-DAD-1NL.B (Sequence Method)
Last changed : 6/3/2017 9:47:59 AM by SYSTEM
(modified after loading)

Additional Info : Peak(s) manually integrated

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Solution : 1.0000
Do not use Multiplier & Dilution Factor with IS/IDs

Signal 1: DA01 A, Stg=229,4 Ref=369,100

Peak RetLine Type Width Area Height Area
μ[ms] [min] [min] [μV] [µA]
1 6.553 0.3997 2.77400e+04 1106.5159 50.1725
2 16.777 1.5977 2.75499e+04 287.39413 49.8374

Totals : 5.52907e+04 1473.9572

1260 6/3/2017 9:47:54 AM SYSTEM
Figure S82. HPLC spectrum of 5u, related to Table 3.
Figure S83. $^1$H NMR spectrum of 1e, related to Table 3.

Figure S84. $^{13}$C NMR spectrum of 1e, related to Table 3.
Figure S85. HPLC spectrum of 1e, related to Table 3.
Figure S86. $^1$H NMR spectrum of 5v, related to Table 3.

Figure S87. $^{13}$C NMR spectrum of 5v, related to Table 3.
Area Percent Report

| Sorted By | Signal |
|-----------|--------|
| Multiplier| 1.0000 |
| Solution  | 1.0000 |

Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: D410 A, Sep=220.4 Ref=369,100

Peak RetTime Type Width Area Height Area
| # | [min] | [min] | [nmol] | [nmol] |
|---|-------|-------|--------|--------|
| 1 | 6.075 | 0.4075 | 2.55859e4 | 949.24066 | 50.9718 |
| 2 | 16.473 | 1.7209 | 2.55125e4 | 245.93962 | 49.9298 |

Totals: 5.10969e4 1195.18828

1260 6/3/2017 10:00:50 AM SYSTEM
Figure S88. HPLC spectrum of 5v, related to Table 3.
Figure S89. $^1$H NMR spectrum of 1f, related to Table 3.

Figure S90. $^{13}$C NMR spectrum of 1f, related to Table 3.
Data File E:\DATA\SC\SC-3-12\SC-3-12-A3-90-DAD 2017-04-05 10-59-02\SC-3-12.D
Sample Name: SC-3-12

===============================================================================
Acq. Operator : SYSTEM  Seq. Line : 1
Acq. Instrument : 1260  Location : 11
Injection Date : 4/5/2017 11:00:25 AM  Inj : 1
Injection Volume : 5.000 µl
Acq. Method : E:\DATA\SC\SC-3-12\SC-3-12-A3-90-DAD 2017-04-05 10-59-02\SC-3-12-A3-90-DAD
-1NLK
Last changed : 4/5/2017 10:59:02 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-12\SC-3-12-A3-90-DAD 2017-04-05 10-59-02\SC-3-12-A3-90-DAD
-1NLK [Sequence Method]
Last changed : 6/4/2017 4:33:24 AM by SYSTEM
(modified after loading)
Additional Info : Peak(s) manually integrated
DAD A Sgn 12604 Ref 369,100 (E:\DATA\SC\SC-3-12\SC-3-12-A3-90-DAD 2017-04-05 10-59-02\SC-3-12.D)

---

Area Percent Report
---

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal #1: DA1 A, Sgn=1260,4 Ref=369,100

Peak RetTime Type Width Area Height Area
[min] [min] [nA/min] [nA] [nA]  
--- --- --- --- --- ---
1 7.163 BB 0.1910 4004.91187 320.04797 50.1550
2 8.059 BB 0.2193 3980.16113 275.93500 49.8450

Totals : 7965.07390 595.98097

1260 6/4/2017 4:33:31 AM SYSTEM
Figure S91. HPLC spectrum of If, related to Table 3.
Figure S92. $^1$H NMR spectrum of $5w$, related to Table 3.

Figure S93. $^{13}$C NMR spectrum of $5w$, related to Table 3.
Data File E:\DATA\SC-3-12-16\SC-3-12-16-170609 2017-06-03 11-09-21\SC-3-12-161.D
Sample Name: SC-3-12

Acq. Operator : SYSTEM
Seq. Line : 2
Acq. Instrument : 1140
Location : 16
Injection Date : 6/3/2017 11:57:20 AM
Inj : 1
Inj Volume : 5.000 µL

Acq. Method : E:\DATA\SC-3-12-16\SC-3-12-16-170609 2017-06-03 11-09-21\SC-1-69-90-10-220NM-LNL-200NM.M
Last changed : 6/3/2017 11:59:21 AM by SYSTEM

Analysis Method : E:\DATA\SC-3-12-16\SC-3-12-16-170609 2017-06-03 11-09-21\SC-1-69-90-10-220NM-LNL-200NM.M (Sequence Method)
Last changed : 6/18/2017 2:49:00 PM by SYSTEM
(modified after loading)

Additional Info : Peak(s) manually integrated

---

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD A, Sgr=220, G Ref=360,100

Peak RetTime Type Width Area Height Area
|   | [min] | [min] | [AU%] | [AU] |
|---|-------|-------|-------|------|
| 1 | 7.304 | 0.9975 | 4029.88547 | 149.41939 | 49.8231 |
| 2 | 12.246 | 1.1670 | 4042.29661 | 57.42923 | 50.0769 |

Totals : 8072.13208 207.14962

L260 6/16/2017 2:49:05 PM SYSTEM
Page 1 of 2
Figure S94. HPLC spectrum of 5w, related to Table 3.
Figure S95. $^1$H NMR spectrum of $1g$, related to Table 3.

Figure S96. $^{13}$C NMR spectrum of $1g$, related to Table 3.
Figure S97. HPLC spectrum of 1g, related to Table 3.
Figure S98. $^1$H NMR spectrum of 5x, related to Table 3.

Figure S99. $^{13}$C NMR spectrum of 5x, related to Table 3.
Acq. Operator : SYSTEM
Seq. Line : 1
Acq. Instrument : 1200
Location : 64
Injection Date : 11/14/2016 1:57:12 PM
Injection : 1
Inj. Volume : 5.000 µl
Acq. Method : E:\DATA\3C\3C-2-45A\3C-2-45A-ASR-90-10 2016-11-13 21:55-45\3C-1-ASR-90-10-DAD-FLN.M
Last changed : 11/14/2016 1:55:49 PM by SYSTEM
Analysis Method : E:\DATA\3C\3C-2-45A\3C-2-45A-ASR-90-10 2016-11-13 21:55-45\3C-1-ASR-90-10-DAD-FLN.M [Sequence Method]
Last changed : 6/3/2017 10:56:38 AM by SYSTEM (modified after loading)

Additional Info : Peak(s) manually integrated

Area Percent Report

Signal : 1.0000
Multiplier : 1.0000

Do not use Multiplier & Dilution Factor with ISIDs

Peaks:

| Peak | RetTime | Width | Area | Height | Area |
|------|---------|-------|------|--------|------|
| 1    | 5.626   | 0.357 | 731.02573 | 50.0028 |
| 2    | 12.028  | 0.360 | 432.14007 | 49.9771 |

Totals : 1163.16580

1200 6/3/2017 10:56:46 AM SYSTEM
Figure S100. HPLC spectrum of 5x, related to Table 3.
Figure S101. $^1$H NMR spectrum of 1h, related to Table 3.

Figure S102. $^{13}$C NMR spectrum of 1h, related to Table 3.
Acq. Operator : SYSTEM  Seq. Line : 1
Acq. Instrument : I560  Location : 83
Injection Date : 11/25/2016 7:07:47 AM
Inj : 1
Inj Volume : 5.000 μL
Acq. Method : X:\DATA\SC\2-2-3B\SC-2-3B-03-98 2016-11-27 15-06-24;SC-5-0H-98-2-DAD-1ML.
Last changed : 11/25/2016 7:06:24 AM by SYSTEM
Analysis Method : X:\DATA\SC\2-2-3B\SC-2-3B-03-98 2016-11-27 15-06-24;SC-5-0H-98-2-DAD-1ML.
Last changed : 11/25/2016 7:06:24 AM by SYSTEM
Additional Info : peak(s) manually integrated

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Solution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DA01 A, Sig=220, Ref=360,100

Peak RetTime Type Width Area Height Area
# [min] [min] [ppm] [ppm] [μl]
-------- -------- -------- -------- -------- --------
1 0.520 VD 0.1775 2.972796d 2540.159434 49.2502
2 10.503 BB 0.2196 2.976623e4 2013.00349 50.0498

Totals : 5.95132ed 4555.97192

1,360 6/4/2017 4:44:26 AM SYSTEM
Figure S103. HPLC spectrum of 1h, related to Table 3.
Figure S104. $^1$H NMR spectrum of 5y, related to Table 3.

Figure S105. $^{13}$C NMR spectrum of 5y, related to Table 3.
Acq. Operator : SYSTEM
Acq. Instrument : Jasco 1260
Injection Date : 11/14/2016 3:34:26 PM
Injection Volume : 5.000 µl

Last changed : 11/14/2016 3:34:26 PM by SYSTEM
Approved Method : E:\DATA\SC\3C-2-478\SC-2-478-ASH-90-10-2015-11-13 23-34-26\SC-2-478-ASH-90-10-
PDA-IRL.M (modified after loading)

Additional Info : Peak(s) manually integrated

Area Percent Report

| Peak ReTTime Type Width Area Height Area | [min] | [min] | [µ][µ] | [µ][µ] |
|----------------------------------------|-------|-------|--------|--------|
| 1.413 RHN | 0.2941 | 3.9740e-04 | 2251.75903 | 49.7197 |
| 1.657 BB  | 1.0093 | 4.01886e-04 | 606.70370 | 50.3803 |

Totals : 9.99290e-04 2660.46175
Figure S106. HPLC spectrum of 5y, related to Table 3.
Figure S107. $^1$H NMR spectrum of 1i, related to Table 3.

Figure S108. $^{13}$C NMR spectrum of 1i, related to Table 3.
Acq. Operator : SYSTEM  Seq. Line : 10
Acq. Instrument : 1360  Location : 80
Injection Date : 6/5/2017 12:50:07 AM  Inj. : 1
Injection Volume : 5.000 μl
Acq. Method : E:\DATA\SC\SC-170694-bu\SC-170694-BU 2017-06-04 15-54-34\SC-5-00H-98-2-300HH-I1L-35HH.T
Last changed : 6/4/2017 3:54:36 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-170694-bu\SC-170694-BU 2017-06-04 15-54-34\SC-5-00H-98-2-300HH-I1L-35HH.T (Sequence Method)
Last changed : 6/5/2017 8:56:33 PM by SYSTEM (modified after loading)
Additional Info : Peak(s) manually integrated

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with IS/STDs

Signal 1: DAUL A, Stg=300,4 Ref=369,100

Peak RetTime Type Width Area Height Area
\[ \frac{t}{[\text{min]}} \] \[ [\text{min}] \] \[ [\text{μAU}^2] \] \[ [\text{μAU}] \]
\[ \frac{t}{[\text{min}]} \| \frac{[\text{min}]}{[\text{μAU}^2]} \] \[ [\text{μAU}] \] \[ [\text{μAU}] \]
\[ \frac{t}{[\text{min}]} \| \frac{[\text{min}]}{[\text{μAU}^2]} \] \[ [\text{μAU}] \] \[ [\text{μAU}] \]

\[ 23.702 \text{ min} \] \[ 0.6005 \] \[ 1.90182e+4 \] \[ 527.01378 \] \[ 50.0455 \]
\[ 31.213 \text{ min} \] \[ 0.8980 \] \[ 1.898376 \] \[ 400.51453 \] \[ 49.9545 \]

Totals : 3.80019e+4 926.32831
Figure S109. HPLC spectrum of 1i, related to Table 3.
Figure S110. $^1$H NMR spectrum of $5z$, related to Table 3.

Figure S111. $^{13}$C NMR spectrum of $5z$, related to Table 3.
Figure S112. HPLC spectrum of 5z, related to Table 3.
**Figure S113.** $^1$H NMR spectrum of 1j, related to Table 3.

**Figure S114.** $^1$H NMR spectrum of 1j, related to Table 3.
Area Percent Report

Sorted By:  Signal
Multiplier:  1.0000
Solution:  1.0000
Do not use Multiplier & Dilution Factor with IS/STDs

Signal 1:  DPAH A, Stg=223, 4 Ref=369, 100

| Peak | RetTime Type | Width | Height | Area       | Result       |
|------|--------------|-------|--------|------------|--------------|
|      |              | [min] | [min]  | [amu/min]  | [amu]        |
| 1    | 11.044       | 0.469 | 2.366 | 2.36626e4  | 152.120     |
| 2    | 13.360       | 0.531 | 1.278 | 1.27852e4  | 80.1081     |

Totals:  4.74278e4  1410.60844

1260 6/4/2017 4:57:50 AM SYSTEM
Figure S115. HPLC spectrum of 1j, related to Table 3.
Figure S116. $^1$H spectrum of 5A, related to Table 3.

Figure S117. $^{13}$C NMR spectrum of 5A, related to Table 3.
Area Percent Report

Signal: DA31 A, Sig=229, D Eff=369,100

| Peak RetTime Type | Width | Area | Height | Area % |
|------------------|-------|------|--------|-------|
|                  | [min] | [min] | [nAmps] | [nA]   |
| 1                | 4.932 | 0.4722 | 2.12262e+04 | 679.97308 | 49.8013 |
| 2                | 12.240 | 1.7772 | 2.13959e+04 | 200.65399 | 50.1987 |

Totals: 4.26223e+04 880.62708

1260 6/3/2017 11:20:43 AM SYSTEM
Figure S118. HPLC spectrum of 5A, related to Table 3.
Figure S119. $^1$H NMR spectrum of 1k, related to Table 3.

Figure S120. $^{13}$C NMR spectrum of 1k, related to Table 3.
Figure S121. HPLC spectrum of 1k, related to Table 3.
Figure S122. $^1$H NMR spectrum of 5B, related to Table 3.

Figure S123. $^{13}$C NMR spectrum of 5B, related to Table 3.
Figure S124. HPLC spectrum of 5B, related to Table 3.
Figure S125. $^1$H NMR spectrum of 1l, related to Table 3.

Figure S126. $^{13}$C NMR spectrum of 1l, related to Table 3.
Figure S127. HPLC spectrum of 1l, related to Table 3.
Figure S128. $^1$H NMR spectrum of 5C, related to Table 3.

Figure S129. $^{13}$C NMR spectrum of 5C, related to Table 3.
Data File E:\DATA\SC\SC-2-52B\SC-2-S2B-ASH-90-10 2016-11-14 10-23-11\SC-2-S2B.D
Sample Name: SC-2-S2B-ASH-90-10

=====================================================================
Acq. Operator : SYSTEM
Seq. Line : 1
Acq. Instrument : 1260
Location : 92
Injection Date : 11/15/2016 2:24:27 AM
Inj. : 1
Inj. Volume : 5.000 µl
Acq. Method : E:\DATA\SC\SC-2-52B\SC-2-S2B-ASH-90-10 2016-11-14 10-23-11\SC-1-ASH-90-10-DAD-ILN.M
Last changed : 11/15/2016 2:23:11 AM by SYSTEM
Analysis Method : E:\DATA\SC\SC-2-52B\SC-2-S2B-ASH-90-10 2016-11-14 10-23-11\SC-1-ASH-90-10-DAD-ILN.M [Sequence Method]
Last changed : 6/3/2017 11:45:39 AM by SYSTEM
(modified after loading)
Additional Info : Peak(s) manually integrated

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISIDs

Signal 1: DAK1 A, Sig=220,4 Ref=369,100
Peak RetTime Type Width Area Height Area
[min] [min] [µl/µs] [µl] [µl] [µl]
--- --- --- --- --- ---
1 0.917 BB 0.5172 2.35650e4 700.90344 50.0115
2 14.354 BB 1.0250 2.35542e4 340.17953 49.9905

Totals : 4.71192e4 1050.00290
Figure S130. HPLC spectrum of 5C, related to Table 3.
Figure S131. $^1$H NMR spectrum of 1m, related to Table 3.

Figure S132. $^{13}$C NMR spectrum of 1m, related to Table 3.
Figure S133. HPLC spectrum of 1m, related to Table 3.
Figure S134. $^1$H NMR spectrum of 5D, related to Table 3.

Figure S135. $^{13}$C NMR spectrum of 5D, related to Table 3.
A quantitative chromatogram with peak areas and retention times. The report includes the following details:

**Signal 1:** DA1 A, Sig=229.4 Ref=360.100

| Peak | RetTime Type | Width | Area | Height | Area |
|------|--------------|-------|------|--------|------|
| 1    |    | 11.14d | 0.5275 | 7642.99699 | 241.44102 | 49.9295 |
| 2    |    | 24.09d | 1.0049 | 7664.58838 | 106.72145 | 50.0705 |

**Totals:** 1.530764 340.21327

Additional information includes the method details and the user who performed the analysis.
Figure S136. HPLC spectrum of 5D, related to Table 3.
**Figure S137.** $^1$H NMR spectrum of 1n, related to Table 3.

**Figure S138.** $^{13}$C NMR spectrum of 1n, related to Table 3.
Figure S139. HPLC spectrum of In, related to Table 3.
Figure S140. $^1$H NMR spectrum of 5E, related to Table 3.

Figure S141. $^{13}$C NMR spectrum of 5E, related to Table 3.
**Area Percent Report**

**Sorted By**: Signal
**Multiplier**: 1.0000
**Solution**: 1.0000

**Signal 1**: DAD1 A, Sgr=220, d Pe=369,100

| Peak | RetTime | Width | Area  | Height | Area  |
|------|---------|-------|-------|--------|-------|
| 1    | 15.674  | 0.577 | 63802 | 79102  | 160.19650 | 50.953 |
| 2    | 25.763  | 0.806 | 63869 | 29053  | 116.13609 | 49.947 |

**Totals**: 1.27921e4 204.33259

**Data File**: E:\DATA\5C\5C-4-66\SC-4-66-AD-90 2017-03-28 16-57-31\5C-4-66.D

Sample Name: SC-4-66

---

Injection Date: 3/28/2017 4:59:01 PM
Injection Volume: 5.000 µL

---

Additional Info: Peak(s) manually integrated

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(modified after loading)
Figure S142. HPLC spectrum of 5E, related to Table 3.
Figure S143. $^1$H NMR spectrum of 1o, related to Table 3.

Figure S144. $^{13}$C NMR spectrum of 1o, related to Table 3.
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISIDs

Signal 1: D41L A, Sig=229, D Ref=362,100

Peak RetTime Type Width Area Height Area %
--- -------- -------- -------- -------- -------- ————
1 14.187 BB 0.3021 1.2282254 612.48799 50.0043
2 16.887 BB 0.4516 1.2290444 413.70169 49.9957
Totals : 2.456269 1026.19961

1260 6/5/2017 6:33:41 PM SYSTEM
Figure S145. HPLC spectrum of 10, related to Table 3.
Figure S146. $^1$H NMR spectrum of 5F, related to Table 3.

Figure S147. $^{13}$C NMR spectrum of 5F, related to Table 3.
Data File E:\DATA\SC\SC-3-99\SC-3-99-AS-90 2017-02-13 19-36-00\SC-3-99.D
Sample Name: SC-3-99

Acq. Operator : SYSTEM
Acq. Instrument : 1260
Injection Date : 2/13/2017 7:37:23 PM
Inj Volume : 5.000 µL
Acq. Method : E:\DATA\SC\SC-3-99\SC-3-99-AS-90 2017-02-13 19-36-00\SC-1-ASH-90-10-MPL
Last changed : 2/13/2017 7:38:00 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-3-99\SC-3-99-AS-90 2017-02-13 19-36-00\SC-1-ASH-90-10-MPL
Last changed : 2/3/2017 8:10:42 PM by SYSTEM

Additional Info : Peak(s) manually incorporated

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multipliers & Dilution Factor with ISTDs

Signal 1: DAD A, Sig=220.4 Ref=366,100

Peak RetTime Type Width Area Height Area
--- | [min] | [min] | [Å2ÅU] | [ÅÅ] | %
--- |-------- |-------- |-------- |-------- |-------- |
1 9.483 BE 0.8785 7806.53447 307.34389 49.4435
2 17.004 MX 1.0002 7902.25791 133.01590 50.5565

Totals : 1.57888e4 340.35977

1260 6/3/2017 8:10:42 PM SYSTEM
Figure S148. HPLC spectrum of 5F, related to Table 3.
Figure S149. HPLC spectrum of 1a, related to Table 1.
Figure S150. $^1$H NMR spectrum of 3a, related to Table 1.

Figure S151. $^{13}$C NMR spectrum of 3a, related to Table 1.
Figure S152. HPLC spectrum of 3a, related to Table 1.
Figure S153. $^1$H NMR spectrum of 6, related to Scheme 4.

Figure S154. $^{13}$C NMR spectrum of 6, related to Scheme 4.
Acq. Operator : SYSTEM
Acq. Instrument : 1260
Injection Date : 5/30/2017 9:58:36 PM
Inj. Volume : 5.000 µl
Acq. Method : E:\DATA\SC\SC-5-57\SC-5-57-RAC-AS-95 2017-05-30 21-57-14\SC-1-ASH-95-5-DAD-
       INL.M
Last changed : 5/30/2017 9:57:14 PM by SYSTEM
Analysis Method : E:\DATA\SC\SC-5-57\SC-5-57-RAC-AS-95 2017-05-30 21-57-14\SC-1-ASH-95-5-DAD-
       INL.M (Sequence Method)
Last changed : 6/22/2017 3:36:03 PM by SYSTEM
       (modified after loading)
Additional Info : Peak(s) manually integrated

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with TMDs

Signal #1: DAD1 A, Sig-220,4 Ref-360,100

| Peak No. | Ret Time [min] | Width [min] | Area [µAU*²] | Height [µAU] | Area % |
|----------|----------------|-------------|--------------|--------------|--------|
| 1        | 7.180          | 0.2158      | 814.45067    | 50.2217      |        |
| 2        | 8.015          | 0.2588      | 728.02155    | 49.7783      |        |

Totals : 2.21248e4 1542.47241

8/22/2017 3:36:18 PM SYSTEM
Figure S155. HPLC spectrum of 6, related to Scheme 4.
Figure S156. $^1$H NMR spectrum of 7, related to Scheme 4.

Figure S157. $^{13}$C NMR spectrum of 7, related to Scheme 4.
Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISSTDs

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

| Peak RetTime | Type | Width | Area | Height | Area |
|--------------|------|-------|------|--------|------|
|              |      | [min] | [min]| [NAU^2] | [NAU] | %   |
| 1            | 11.099 | 0.2462 | 3960.000998 | 306.398969 | 49.90175 |
| 2            | 12.061 | 0.2611 | 5990.104300 | 347.556033 | 50.09824 |

Totals: 1.19581e4 733.92499
Figure S158. HPLC spectrum of 7, related to Scheme 4.
Figure S159. $^1$H NMR spectrum of 8, related to Scheme 4.

Figure S160. $^1$H NMR spectrum of 8, related to Scheme 4.
Figure S161. NOESY NMR spectrum of 8, related to Scheme 4.
Area Percent Report

Sorted By:  Signal
Multiplier:  1.0000
Dilution:  1.0000

Signal:  ID:1 A, Size=210,0 Ref=360,100

| Peak Rect | Type Width Area Height Area | % |
|-----------|-----------------------------|---|
| 1         | VB                          | 27.173  1.2168 5.5425754c 585.53690 49.8966 |
| 2         | MH                          | 42.010  2.3166 5.362464e4 395.00280 50.1014 |

Totals:  1.07022e5  969.33960

1260 6/22/2017 3:26:52 PM SYSTEM
Figure S162. HPLC spectrum of 8, related to Scheme 4.
Figure S163. $^1$H NMR spectrum of 9, related to Scheme 4.

Figure S164. $^{13}$C NMR spectrum of 9, related to Scheme 4.
Figure S165. HPLC spectrum of 9, related to Scheme 4.
Figure S166. $^1$H NMR spectrum of 11, related to Scheme 4.

Figure S167. $^{13}$C NMR spectrum of 11, related to Scheme 4.
Supplemental Figures for X-ray Structures of the Tosylated Cycloadduct (±)-3a, Tosylated Cycloadduct (1S,2S,2'S,4R,5'R)-5a, Cycloadduct (1S,2S,2'S,4R,5'R)-5b, Tosylated (1S,2R,2'S,4R,4'R,5'R)-5s, Cycloadduct (±)-5u and Alkylidene Norcamphor (±)-1d

Crystal data for tosylated (±)-3a: C_{25}H_{26}ClNO_{5}S, \( M_r = 487.98 \), \( T = 296 \) K, Monoclinic, space group \( P2(1)/n \), \( a = 10.1095(14) \), \( b = 13.7964(19) \), \( c = 17.127(2) \) Å, \( V = 2338.0(6) \) Å³, \( Z = 4 \), 4613 unique reflections, final \( R_1 = 0.0390 \) and \( wR_2 = 0.1074 \) for 5863 observed \([I>2\sigma(I)]\) reflections. CCDC 1562399 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Crystal data for tosylated (1S,2S,2'S,4R,5'R)-5a: 2(C_{25}H_{26}ClNO_{5}S), \( M_r = 975.95 \), \( T = 293 \) K, Triclinic, space group \( P1 \), \( a = 7.2009(8) \), \( b = 7.6006(9) \), \( c = 22.280(3) \) Å, \( V = 1212.4(3) \) Å³, \( Z = 1 \), 6117 unique reflections, final \( R_1 = 0.0428 \) and \( wR_2 = 0.1041 \) for 7406 observed \([I>2\sigma(I)]\) reflections, Flack \( \chi = 0.04(3) \). CCDC 1562400 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
Figure S170. X-ray structure of (1S,2S,2'S,4R,5'R)-5b
(Hydrogen atoms were deleted for clarity), related to Table 2.

Crystal data for (1S,2S,2'S,4R,5'R)-5b: C$_{18}$H$_{20}$ClNO$_3$, $M_r = 333.80$, $T = 296$ K, Orthorhombic, space group $P2(1)2(1)2(1)$, $a = 6.7241(16)$, $b = 6.8383(16)$, $c = 35.075(8)$ Å, $V = 1612.8(7)$ Å$^3$, $Z = 4$, 3043 unique reflections, final $R_1 = 0.0430$ and $wR_2 = 0.1098$ for 4003 observed $[I>2\sigma(I)]$ reflections, Flack $\chi = -0.01(4)$. CCDC 1562402 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Figure S171. X-ray structure of tosylated (1S,2R,2'S,4R,4'R,5'R)-5s
(Hydrogen atoms were deleted for clarity), related to Table 3.

Crystal data for tosylated (1S,2R,2'S,4R,4'R,5'R)-5s: C$_{31}$H$_{30}$ClNO$_5$S, $M_r = 564.07$, $T = 296$ K, Orthorhombic, space group $P2(1)2(1)2(1)$, $a = 9.509(3)$, $b = 10.371(3)$, $c = 27.390(7)$ Å, $V = 2701.0(12)$ Å$^3$, $Z = 4$, 6637 unique reflections, final $R_1 = 0.0317$ and $wR_2 = 0.0855$ for 6911 observed $[I>2\sigma(I)]$ reflections, Flack $\chi = 0.004(11)$. CCDC 1562404 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htmL (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
Crystal data for (±)-5u: C_{24}H_{23}BrClNO_3, \( M_r = 488.79 \), \( T = 293 \) K, Hexagonal, space group \( R-3, a = 19.3385(9), b = 19.3385(9), c = 30.7638(12) \) Å, \( V = 9963.6(8) \) Å\(^3\), \( Z = 18 \), 2697 unique reflections, final \( R_1 = 0.0484 \) and \( wR_2 = 0.1373 \) for 5510 observed \([I>2\sigma(I)]\) reflections. CCDC 1562405 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Crystal data for (±)-1d: C_{14}H_{13}BrO, \( M_r = 277.15 \), \( T = 293 \) K, Triclinic, space group \( P-1, a = 6.4885(14), b = 9.451(2), c = 10.440(2) \) Å, \( V = 600.7(2) \) Å\(^3\), \( Z = 2 \), 1874 unique reflections, final \( R_1 = 0.0376 \) and \( wR_2 = 0.0904 \) for 2960 observed \([I>2\sigma(I)]\) reflections. CCDC 1562406 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
Computational Details

Density functional theory (DFT) calculations were carried out to understand the regioselectivity and key kinetic resolution of the ligand-controlled umpolung-type 1,3-dipolar cycloaddition. B3LYP (Becke, 1993; Lee et al., 1988; Stephens et al., 1994) method combined with a mixed basis set of SDD (Dolg et al., 1987) for Cu and 6-31G(d) (Ditchfield et al., 1971; Hehre et al., 1972; Harirhan and Pople, 1973) for the other atoms were used to optimize all the structures in gas phase. Such method was used to study the related Cu-catalyzed 1,3-dipolar cycloaddition (Wang et al., 2012). The effect of the solvent in DCM was then included by single-point calculation with the polarizable continuum model (PCM) (Tomasi et al., 2005; Scalmani and Frisch, 2010) using UAKS radii and including effects of solute-solvent dispersion interaction energy, solute-solvent repulsion interaction energy and solute cavitation energy. The electron distribution, in terms of natural population analysis (NPA) charges, for the two reacting carbon atoms of the complexes with \textbf{L1D}, \textbf{L5D}, \textbf{L1U} and \textbf{L5U} were calculated. All calculations were carried out by Gaussian 09 package (Gaussian 09, Revision D.01, 2009). All 3D images of the optimized structures were illustrated by CYLview (CYL View, version 1.0 b, 2009).
Table S1. The overall free-energy barrier (in kcal/mol) for the formation of several possible products from the reaction with 1a-(1R,4S) and 1a-(1S,4R) catalyzed by Cu(I)-LI in DCM solution by the PCM-B3LYP//B3LYP method, related to Scheme 2 and Scheme 3.

| Producta | $\Delta G_{\text{soln}}$ |
|----------|----------------------|
| L1D      |                      |
| (1S,2S,2'R,4R,5'R)-3a | 16.4 |
| (1R,2R,2'S,4S,5'S)-3a' | 18.5 |
| (1S,2S,2'S,4R,5'S)-4a | 25.6 |
| (1R,2R,2'R,4S,5'R)-4a' | 27.0 |
| (1S,2S,2'S,4R,5'R)-5a | 19.4 |
| (1R,2R,2'R,4S,5'R)-5a' | 20.4 |
| (1S,2S,2'R,4R,5'R)-6a | 28.9 |
| (1R,2R,2'S,4S,5'R)-6a' | 28.9 |
| (1S,2R,2'S,4R,5'S)-7a | 20.0 |
| (1R,2R,2'R,4S,5'R)-7a' | 19.5 |
| (1S,2R,2'R,4R,5'R)-8a | 28.0 |
| (1R,2S,2'S,4S,5'S)-8a' | 28.6 |
| (1S,2R,2'R,4R,5'S)-9a | 23.2 |
| (1R,2S,2'S,4S,5'R)-9a' | 21.6 |
| (1S,2R,2'S,4R,5'R)-10a | 30.4 |
| (1R,2S,2'R,4S,5'S)-10a' | 29.0 |
| L1U      |                      |
| (1S,2S,2'R,4R,5'R)-3a | 22.7 |
| (1R,2R,2'S,4S,5'S)-3a' | 22.8 |
| (1S,2S,2'S,4R,5'R)-5a | 19.7 |
| (1R,2R,2'R,4S,5'R)-5a' | 28.9 |
| (1S,2R,2'S,4R,5'S)-7a | 23.3 |
| (1R,2S,2'R,4S,5'R)-7a' | 28.5 |

a. The two coordination modes of Ar in the Cu-azomethine ylide intermediates (L1D and L1U) were considered (D: Ar downward; U: Ar upward).
**Table S2.** The overall free-energy barrier (in kcal/mol) for the formation of the most important products from the reaction with 1a-(1R,4S) and 1a-(1S,4R) catalyzed by Cu(I)-L5D in DCM solution by the PCM-B3LYP//B3LYP method, related to Scheme 3.

| Product | ΔG<sub>solv</sub> |
|---------|------------------|
| L5D<sup>a</sup> |                  |
| (1S,2S,2'R,4R,5'R)-3a | 18.9   |
| (1S,2S,2'S,4R,5'R)-5a | 18.0   |
| (1R,2R,2'R,4S,5'S)-5a<sup>a</sup> | 19.2   |
| L5U<sup>a</sup> |                  |
| (1S,2S,2'R,4R,5'R)-3a | 29.3   |
| (1S,2S,2'S,4R,5'R)-5a | 22.3   |
| (1R,2R,2'R,4S,5'S)-5a<sup>a</sup> | 25.9   |

<sup>a</sup> The two coordination modes of Ar in the Cu-azomethine ylide intermediates (L1D and L1U) were considered (D: Ar downward; U: Ar upward).

**Figure S174.** Optimized structures of Cu(I)-L1 intermediates (L1D and L1U) with the key bond lengths (in angstrom), the NPA charge of the two reacting carbons and HOMO energies by the B3LYP method. Their relative free energies (in kcal/mol) in DCM solution are given. All hydrogen atoms were omitted for clarification, related to Scheme 2 and Figure 2.
Figure S175. Optimized transition states for the reaction with 1a-(1R,4S) catalyzed by L1D in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to Scheme 2.
Figure S176. Optimized transition states for the reaction with 1a-(1R,4S) catalyzed by L1\textsubscript{D} in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to Scheme 2.
Figure S177. Optimized transition states for the reaction with 1a-(1S,4R) catalyzed by L1D in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to Scheme 3.
Figure S178. Optimized transition states for the reaction with 1a-(1S,4R) catalyzed by L1D in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to Scheme 3.
Figure S179. Optimized key transition states for the reaction with 1a-(1R,4S) and 1a-(1S,4R) catalyzed by L1u in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to Scheme 2 and Scheme 3.
Figure S180. Optimized structures of Cu(I)-L5 intermediates (L5D and L5U) with the key bond lengths (in angstrom), the NPA charge of the two reacting carbons and HOMO energies by the B3LYP method. Their relative free energy (in kcal/mol) in DCM solution are given. All hydrogen atoms were omitted for clarification, related to Figure 2 and Scheme 3.
Figure S181. Optimized key transition states for the reaction with 1a-(1R,4S) and 1a-(1S,4R) catalyzed by L5D in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to Scheme 3.

Figure S183. Optimized key transition states for the reaction with 1a-(1R,4S) and 1a-(1S,4R) catalyzed by L5U in DCM solution by the B3LYP method with the key bond lengths (in angstrom). Their relative free energies (in kcal/mol) in DCM are given. Unimportant hydrogen atoms were omitted for clarification, related to Scheme 3.
Table S3. The absolute (in Hartree) energies in gas phase and single point energies in DCM solution for the reaction catalyzed by Cu(I)-L1 by the B3LYP method, related to Scheme 2 and Scheme 3.

|                  | $E_{\text{gas}}$  | ($E+\text{ZPE})_{\text{gas}}$ | $G_{\text{gas}}$  | $E_{\text{soln}}$  |
|------------------|-------------------|--------------------------------|-------------------|-------------------|
| **L1**           |                   |                                |                   |                   |
| L1D              | -3975.508919      | -3974.926423                   | -3975.023118      | -3975.52314       |
| L1U              | -3975.506122      | -3974.923461                   | -3975.018880      | -3975.520437      |
| **1a-(1R,4S)**   |                   |                                |                   |                   |
| 3a-L1U-TS1endo   | -4361.582085      | -4360.833287                   | -4360.937046      | -4361.595674      |
| 3a-L1U-TS2endo   | -4361.586368      | -4360.835435                   | -4360.937814      | -4361.600515      |
| 4a-L1U-TS1exo    | -4361.555589      | -4360.807283                   | -4360.913976      | -4361.577559      |
| 5a-L1U-TS1endo   | -4361.577078      | -4360.829568                   | -4360.933208      | -4361.589614      |
| 5a-L1U-TS2endo   | -4361.582363      | -4360.832560                   | -4360.936949      | -4361.596926      |
| 6a-L1U-TS1exo    | -4361.552071      | -4360.804264                   | -4360.911095      | -4361.571714      |
| 7a-L1U-TS1endo   | -4361.575110      | -4360.828142                   | -4360.933877      | -4361.587674      |
| 7a-L1U-TS2endo   | -4361.573629      | -4360.824295                   | -4360.930177      | -4361.588277      |
| 8a-L1U-TS1exo    | -4361.554115      | -4360.806019                   | -4360.912416      | -4361.574074      |
| 8a-L1U-TS2exo    | -4361.554124      | -4360.804736                   | -4360.911517      | -4361.574689      |
| 9a-L1U-TS1endo   | -4361.569399      | -4360.821073                   | -4360.925575      | -4361.583639      |
| 9a-L1U-TS2endo   | -4361.572217      | -4360.822106                   | -4360.927193      | -4361.586313      |
| 10a-L1U-TS1exo   | -4361.549101      | -4360.801350                   | -4360.908659      | -4361.568782      |
| **3a'-L1D-TS1endo** | -4361.569396      | -4360.822588                   | -4360.928303      | -4361.581683      |
| **4a'-L1D-TS1endo** | -4361.575519      | -4360.826951                   | -4360.931116      | -4361.589744      |
| **5a'-L1D-TS1endo** | -4361.573865      | -4360.825507                   | -4360.929962      | -4361.588062      |
| **5a'-L1D-TS2endo** | -4361.581261      | -4360.830795                   | -4360.934205      | -4361.595991      |
| **6a'-L1D-TS1exo** | -4361.552208      | -4360.804294                   | -4360.910853      | -4361.572065      |
| **7a'-L1D-TS1endo** | -4361.579153      | -4360.830461                   | -4360.934283      | -4361.592828      |
| **7a'-L1D-TS2endo** | -4361.578478      | -4360.828152                   | -4360.932141      | -4361.592043      |
| **8a'-L1D-TS1exo** | -4361.553392      | -4360.805264                   | -4360.909320      | -4361.575257      |
| **9a'-L1D-TS1endo** | -4361.574283      | -4360.826857                   | -4360.930033      | -4361.586508      |
| **9a'-L1D-TS2endo** | -4361.574809      | -4360.825215                   | -4360.928952      | -4361.589161      |
| **10a'-L1D-TS1exo** | -4361.553465      | -4360.806179                   | -4360.913208      | -4361.570703      |
| **3a'-L1U-TS1endo** | -4361.569348      | -4360.821439                   | -4360.925671      | -4361.583984      |
| **5a'-L1U-TS1endo** | -4361.559387      | -4360.812157                   | -4360.916755      | -4361.573373      |
| **7a'-L1U-TS1endo** | -4361.559361      | -4360.811209                   | -4360.915814      | -4361.576873      |
| **7a'-L1U-TS2endo** | -4361.562077      | -4360.811858                   | -4360.914417      | -4361.579022      |
|                | $E_{\text{gas}}$ | $(E+\text{ZPE})_{\text{gas}}$ | $G_{\text{gas}}$ | $E_{\text{soln}}$ |
|----------------|------------------|-------------------------------|-----------------|------------------|
| **L5**         |                  |                               |                 |                  |
| $L_5^D$        | -9117.713339     | -9117.150688                  | -9117.248328    | -9117.725244     |
| $L_5^U$        | -9117.709710     | -9117.147019                  | -9117.245311    | -9117.722830     |
| **1a-(1R,4S)** |                  |                               |                 |                  |
| 3a-$L_5^D$-TS1endo | -9503.779903     | -9503.051551                  | -9503.156845    | -9503.792486     |
| 3a-$L_5^U$-TS2endo | -9503.785237     | -9503.054985                  | -9503.159414    | -9503.798144     |
| 5a-$L_5^D$-TS1endo | -9503.776854     | -9503.049918                  | -9503.158711    | -9503.789010     |
| 5a-$L_5^U$-TS2endo | -9503.782951     | -9503.053872                  | -9503.161882    | -9503.795381     |
| 3a-$L_5^U$-TS1endo | -9503.763335     | -9503.035774                  | -9503.141595    | -9503.774688     |
| 5a-$L_5^U$-TS1endo | -9503.772176     | -9503.044009                  | -9503.150394    | -9503.785862     |
| **1a-(1S,4R)** |                  |                               |                 |                  |
| 5a’-$L_5^D$-TS1endo | -9503.777596     | -9503.049268                  | -9503.156014    | -9503.790568     |
| 5a’-$L_5^U$-TS1endo | -9503.764974     | -9503.037612                  | -9503.144511    | -9503.778813     |

**Table S4.** The absolute (in Hartree) energies in gas phase and single point energies in DCM solution for the reaction catalyzed by Cu(I)-L5 by the B3LYP method, related to Scheme 3.
Table S5. Re-optimization Studies for Kinetic Resolution of Alkylidene Norcamphors related to Table 3.a

![Reaction Scheme]

| entry | T (°C) | t (h) | ratio 1a:2a | 1a yield (ee) (%)<sup>b</sup> | 5a yield (ee) (%)<sup>b</sup> | S<sup>c</sup> |
|-------|--------|-------|-------------|-----------------|-----------------|--------|
| 1     | -20    | 2     | 1:1.5       | 39(98)          | 47(87)          | 65     |
| 2     | -20    | 3     | 1:1         | 38(99)          | 48(88)          | 82     |
| 3     | -20    | 5     | 1:0.75      | 38(99)          | 47(89)          | 90     |
| 4     | -40    | 4     | 1:1         | 41(97)          | 46(90)          | 90     |
| 5     | -40    | 8     | 1:0.75      | 43(95)          | 46(90)          | 70     |
| 6     | -60    | 35    | 1:1         | 40(95)          | 46(92)          | 89     |
| 7     | -60    | 56    | 1:0.75      | 42(91)          | 45(93)          | 88     |
| 8     | -60    | 21    | 1:1.5       | 44(92)          | 46(94)          | 106    |

<sup>a</sup> All reactions were carried out with 0.40 mmol of rac-1a in 2 mL of CH₂Cl₂. <sup>b</sup> Isolated yields based on rac-1a, >20:1 dr was determined by crude ¹H NMR, and ee value of 5a and the recovered 1a were determined by HPLC and GC analysis, respectively. <sup>c</sup> S = ln((1 - Conv.)(1 - ee₁))/ln((1 - Conv.)(1 + ee₁)), Conv. = ee₁/(ee₁ + ee₅).
Supplemental Item Legends

**Table S6.** Cartesian Coordinates for Optimized Structures of reactants, related to Scheme 2 and Figure 2.

**Table S7.** Cartesian Coordinates for Optimized Structures of L1-1a-(1R,4S), related to Scheme 2.

**Table S8.** Cartesian Coordinates for Optimized Structures of L1-1a-(1S,4R), related to Scheme 2 and Scheme 3.

**Table S9.** Cartesian Coordinates for Optimized Structures of L5-1a-(1R,4S), related to Figure 2 and Scheme 3.

**Table S10.** Cartesian Coordinates for Optimized Structures of L5-1a-(1S,4R), related to Scheme 3.

**Data S1.** Crystal Data and Structure Refinement for tosylated (±)-endo-3a, related to Scheme 1.

**Data S2.** Crystal Data and Structure Refinement for tosylated (±)-endo-5a, related to Scheme 1.

**Data S3.** Crystal Data and Structure Refinement for 5b, related to Table 3.

**Data S4.** Crystal Data and Structure Refinement for 5s, related to Table 3.

**Data S5.** Crystal Data and Structure Refinement for (±)-5u, related to Table 3.

**Data S6.** Crystal Data and Structure Refinement for (±)-1d, related to Table 3.
Transparent Methods

$^1$H NMR spectra were recorded on a Bruker 400 MHz spectrometer in CDCl₃. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = single, d = double, t = triple, q = quarter, m = multiple or unresolved, br s = broad single, coupling constant(s) in Hz, integration). $^{13}$C NMR spectra were recorded on a Bruker 100 MHz spectrometer in CDCl₃. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Commercially obtained reagents were used without further purification. Solvents were purified prior to use according to the standard methods. Unless otherwise noted, all reactions were carried out under nitrogen atmosphere. Enantiomeric ratios were determined by chiral-phase HPLC and GC analysis in comparison with authentic racemic materials. 3-Methylene-2-norcamphor $^{1a}$ is commercially-available or prepared according to the literature procedure (Kleinfelter and Schleyer, 1973; Fehr et al., 2009). Racemic substituted methylene norcamphors $^{1b-1l}$ were synthesized by aldol condensation reaction (Satam et al., 2011). Racemic substituted methylene norcamphors $^{1m}$ and $^{1n}$ were prepared according to the literature procedure (Kleinfelter and Schleyer, 1973; Gebregziorgiset al., 2012), $^{1o}$, $^{1p}$ and $^{1q}$ was prepared according to the literature procedure (Kleinfelter and Schleyer, 1973; Coe et al., 2004; Berthelette et al., 1997; Chuiko et al., 2002). Chiral ligands $^{L1-L5}$ were prepared according our previous procedure (Wang et al., 2008).

General Procedure for the Preparation of Alkylidene Norcamphors

Procedure A: Preparation of Racemic Alkylidene Norcamphors $^{1b-1l}$:

In a 100 mL round-bottom flask, norcamphor (5.0 mmol, 1.0 equiv.) and aryl aldehyde (5.0 mmol, 1.0 equiv.) were dissolved with 20 mL ethanol, and then sodium hydroxide solution (10% in ethanol, 2.0 mL) was added dropwise to the solution. The reaction mixture was stirred at room temperature until TLC revealed complete conversion of norcamphor. After reaction completed, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 20 mL of CH₂Cl₂ and washed with 20 mL of sat. NaCl solution. Organic phase was separated and the aqueous phase was extracted with additional CH₂Cl₂ (2 × 20 mL).
Combined organic phase was dried over Na₂SO₄ and concentrated under reduced pressure, the crude mixture was purified by silica-gel flash column chromatography to obtain the racemic compounds 1b-1l in moderate to good yields.

**Procedure B: Preparation of Racemic 1m:**

\[
\text{H} - \text{O} \quad \text{Et₂NH} \quad \text{HCHO} \quad \text{AcOH} \quad \text{H} - \text{O}
\]

Diethylamine (10.0 mmol, 1.0 equiv.) was added over a 15 min. period to formaldehyde (36% in H₂O, 40.0 mmol, 4.0 equiv.) at 0°C. The resultant mixture was treated over a 33 minutes’ period with acetic acid (20.0 mmol, 2.0 equiv.). Once the addition was finished, the temperature was increased to room temperature and the mixture was added over a 22 minutes’ period to \textit{exo}-octahydro-5H-4,7-methanoinden-5-one (10.0 mmol, 1.0 equiv.) in the presence of a small amount of BHT at 95°C. The mixture was refluxed for 5 hours and cooled down to room temperature. The yellow mixture was hydrolyzed with aqueous 5% HCl and ice (pH = 1). The aqueous layer was extracted twice with Et₂O, and the combined organic layers were washed with H₂O, aqueous 5% NaOH and twice with brine, dried over Na₂SO₄ and filtered off. Et₂O was distilled under atmospheric pressure to give a crude which was purified by silica-gel flash column chromatography to obtain the racemic compound 1m in 55% yield.

**Procedure C: Preparation of Racemic 1n:**
A solution of dicyclopentadiene (40 mmol, 1.0 equiv.) in THF (3.5 mL) was added over 2 minutes at room temperature to a yellow suspension of mercury(II) acetate (40 mmol, 1.0 equiv.) in THF/H₂O (35 mL/35 mL). After 5 minutes, the reaction mixture became colorless and was stirred at the same temperature for 20 minutes. The reaction was carefully quenched with slow addition of 3 M NaOH (44 mL of an aqueous solution) followed by dropwise addition of 0.5 M NaBH₄ (44 mL of a 3 M NaOH aqueous solution) at 0°C. Liquid mercury (0) was filtered over celite and rinsed with diethyl ether (70 mL). The organic layer was separated, dried over MgSO₄, reduced under vacuum and the colorless oil obtained was used in the next step without further purification. PCC (80 mmol, 2.0 equiv.) was added over 5 minutes at room temperature to a crude material (40 mmol, 1.0 equiv.) in DCM (80 mL). The mixture was refluxed for 10 hours and cooled down to room temperature. The reaction mixture was filtered through a short plug of silica (eluted with DCM) and the organic layer was washed with 5% KOH, 5% HCl, saturated NaHCO₃, saturated NaCl, and dried over Na₂SO₄. The solvent was removed by rotary evaporation and the crude product was purified by column chromatography (EtOAc:hexane = 1:10) to give endo-3,3a,4,6,7,7a-hexahydro-5H-4,7-methanoinden-5-one and 1,3a,4,6,7,7a-hexahydro-5H-4,7-methanoinden-5-one in 50% yield for three steps.

A solution of ketones (20 mmol, 2.96 g) in 20 mL EtOH was added 100 mg Pd/C (10%). The reaction mixture was stirred at 50 °C under hydrogen atmosphere (80 bar) for 48 h. The reaction mixture was filtered through a short plug of silica (eluted with EtOAc) and The solvent was removed by rotary evaporation and the crude product was purified by column chromatography (EtOAc:hexane = 1:10) to give octahydro-5H-4,7-methanoinden-5-one in 60% yield.

Diethylamine (10.0 mmol, 1.0 equiv.) was added over a 15 minutes’ period to formaldehyde (36% in H₂O, 40.0 mmol, 4.0 equiv.) at 0 °C. The resultant mixture was treated over a 33 minutes’ period with acetic acid (20.0 mmol, 2.0 equiv.). Once the addition was finished, the temperature was increased to room temperature and the mixture was added over a 22 minutes’ period to endo-octahydro-5H-4,7-methanoinden-5-one (10.0 mmol, 1.0 equiv.) in the presence of a small amount of BHT at 95°C. The mixture was refluxed for 5 hours and cooled down to room temperature. The yellow mixture was hydrolyzed with aqueous 5% HCl and ice (pH = 1). The aqueous layer was extracted twice with Et₂O, and the combined organic layers were washed with H₂O,
aqueous 5% NaOH and twice with brine, dried over Na$_2$SO$_4$ and filtered off. Et$_2$O was distilled under atmospheric pressure to give a crude which was purified by silica-gel flash column chromatography (EtOAc:hexane = 1:20) to obtain the racemic compound 1n in 40% yield.

**Procedure D: Preparation of Racemic 1o:**

\[
\begin{align*}
\text{Br} \quad \text{Br} & \quad + \quad n\text{BuLi} \quad \text{toluene} \\
\text{Br} \quad \text{Br} & \quad \text{HCOOH} \quad \text{reflux} \\
\text{O} & \quad \text{CrO}_3 \quad \text{H}_2\text{SO}_4 \quad \text{acetone} \\
\text{O} & \quad + \quad \text{Et}_2\text{NH} \quad + \quad \text{HCHO} \quad \text{AcOH}
\end{align*}
\]

1,2-Dibromobenzene (40 mmol, 1 equiv.) and cyclopentadiene (40 mmol, 1 equiv.) were stirred in toluene (40 mL) at 0 °C under N$_2$. To this solution was added $n$-BuLi (16 mL, 2.5M in hexane, 40 mmol) dropwise over 30 min during which the reaction solution became first yellow then cloudy white. After an additional 10 min at 0 °C the mixture was allowed to warm to room temperature, stirred overnight and treated with H$_2$O (20 mL) and extracted with hexane (3 × 15 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated to obtain a yellow oil. The product was purified by chromatography on silica gel eluting with hexane to provide 1,4-dihydro-1,4-methano-naphthalene as a clear, colorless oil (5.49 g, 97%).

Approximately 7 g (152 mmol, 4 equiv.) of 98–100% formic acid is added to 5.49 g (38 mmol, 1 equiv.) of 1,4-dihydro-1,4-methano-naphthalene in a 100 mL round-bottomed flask equipped with a condenser, and the mixture is boiled under reflux for 4 hours. The dark solution is cooled and formic acid was removed by rotary evaporation. The crude product was purified by column chromatography to give 1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl formate in 58% yield. A solution of 4.14 g (22 mmol, 1 equiv.) of 1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl formate in 10 mL of reagent grade acetone is contained in a 100 mL three-necked flask equipped with a thermometer, stirrer, and dropping funnel containing 8 N chromic acid solution. The flask is cooled with an ice bath and the oxidant is added at a rate such that the reaction temperature is maintained at 20–30 °C. Approximately 11 mL of oxidant solution is required; completion of the
reaction being shown by the persistence of the brownish orange color. A slight excess of oxidant is added, and the solution is stirred overnight at room temperature. Solid sodium bisulfite is added in portions to reduce the excess oxidant. The reaction mixture is poured into a large separatory funnel. The dark green chromic sulfate sludge, which has formed during the course of the reaction, is separated either by decantation and washing or by drawing it off from the bottom of the funnel. The acetone solution is washed three times with 10–15 mL portions of an aqueous saturated potassium carbonate solution and finally is dried over anhydrous Na₂SO₄ and concentrated. The product was purified by silica-gel flash column chromatography to provide 3,4-dihydro-1,4-methanonaphthalen-2(1H)-one as a clear, colorless oil (2.78 g, 80%).

Diethylamine (10.0 mmol, 1.0 equiv.) was added over a 15 minutes’ period to formaldehyde (36% in H₂O, 40.0 mmol, 4.0 equiv.) at 0°C. The resultant mixture was treated over a 33 minutes’ period with acetic acid (20.0 mmol, 2.0 equiv.). Once the addition was finished, the temperature was increased to room temperature and the mixture was added over a 22 minutes’ period to 3,4-dihydro-1,4-methanonaphthalen-2(1H)-one (10.0 mmol, 1.0 equiv.) in the presence of a small amount of BHT at 95°C. The mixture was refluxed for 5 hours and cooled down to room temperature. The yellow mixture was hydrolyzed with aqueous HCl 5% and ice (pH = l). The aqueous layer was extracted twice with Et₂O, and the combined organic layers were washed with H₂O, aqueous NaOH 5% and twice with brine, dried over Na₂SO₄ and filtered off. Et₂O was distilled under atmospheric pressure to give a crude which was purified by silica-gel flash column chromatography to obtain the racemic compound 1o in 45% yield.

Procedure E: Preparation of Racemic 1p:

\[
\text{(E)-3-benzylidenebicyclo[2.2.1]heptan-2-one 1b (0.500 g, 2.5 mmol) was dissolved in CH₃CN (60 mL) and irradiated with a UV mercury lamp for 48 h while stirring at room temperature. The solvent was removed under reduced pressure, and the product was purified by silica-gel flash column chromatography to provide 1p in 30% yield.}
\]
Procedure F: Preparation of Racemic 1q:

\[
\text{Camphor} + \text{PhCHO} \xrightarrow{t\text{-BuOLi}} \text{DMSO, rt.} \quad 50\% \text{ yield}
\]

In 10 ml of anhydrous DMSO were dissolved 1.52 g (10 mmol) of camphor and 11 mmol of bezaldehyde. To a mixture of 0.96 g (12 mmol) of \( t\)-BuOLi and 10 ml of anhydrous DMSO was added dropwise the solution of reagents controlling the rate of addition so as the temperature of the reaction mixture did not exceed 20 °C; the reaction mixture was cooled with water bath. The stirring was continued till complete consumption of the camphor. Then the reaction mixture was poured into 150 ml of ice water containing 5 ml of acetic acid. The precipitate was filtered off, washed with water, and recrystallized from ethanol.

General Procedure for the Umpolung-Type 1,3-Dipolar Cycloaddition of 3-Methylene-2-Norcamphor with Azomethine Ylides

(S)-TF-BiphamPhos \( \text{L5} \) (17.6 mg, 0.022 mmol) and Cu(CH\(_3\)CN)\(_4\)BF\(_4\) (6.3 mg, 0.020 mmol) were dissolved in 2.0 mL CH\(_2\)Cl\(_2\), and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -40 °C (unless otherwise noted) and the imino ester \( 2 \) (0.20 mmol), Et\(_3\)N (0.060 mmol) were added sequentially. Then 3-methylene-2-norcamphor \( 1a \) (0.40 mmol) was added. After the reaction completed, the reaction mixture was quenched by silica-gel. The organic solvent was removed and the residue was purified by column chromatography to give the products, which was then directly analyzed by chiral-phase HPLC to determine the enantiomeric excess.
Methyl (1S,2S,2'S,4R,5'R)-5'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5a): Yield (91%); yellow solid; m.p. 109-111 °C; [α]^{30}_D = +21.5 (c 0.52, CH_{2}Cl_{2}); ^1H NMR (400 MHz, CDCl_{3}) δ 7.47 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.14 (dd, J = 11.6, 5.2 Hz, 1H), 3.84 (s, 1H), 3.68 (s, 3H), 2.70 - 2.62 (m, 2H), 2.30 - 2.24 (m, 1H), 2.06 - 1.86 (m, 3H), 1.80 - 1.68 (m, 3H), 1.53 - 1.39 (m, 1H). ^13C NMR (100 MHz, CDCl_{3}) δ 217.8, 173.2, 139.8, 133.4, 128.7, 128.5, 68.6, 64.8, 62.2, 52.3, 48.9, 45.1, 40.3, 34.7, 25.1, 23.4.; HRMS (ESI+) Calcd. For C_{18}H_{20}ClNNaO_{3} ([M+Na]^+): 356.1024, found: 356.1022. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AD-H, i-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 12.94 and 23.80 min.

Methyl (1S,2S,2'S,4R,5'R)-5'-(3-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5b): Yield (88%); white solid; m.p. 130-132 °C; [α]^{30}_D = +42.1 (c 0.3, CH_{2}Cl_{2}); ^1H NMR (400 MHz, CDCl_{3}) δ 7.52 (s, 1H), 7.43 (d, J = 6.8 Hz, 1H), 7.32 - 7.24 (m, 2H), 4.14 (dd, J = 11.6, 5.2 Hz, 1H), 3.85 (s, 1H), 3.68 (s, 3H), 2.68 - 2.63 (m, 2H), 2.60 (brs, 1H), 2.31 - 2.24 (m, 1H), 2.11 - 1.97 (m, 2H), 1.96 - 1.86 (m, 1H), 1.83 - 1.65 (m, 3H), 1.51 - 1.41 (m, 1H). ^13C NMR (100 MHz, CDCl_{3}) δ 217.7, 173.1, 143.5, 134.3, 129.9, 127.8, 127.3, 125.1, 68.6, 64.7, 62.3, 52.3, 48.9, 45.1, 40.2, 34.7, 25.1, 23.4.; HRMS (ESI+) Calcd. For C_{18}H_{21}ClNO_{3} ([M+H]^+): 334.1204, found: 334.1207. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak ASH, i-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); t_r = 14.72 and 24.80 min.
Methyl (1S,2S,2'S,4R,5'R)-5'-(4-bromophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5c): Yield (84%); white solid; m.p. 108-110 °C; [α]_{D}^{30} = +12.3 (c 0.33, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.51 - 7.45 (m, 2H), 7.44 - 7.38 (m, 2H), 4.13 (dd, J = 11.6, 5.2 Hz, 1H), 3.84 (s, 1H), 3.68 (s, 3H), 2.68 - 2.64 (m, 2H), 2.31 - 2.24 (m, 1H), 2.09 - 1.97 (m, 2H), 1.95 - 1.86 (m, 1H), 1.79 - 1.66 (m, 3H), 1.51 - 1.41 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 217.7, 173.2, 140.4, 131.7, 128.8, 121.5, 68.6, 64.8, 62.2, 52.3, 48.9, 45.1, 40.2, 34.7, 25.1, 23.4.; HRMS (ESI+) Calcd. For C₁₈H₂₀BrNNaO₃ ([M+Na]⁺): 400.0519, found: 400.0520. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak AD-H, i-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 13.83 and 25.28 min.

Methyl (1S,2S,2'S,4R,5'R)-5'-(3-bromophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5d): Yield (85%); white solid; m.p. 117-118 °C; [α]_{D}^{30} = +36.2 (c 0.46, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, J = 1.2 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.23 (td, J = 7.6, 2.0 Hz, 1H), 4.13 (dd, J = 11.6, 4.8 Hz, 1H), 3.84 (s, 1H), 3.68 (s, 3H), 2.67 - 2.63 (m, 2H), 2.59 (brs, 1H), 2.32 - 2.24 (m, 1H), 2.11 - 1.96 (m, 2H), 1.96 - 1.85 (m, 1H), 1.81 - 1.65 (m, 3H), 1.50 - 1.41 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 217.7, 173.1, 143.8, 130.8, 130.3, 130.2, 125.6, 122.6, 68.6, 64.7, 62.2, 52.3, 48.9, 45.0, 40.2, 34.7, 25.1, 23.4.; HRMS (ESI+) Calcd. For C₁₈H₂₀BrNNaO₃ ([M+Na]⁺): 400.0519, found: 400.0521. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, i-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); t_r = 18.15 and 32.73 min.
Methyl (1S,2S,2'S,4R,5'R)-5'-(2-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5e): Yield (94%); white solid; m.p. 128-130 °C; [α]30 D = +53.5 (c 0.53, CH2Cl2); 1H NMR (400 MHz, CDCl3) δ 7.95 (dd, J = 8.0, 1.2 Hz, 1H), 7.32 (m, 2H), 7.20 (m, 1H), 4.67 (dd, J = 11.6, 4.8 Hz, 1H), 3.90 (s, 1H), 3.67 (s, 3H), 2.71 – 2.63 (m, 2H), 2.59 (brs, 1H), 2.30 – 2.24 (m, 1H), 2.23 – 2.16 (m, 1H), 1.97 – 1.86 (m, 2H), 1.80 – 1.69 (m, 3H), 1.51 – 1.42 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 217.5, 173.2, 139.1, 133.2, 129.3, 128.5, 127.5, 127.4, 68.1, 64.5, 58.3, 52.1, 49.0, 45.0, 38.7, 34.8, 25.1, 23.3.; HRMS (ESI+) Calcd. For C18H21ClNO3 ([M+H]+): 334.1204, found: 334.1204. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AS-H, i-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); tR = 10.39 and 18.26 min.

methyl (1S,2S,2'S,4R,5'R)-5'-(4-nitrophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5f): Yield (72%); yellow solid; m.p. 102 – 103 °C; [α]15 D = +7.4 (c 0.61, CH2Cl2); 1H NMR (400 MHz, CDCl3) δ 8.25 – 8.17 (m, 2H), 7.82 – 7.70 (m, 2H), 4.32 (dd, J = 11.7, 5.3 Hz, 1H), 3.91 (s, 1H), 3.68 (s, 3H), 2.69 – 2.64 (m, 2H), 2.30 – 2.25 (m, 1H), 2.16 – 2.10 (m, 1H), 2.07 – 2.01 (m, 1H), 1.97 – 1.89 (m, 1H), 1.83 – 1.70 (m, 3H), 1.51 – 1.43 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 217.0, 173.1, 149.7, 147.3, 127.9, 123.7, 68.3, 64.6, 61.8, 52.2, 48.9, 44.8, 40.1, 34.8, 25.1, 23.2.; HRMS (ESI+) Calcd. For C18H21N2O5 ([M+H]+): 345.1445, found: 345.1443. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AD-H, i-propanol /hexane = 30/70, flow rate 1.0 mL/min, λ = 220 nm); tR = 10.35 and 17.80 min.
methyl (1S,2S,2'S,4R,5'R)-5'-(4-cyanophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5g): Yield (83%); white solid; m.p. 107 – 108 °C; \([\alpha]^{15}_D = +20.0 \ (c \ 0.60, \ CH_2Cl_2); \) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.73 – 7.61 (m, 4H), 4.25 (dd, \(J = 11.7, 5.2 \ Hz, 1H\)), 3.88 (s, 1H), 3.68 (s, 3H), 2.70 – 2.62 (m, 2H), 2.31 – 2.22 (m, 1H), 2.14 – 2.05 (m, 1H), 2.07 – 1.99 (m, 1H), 2.01 – 1.86 (m, 1H), 1.85 – 1.65 (m, 3H), 1.52 – 1.40 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 217.1, 173.2, 147.5, 132.4, 127.9, 118.8, 111.4, 68.3, 64.7, 62.2, 52.3, 49.8, 44.9, 40.1, 34.8, 25.1, 23.3.; HRMS (ESI+) Calcd. For C\(_{19}\)H\(_{21}\)N\(_2\)O\(_3\) ([M+H]+): 325.1547, found: 325.1549. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AD-H, \(i\)-propanol/hexane = 30/70, flow rate 1.0 mL/min, \(\lambda = 220 \ nm\)); \(t_r = 8.67 \) and 15.84 min.

Methyl (1S,2S,2'S,4R,5'R)-3-oxo-5'-phenylspiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5h): Yield (86%); white thick liquid; \([\alpha]^{30}_D = +44.7 \ (c \ 0.43, \ CH_2Cl_2); \) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.56 – 7.49 (m, 2H), 7.41 – 7.33 (m, 2H), 7.32 – 7.28 (m, 1H), 4.15 (dd, \(J = 10.0, 6.8 \ Hz, 1H\)), 3.85 (s, 1H), 3.68 (s, 3H), 2.72 – 2.67 (m, 1H), 2.67 – 2.62 (m, 1H), 2.31 – 2.27 (m, 1H), 2.09 – 2.07 (m, 1H), 2.07 – 2.03 (m, 1H), 1.95 – 1.86 (m, 1H), 1.80 – 1.68 (m, 3H), 1.50 – 1.43 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 218.1, 173.2, 140.9, 128.6, 127.8, 127.0, 68.7, 64.9, 62.9, 52.3, 48.9, 45.2, 40.4, 34.7, 25.1, 23.5.; HRMS (ESI+) Calcd. For C\(_{18}\)H\(_{22}\)NO\(_3\) ([M+H]+): 300.1594, found: 300.1597. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AD-H, \(i\)-propanol /hexane = 5/95, flow rate 1.0 mL/min, \(\lambda = 220 \ nm\)); \(t_r = 16.86 \) and 28.61 min.
Methyl (1S,2S,2'S,4R,5'R)-5'-(4-methoxyphenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5i): Yield (59%); yellow thick liquid; $[\alpha]_{D}^{30} = +36.2$ (c 0.39, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 – 7.40 (m, 2H), 6.94 – 6.86 (m, 2H), 4.12 (dd, $J = 9.0, 8.4$ Hz, 1H), 3.84 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 2.77 (s, 1H), 2.71 – 2.68 (m, 1H), 2.66 – 2.63 (m, 1H), 2.30 – 2.26 (m, 1H), 2.05 – 2.01 (m, 2H), 1.95 – 1.86 (m, 1H), 1.78 – 1.68 (m, 3H), 1.50 – 1.42 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 218.2, 173.1, 159.2, 132.7, 128.2, 114.0, 68.4, 64.8, 62.2, 55.3, 52.3, 48.9, 45.1, 40.2, 34.7, 25.1, 23.5.; HRMS (ESI+) Calcd. For C$_{18}$H$_{22}$NO$_3$ ([M+H]+): 330.1700, found: 330.1700. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak OD-H, $i$-propanol/hexane = 10/90, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 16.72$ and 22.88 min.

Methyl (1S,2S,2'S,4R,5'R)-3-oxo-5'-(p-tolyl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5j): Yield (74%); yellow solid; m.p. 76-78 °C; $[\alpha]_{D}^{30} = +49.4$ (c 0.36, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 4.15 – 4.08 (m, 1H), 3.83 (s, 1H), 3.68 (s, 3H), 2.72 – 2.67 (m, 1H), 2.67 – 2.62 (m, 1H), 2.35 (s, 3H), 2.32 – 2.26 (m, 1H), 2.06 – 2.04 (m, 1H), 2.03 – 2.00 (m, 1H), 1.97 – 1.84 (m, 1H), 1.80 – 1.66 (m, 3H), 1.50 – 1.40 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 218.2, 173.2, 137.9, 137.5, 129.3, 127.0, 68.8, 65.0, 62.7, 52.3, 48.9, 45.2, 40.4, 34.7, 25.1, 23.6, 21.1.; HRMS (ESI+) Calcd. For C$_{19}$H$_{23}$NO$_3$ ([M+H]$^+$): 314.1751, found: 314.1751. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AD-H, $i$-propanol/hexane = 10/90, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 11.78$ and 20.79 min.
Methyl \((1S,2S,2'S,4R,5'R)-3\text{-oxo-5'}-(o\text{-tolyl})\text{spiro[bicyclo[2.2.1]heptane-2,3'}\text{'-pyrrolidine]-2'}\text{-carboxylate}}\) (5l): Yield (64%); white solid; m.p. 126-128 °C; \([\alpha]^{20}_D = +58.7\) (c 0.45, CH₂Cl₂); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.68 (d, \(J = 7.6\) Hz, 1H), 7.27 – 7.23 (m, 1H), 7.18 (m, 2H), 4.35 (dd, \(J = 10.4, 6.0\) Hz, 1H), 3.85 (s, 1H), 3.68 (s, 3H), 2.73 – 2.69 (m, 1H), 2.68 – 2.63 (m, 1H), 2.57 (brs, 1H), 2.41 (s, 3H), 2.34 – 2.28 (m, 1H), 2.08 – 2.01 (m, 2H), 1.96 – 1.86 (m, 1H), 1.80 – 1.67 (m, 3H), 1.51 – 1.43 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 218.3, 173.1, 138.6, 136.3, 130.3, 127.4, 126.5, 125.3, 68.7, 64.7, 58.6, 52.3, 48.9, 45.3, 39.2, 34.6, 25.1, 23.6, 19.4.; HRMS (ESI+) Calcd. For C₁₉H₂₃NO₃ ([M+H]⁺): 314.1751, found: 314.1751. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AD-H, \(i\)-propanol/hexane = 10/90, flow rate 1.0 mL/min, \(\lambda = 220\) nm); \(t_r = 8.67\) and 12.03 min.
Methyl (1S,2S,2'S,4R,5'R)-5'-(naphthalen-1-yl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5m): Yield (73%); yellow solid; m.p. 123-125 °C; [α]_D^20 = +77.0 (c 0.46, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.29 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.79 (m, 2H), 7.56 – 7.46 (m, 3H), 4.87 (d, J = 8.4 Hz, 1H), 3.95 (s, 1H), 3.66 (s, 3H), 2.87 – 2.75 (m, 1H), 2.71 – 2.63 (m, 1H), 2.38 – 2.33 (m, 1H), 2.32 – 2.25 (m, 1H), 2.25 – 2.16 (m, 1H), 1.97 – 1.88 (m, 1H), 1.81 – 1.70 (m, 3H), 1.54 – 1.46 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 218.4, 172.8, 136.0, 133.7, 132.0, 128.6, 128.2, 126.1, 125.6, 125.5, 123.8, 122.9, 69.0, 64.4, 58.4, 52.3, 48.9, 45.5, 38.6, 34.6, 25.1, 23.7.; HRMS (ESI+) Calcd. For C₂₂H₂₄NO₃ ([M+H]⁺): 350.1751, found: 350.1751. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak AS-H, i-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); tᵣ = 10.80 and 17.05 min.

Methyl (1S,2S,2'S,4R,5'R)-5'-(naphthalen-2-yl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5n): Yield (88%); white solid; m.p. 138-140 °C; [α]_D^20 = +34.4 (c 0.43, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.90 (s, 1H), 7.88 – 7.81 (m, 3H), 7.72 (dd, J = 8.4, 1.6 Hz, 1H), 7.50 – 7.44 (m, 2H), 4.33 (dd, J = 10.8, 6.0 Hz, 1H), 3.89 (s, 1H), 3.71 (s, 3H), 2.74 – 2.69 (m, 1H), 2.69 – 2.65 (m, 1H), 2.35 – 2.29 (m, 1H), 2.21 – 2.10 (m, 2H), 1.98 – 1.87 (m, 1H), 1.83 – 1.70 (m, 3H), 1.54 – 1.44 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 218.1, 173.2, 138.4, 133.3, 133.0, 128.5, 127.9, 127.6, 126.1, 125.9, 125.0, 68.9, 65.0, 63.1, 52.4, 49.0, 45.3, 40.3, 34.7, 25.1, 23.6.; HRMS (ESI+) Calcd. For C₂₂H₂₄NO₃ ([M+H]⁺): 350.1751, found: 350.1751. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, i-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); tᵣ = 14.89 and 23.96 min.
Methyl (1S,2S,2'S,4R,5'R)-5'-(4-chlorophenyl)-2'-methyl-3-oxospiro[bicyclo[2.2.1]heptane-2',3']-pyrrolidine]-2'-carboxylate (5o): Yield (70%); white solid; m.p. 116-118 °C; \([\alpha]^{30}_{D} = +14.1 \text{ (c 1.02, CH}_2\text{Cl}_2); \]

\(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta\) 7.47 (d, \(J = 8.4 \text{ Hz, 2H}), 7.31 (d, \(J = 8.4 \text{ Hz, 2H}), 4.15 \text{ (dd, } J = 9.2, 7.2 \text{ Hz, 1H}), 3.69 \text{ (s, 3H}, 3.11 \text{ (brs, 1H), 2.79 – 2.74 \text{ (m, 1H)}, 2.65 – 2.59 \text{ (m, 1H)}, 2.34 – 2.23 \text{ (m, 2H)}, 2.11 – 2.02 \text{ (m, 1H), 1.92 – 1.72 \text{ (m, 2H), 1.71 – 1.61 \text{ (m, 1H)}, 1.59 – 1.53 \text{ (m, 1H)}, 1.56 \text{ (s, 3H), 1.51 – 1.42 \text{ (m, 1H)}). \(^{13}\text{C NMR (100 MHz, CDCl}_3\) \(\delta\) 220.5, 174.2, 139.9, 133.1, 128.6, 72.0, 65.7, 59.5, 52.6, 49.4, 44.0, 42.1, 35.6, 25.9, 25.9, 22.0.; HRMS (ESI+) Calcd. For C\(_{19}\)H\(_{23}\)ClNO\(_3\) ([M+H]\(^+\): 348.1361, found: 348.1361. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AS-H, \(i\)-propanol/hexane = 10/90, flow rate 1.0 mL/min, \(\lambda = 220 \text{ nm}); t\(_r\) = 6.25 and 10.23 min.

Methyl (1S,2S,2'S,4R,5'R)-5'-(4-methoxyphenyl)-2'-methyl-3-oxospiro[bicyclo[2.2.1]heptane-2',3']-pyrrolidine]-2'-carboxylate (5p): Yield (57%); white solid; m.p. 106-109 °C; \([\alpha]^{30}_{D} = +7.6 \text{ (c 0.46, CH}_2\text{Cl}_2); \]

\(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta\) 7.47 – 7.42 \text{ (m, 2H), 6.90 – 6.85 \text{ (m, 2H), 4.13 \text{ (dd, } J = 9.6, 6.8 \text{ Hz, 1H), 3.80 \text{ (s, 3H), 3.69 \text{ (s, 3H), 3.16 \text{ (brs, 1H), 2.81 – 2.75 \text{ (m, 1H)}, 2.64 – 2.59 \text{ (m, 1H)}, 2.32 – 2.24 \text{ (m, 2H), 2.14 – 2.06 \text{ (m, 1H), 1.93 – 1.72 \text{ (m, 2H), 1.72 – 1.62 \text{ (m, 1H)}, 1.56 \text{ (s, 3H), 1.55 – 1.52 \text{ (m, 1H)}, 1.52 – 1.42 \text{ (m, 1H). \(^{13}\text{C NMR (100 MHz, CDCl}_3\) \(\delta\) 220.7, 174.4, 158.9, 133.3, 128.4, 113.9, 72.0, 65.9, 59.7, 55.3, 52.6, 49.4, 44.3, 42.2, 35.6, 26.1, 25.9, 22.1.; HRMS (ESI+) Calcd. For C\(_{20}\)H\(_{26}\)NO\(_4\) ([M+H]\(^+\): 344.1856, found: 344.1856. The product was analyzed by HPLC to determine the enantiomeric excess: >99% ee (Chiralpak AD-H, \(i\)-propanol/hexane = 30/70, flow rate 1.0 mL/min, \(\lambda = 220 \text{ nm); t\(_r\) = 6.58 and 9.45 min.}
Methyl (1S,2S,2'S,4R,5'R)-2'-methyl-3-oxo-5'-(thiophen-2-yl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5q): Yield (64%); yellow solid; m.p. 94-96 °C; [α]30D = +3.1 (c 0.32, CH2Cl2); 1H NMR (400 MHz, CDCl3) δ 7.25 – 7.19 (m, 1H), 7.10 (d, J = 2.4 Hz, 1H), 6.97 (m, 1H), 4.46 – 4.36 (m, 1H), 3.69 (s, 3H), 3.23 (brs, 1H), 2.79 – 2.73 (m, 1H), 2.64 – 2.58 (m, 1H), 2.43 – 2.35 (m, 1H), 2.31 – 2.23 (m, 1H), 2.22 – 2.13 (m, 1H), 1.94 – 1.74 (m, 2H), 1.72 – 1.64 (m, 1H), 1.59 – 1.56 (m, 1H), 1.56 (s, 3H), 1.53 – 1.45 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 220.1, 174.0, 144.4, 126.7, 124.6, 124.5, 72.0, 65.8, 55.7, 52.6, 49.2, 44.6, 42.0, 35.7, 26.0, 25.8, 22.0.; HRMS (ESI+) Calcd. For C17H21NNaO3S+ ([M+Na]+): 342.1134, found: 342.1137. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, i-propanol/hexane = 3/97, flow rate 1.0 mL/min, λ = 220 nm); tR = 30.50 and 34.22 min.

Methyl (1S,2S,2'S,4R,5'R)-2'-benzyl-5'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5r): Yield (68%); colorless thick liquid; [α]30D = -16.3 (c 0.42, CH2Cl2); 1H NMR (400 MHz, CDCl3) δ 7.49 – 7.42 (m, 2H), 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 5H), 4.27 (dd, J = 10.0, 6.0 Hz, 1H), 3.52 (s, 3H), 3.42 (d, J = 13.2 Hz, 1H), 3.00 (brs, 1H), 2.99 (d, J = 13.2 Hz, 1H), 2.78 – 2.73 (m, 1H), 2.67 – 2.63 (m, 1H), 2.43 – 2.37 (m, 1H), 2.09 – 2.02 (m, 1H), 1.96 – 1.73 (m, 4H), 1.69 – 1.66 (m, 1H), 1.52 – 1.45 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 220.7, 173.2, 140.0, 136.6, 133.1, 130.4, 128.58, 128.56, 128.0, 126.8, 76.7, 65.8, 59.0, 52.2, 49.3, 44.7, 41.6, 39.2, 35.8, 26.5, 25.5.; HRMS (ESI+) Calcd. For C25H26ClNNaO3+ ([M+Na]+): 446.1493, found: 446.1493. The product was analyzed by HPLC to determine the enantiomeric excess: >99% ee (Chiralpak OD-H, i-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); tR = 7.65 and 9.10 min.
General Procedure for the Efficient Kinetic Resolution of Alkylidene Norcamphors with Azomethine Ylides

(S)-TF-BiphamPhos \( \text{L5} \) (17.6 mg, 0.022 mmol) and \( \text{Cu(CH\text{CN})}_4\text{BF}_4 \) (6.3 mg, 0.020 mmol) were dissolved in 2.0 mL \( \text{CH}_2\text{Cl}_2 \), and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -20 °C (unless otherwise noted) and the imino ester \( 2 \) (0.60 mmol), \( \text{Et}_3\text{N} \) (0.060 mmol) were added sequentially. Then 3-alkylidene-2-norcamphor \( 1 \) (0.40 mmol) was added. After the reaction completed (monitored by chiral-phase GC and HPLC), the reaction mixture was quenched by silica-gel. The organic solvent was removed and the residue was purified by column chromatography to give the recovered \( 1 \) and the cycloadduct \( 5 \), which were then directly analyzed by chiral-phase GC or HPLC to determine the enantiomeric excess.

(1S,4R)-3-methylenebicyclo[2.2.1]heptan-2-one (1a): 44% yield; yellow liquid; [\( \alpha \)]\text{D}\text{30} = -3.0 (c 0.29, \text{CH}_2\text{Cl}_2); 1H NMR (400 MHz, CDCl\text{3}) \( \delta \) 5.73 (s, 1H), 5.17 (s, 1H), 3.17 – 3.10 (m, 1H), 2.78 – 2.68 (m, 1H), 1.92 – 1.85 (m, 2H), 1.77 – 1.73 (m, 1H), 1.65 – 1.61 (m, 1H), 1.60 – 1.51 (m, 2H). 13C NMR (100 MHz, CDCl\text{3}) \( \delta \) 206.0, 149.9, 111.8, 49.1, 42.4, 36.8, 28.0, 23.6. The product was analyzed by GC to determine the enantiomeric excess: 92% ee (Chiral Select-1000, 30 m × 0.25 mm, column temperature: 150 °C, carrier gas: \( \text{N}_2 \), 1.0 mL/min); \( t_r = 4.75 \) and 4.95 min.
(1S,4R)-3-((E)-benzylidene)bicyclo[2.2.1]heptan-2-one: 46% yield; yellow solid; $[\alpha]^{30}_D = -552.1$ (c 0.38, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52 – 7.46 (m, 2H), 7.44 – 7.31 (m, 3H), 7.16 (s, 1H), 3.66 – 3.61 (m, 1H), 2.82 – 2.77 (m, 1H), 2.11 – 1.92 (m, 2H), 1.78 – 1.65 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.9, 141.6, 135.3, 129.7, 128.9, 128.6, 127.3, 48.6, 40.2, 37.8, 27.3, 24.3.; The product was analyzed by GC to determine the enantiomeric excess: 94% ee (Chiral Select-1000, 30 m × 0.25 mm, column temperature: 180 °C, carrier gas: N$_2$, 1.0 mL/min); $t_r =$ 29.13 and 30.76 min.

(1S,4R)-3-((E)-4-chlorobenzylidene)bicyclo[2.2.1]heptan-2-one (1c): 45% yield; yellow solid; $[\alpha]^{30}_D = -415.9$ (c 0.27, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44 – 7.34 (m, 4H), 7.09 (s, 1H), 3.63 – 3.55 (m, 1H), 2.84 – 2.76 (m, 1H), 2.10 – 1.93 (m, 2H), 1.79 – 1.61 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.6, 142.1, 134.8, 133.8, 130.9, 128.9, 125.9, 48.5, 40.2, 37.8, 27.3, 24.3.; The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak OJ-H, i-propanol/hexane = 2/98, flow rate 1.0 mL/min, $\lambda = 300$ nm); $t_r =$ 11.00 and 12.42 min.
(1S,4R)-3-((E)-4-bromobenzylidene)bicyclo[2.2.1]heptan-2-one (1d): 45% yield; white solid; m.p. 85-86 °C; 
[α]_{30}^{D} = -331.4 (c 0.36, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.49 (m, 2H), 7.37 – 7.30 (m, 2H), 7.07 (s, 1H), 3.61 – 3.55 (m, 1H), 2.84 – 2.77 (m, 1H), 2.11 – 1.92 (m, 2H), 1.80 – 1.62 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 206.5, 142.2, 134.2, 131.9, 131.1, 125.9, 123.1, 48.5, 40.2, 37.7, 27.2, 24.3.; HRMS (ESI+) Calcd. For C₁₄H₁₃BrNaO⁺ ([M+Na]⁺): 299.0042, found: 299.1110. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak OJ-H, i-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 300 nm); tᵣ = 12.94 and 13.78 min.

(1S,4R)-3-((E)-3-chlorobenzylidene)bicyclo[2.2.1]heptan-2-one (1e): 45% yield; yellow liquid; [α]_{30}^{D} = -313.1 (c 0.26, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.44 (s, 1H), 7.37 – 7.28 (m, 3H), 7.07 (s, 1H), 3.64 – 3.57 (m, 1H), 2.85 – 2.77 (m, 1H), 2.12 – 1.93 (m, 2H), 1.79 – 1.63 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 206.5, 142.9, 137.2, 134.6, 129.9, 129.3, 128.8, 127.9, 125.6, 48.5, 40.2, 37.7, 27.3, 24.3.; HRMS (ESI+) Calcd. For C₁₄H₁₃ClNaO⁺ ([M+Na]⁺): 255.0547, found: 255.0551. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak OJ-H, i-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 300 nm); tᵣ = 9.97 and 11.39 min.

(1S,4R)-3-((E)-2-fluorobenzylidene)bicyclo[2.2.1]heptan-2-one (1f): 43% yield; yellow liquid; [α]_{25}^{D} = -261.1 (c 0.26, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.47 (t, J = 7.6 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.14 – 7.06 (m, 1H), 3.54 – 3.48 (m, 1H), 2.85 – 2.77 (m, 1H), 2.10 – 1.92 (m, 2H), 1.81 – 1.65 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 206.3, 161.2 (d, J = 251.0 Hz), 143.5, 130.5 (d, J = 8.0 Hz), 130.1 (d, J
= 3.0 Hz), 124.0 (d, \( J = 4.0 \) Hz), 123.3 (d, \( J = 13.0 \) Hz), 119.4 (d, \( J = 5.0 \) Hz), 115.8 (d, \( J = 22.0 \) Hz), 48.6, 40.4 (d, \( J = 2.0 \) Hz), 37.6, 27.3, 24.3.; HRMS (ESI+) Calcd. For \( \text{C}_{14}\text{H}_{13}\text{FNaO}^+ \) ([M+Na]+): 239.0843, found: 239.0845. The product was analyzed by HPLC to determine the enantiomeric excess: 99% ee (Chiralpak AS-H, \( \text{i}-\text{propanol/hexane} = 10/90 \), flow rate 1.0 mL/min, \( \lambda = 290 \) nm); \( t_r = 7.13 \) and 8.03 min.

(1S,4R)-3-((E)-4-methylbenzylidene)bicyclo[2.2.1]heptan-2-one \((1g)\): 46% yield; \([\alpha]^{30}_D = -529.1 \) (c 0.47, \( \text{CH}_2\text{Cl}_2 \)); \( ^1\text{H} \) NMR (400 MHz, \( \text{CDCl}_3 \)) \( \delta \) 7.39 (d, \( J = 8.4 \) Hz, 2H), 7.21 (d, \( J = 8.0 \) Hz, 2H), 7.13 (s, 1H), 3.65 – 3.61 (m, 1H), 2.80 – 2.75 (m, 1H), 2.38 (s, 3H), 2.09 – 1.91 (m, 2H), 1.79 – 1.63 (m, 4H). \( ^{13}\text{C} \) NMR (100 MHz, \( \text{CDCl}_3 \)) \( \delta \) 207.1, 140.8, 139.2, 132.5, 129.8, 129.4, 127.4, 48.6, 40.3, 37.9, 27.3, 24.4, 21.4.; The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak OJ-H, \( \text{i}-\text{propanol/hexane} = 2/98 \), flow rate 1.0 mL/min, \( \lambda = 300 \) nm); \( t_r = 8.59 \) and 11.27 min.

(1S,4R)-3-((E)-3-methylbenzylidene)bicyclo[2.2.1]heptan-2-one \((1h)\): 47% yield; yellow liquid; \([\alpha]^{30}_D = -293.9 \) (c 0.36, \( \text{CH}_2\text{Cl}_2 \)); \( ^1\text{H} \) NMR (400 MHz, \( \text{CDCl}_3 \)) \( \delta \) 7.32 – 7.27 (m, 3H), 7.18 – 7.14 (m, 1H), 7.13 (s, 1H), 3.66 – 3.61 (m, 1H), 2.81 – 2.76 (m, 1H), 2.38 (s, 3H), 2.10 – 1.91 (m, 2H), 1.78 – 1.61 (m, 4H). \( ^{13}\text{C} \) NMR (100 MHz, \( \text{CDCl}_3 \)) \( \delta \) 207.0, 141.5, 138.3, 135.2, 130.5, 129.7, 128.5, 127.4, 126.8, 48.6, 40.3, 37.8, 27.3, 24.3, 21.4.; HRMS (ESI+) Calcd. For \( \text{C}_{15}\text{H}_{16}\text{NaO}^+ \) ([M+Na]+): 235.1093, found: 235.1104. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak OJH, \( \text{i}-\text{propanol/hexane} = 2/98 \), flow rate 1.0 mL/min, \( \lambda = 300 \) nm); \( t_r = 8.22 \) and 10.05 min.
(1S,4R)-3-((E)-4-methoxybenzylidene)bicyclo[2.2.1]heptan-2-one (1i): 50% yield; $[\alpha]^{30}_D = -416.0$ (c 0.30, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J = 8.0$ Hz, 2H), 7.11 (s, 1H), 6.93 (d, $J = 8.4$ Hz, 2H), 3.84 (s, 3H), 3.66 – 3.58 (m, 1H), 2.80 – 2.74 (m, 1H), 2.09 – 1.91 (m, 2H), 1.79 – 1.60 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 207.0, 160.2, 139.5, 131.4, 127.8, 127.1, 114.1, 55.3, 48.5, 40.2, 38.0, 27.3, 24.4.; The product was analyzed by HPLC to determine the enantiomeric excess: 87% ee (Chiralpak OJ-H, $i$-propanol/hexane = 2/98, flow rate 1.0 mL/min, $\lambda = 300$ nm); $t_r = 23.87$ and 30.81 min.

(1S,4R,E)-3-(naphthalen-2-ylmethylene)bicyclo[2.2.1]heptan-2-one (1j): 46% yield; yellow solid; m.p. 91-93 °C; $[\alpha]^{30}_D = -504.2$ (c 0.28 CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.93 (s, 1H), 7.89 – 7.80 (m, 3H), 7.61 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.32 (s, 1H), 3.78 – 3.71 (m, 1H), 2.86 – 2.79 (m, 1H), 2.15 – 2.05 (m, 1H), 2.04 – 1.94 (m, 1H), 1.85 – 1.76 (m, 2H), 1.73 – 1.67 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.9, 141.9, 133.24, 133.22, 132.8, 130.1, 128.33, 128.29, 127.7, 127.4, 126.9, 126.5, 48.6, 40.3, 37.9, 27.4, 24.4.; HRMS (ESI+) Calcd. For C$_{18}$H$_{16}$NaO$^+$ ([M+Na$^+$]): 271.1093, found: 271.1100. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak IA, $i$-propanol /hexane = 1/99, flow rate 1.0 mL/min, $\lambda = 300$ nm); $t_r = 11.41$ and 12.92 min.
(1S,4R,E)-3-(thiophen-2-ylmethylene)bicyclo[2.2.1]heptan-2-one (1k): 46% yield; sepia liquid; $[\alpha]_{D}^{30} = -513.5$ (c 0.17, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45 (dd, $J = 4.8, 0.8$ Hz, 1H), 7.31 – 7.24 (m, 2H), 7.11 – 7.05 (m, 1H), 3.76 – 3.70 (m, 1H), 2.81 – 2.75 (m, 1H), 2.04 – 1.90 (m, 2H), 1.82 – 1.77 (m, 1H), 1.72 – 1.67 (m, 1H), 1.66 – 1.57 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.7, 139.1, 139.0, 132.3, 129.0, 127.7, 120.1, 48.8, 40.6, 37.6, 27.1, 24.6.; HRMS (ESI+) Calcd. For C$_{12}$H$_{12}$NaOS$^+$ ([M+Na]$^+$): 227.0501, found: 227.0486. The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (Chiralpak OJ-H, $i$-propanol /hexane = 10/90, flow rate 1.0 mL/min, $\lambda$ = 320 nm); $t_r = 8.51$ and 9.51 min.

(1S,4R,E)-3-(pyridin-2-ylmethylene)bicyclo[2.2.1]heptan-2-one (1l): 45% yield; yellow liquid; $[\alpha]_{D}^{30} = -219.2$ (c 0.25, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.68 (d, $J = 3.6$ Hz, 1H), 7.74 – 7.63 (m, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.26 – 7.14 (m, 1H), 7.08 (s, 1H), 4.34 – 4.26 (m, 1H), 2.83 – 2.75 (m, 1H), 2.08 – 1.89 (m, 2H), 1.83 – 1.75 (m, 1H), 1.74 – 1.61 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 207.5, 154.7, 149.9, 145.2, 136.2, 126.1, 125.0, 122.7, 48.6, 40.2, 37.0, 27.3, 24.2.; HRMS (ESI+) Calcd. For C$_{13}$H$_{14}$NO$^+$ ([M+Na]$^+$): 200.1070, found: 200.1068. The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak OJ-H, $i$-propanol /hexane = 2/98, flow rate 1.0 mL/min, $\lambda$ = 300 nm); $t_r = 13.88$ and 17.92 min.
(3aR,4R,7S,7aS)-6-methyleneoctahydro-5H-4,7-methanoinden-5-one (1m): 45% yield; \([\alpha]_{30}^{\text{D}} = -0.7 (c 0.19, \text{CH}_2\text{Cl}_2)\); \(^1\text{H} \text{NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta 5.71 (s, 1H), 5.13 (s, 1H), 2.91 – 2.85 (m, 1H), 2.54 – 2.47 (m, 1H), 2.24 – 2.13 (m, 2H), 2.04 – 1.95 (m, 2H), 1.85 – 1.76 (m, 2H), 1.58 – 1.51 (m, 1H), 1.34 (m, 1H), 1.17 – 1.05 (m, 2H). \(^{13}\text{C} \text{NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 206.0, 149.8, 111.3, 53.9, 47.0, 46.9, 41.8, 32.1, 31.8, 30.5, 27.9.; \) The product was analyzed by HPLC to determine the enantiomeric excess: 91% ee (Chiralpak AS-H, \(i\)-propanol/hexane = 2/98, flow rate 1.0 mL/min, \(\lambda = 220 \text{ nm})\); \(t_r = 7.55 \text{ and } 8.47 \text{ min.}\)

(1n)

(3aS,4R,7S,7aR)-6-methyleneoctahydro-5H-4,7-methanoinden-5-one (1n): 44% yield; \([\alpha]_{30}^{\text{D}} = +25.0 (c 0.02, \text{CH}_2\text{Cl}_2)\); \(^1\text{H} \text{NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta 5.82 (s, 1H), 5.12 (s, 1H), 3.01 – 2.95 (m, 1H), 2.82 – 2.70 (m, 2H), 2.68 – 2.62 (m, 1H), 1.94 – 1.86 (m, 1H), 1.85 – 1.78 (m, 1H), 1.60 – 1.48 (m, 3H), 1.42 – 1.27 (m, 3H). \(^{13}\text{C} \text{NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 206.4, 148.1, 113.1, 54.9, 47.2, 46.1, 45.1, 39.9, 28.0, 27.9, 27.8.; \) The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralpak AS-H, \(i\)-propanol/hexane = 2/98, flow rate 1.0 mL/min, \(\lambda = 220 \text{ nm})\); \(t_r = 5.27 \text{ and } 6.35 \text{ min.}\)

(1o)

(1R,4S)-3-methylene-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one (1o): 46% yield; \([\alpha]_{30}^{\text{D}} = +36.3 (c 0.47, \text{CH}_2\text{Cl}_2)\); \(^1\text{H} \text{NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta 7.32 – 7.24 (m, 2H), 7.19 – 7.09 (m, 2H), 5.78 (s, 1H), 5.28 (s, 1H), 4.07 – 4.02 (m, 1H), 3.72 – 3.66 (m, 1H), 2.62 – 2.55 (m, 1H), 2.33 – 2.27 (m, 1H). \(^{13}\text{C} \text{NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 202.4, 147.5, 145.2, 140.9, 127.6, 126.9, 123.5, 121.4, 112.6, 56.8, 50.5, 48.9.; \) The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralpak OJ-H, \(i\)-propanol/hexane = 10/90, flow rate 1.0 mL/min, \(\lambda = 220 \text{ nm})\); \(t_r = 13.95 \text{ and } 18.83 \text{ min.}\)
(Z)-3-benzylidenebicyclo[2.2.1]heptan-2-one (1p): 30% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.98 – 7.85 (m, 2H), 7.39 – 7.28 (m, 3H), 6.60 (s, 1H), 3.17 – 3.08 (m, 1H), 2.81 – 2.71 (m, 1H), 1.97 – 1.82 (m, 3H), 1.67 – 1.56 (m, 3H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 205.1, 141.8, 134.7, 133.1, 130.4, 129.1, 128.0, 51.8, 46.8, 37.1, 28.5, 23.7.

(E)-3-benzylidene-7,7-dimethylbicyclo[2.2.1]heptan-2-one (1q): 50% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.51 – 7.45 (m, 2H), 7.44 – 7.31 (m, 3H), 7.24 (s, 1H), 3.11 (d, \(J = 4.2\) Hz, 1H), 2.23 – 2.14 (m, 1H), 1.83 – 1.74 (m, 1H), 1.65 – 1.48 (m, 2H), 1.03 (s, 3H), 1.00 (s, 3H), 0.80 (s, 3H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 208.3, 142.0, 135.6, 129.7, 128.7, 128.6, 127.5, 57.1, 49.1, 46.7, 30.6, 25.9, 20.6, 18.3, 9.3.

Methyl \((1S,2R,2'S,4R,4'R,5'R)-5'-(4-chlorophenyl)-3-oxo-4'-phenylspiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5s): Yield (48%); yellow liquid; \([\alpha]^{30}_D = +57.5\) (c 0.28, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.46 (d, \(J = 8.4\) Hz, 2H), 7.27 – 7.03 (m, 7H), 4.64 (d, \(J = 11.2\) Hz, 1H), 3.98 (s, 1H), 3.76 (d, \(J = 11.2\) Hz, 1H), 3.73 (s, 3H), 2.85 – 2.78 (m, 1H), 2.66 – 2.61 (m, 1H), 2.24 – 2.17 (m, 1H), 1.67 – 1.56 (m, 1H), 1.56 – 1.48 (m, 1H), 1.17 – 1.06 (m, 1H), 1.06 – 0.96 (m, 1H), 0.83 – 0.72 (m, 1H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 217.9, 173.0, 138.2, 137.0, 133.5, 129.1, 128.8, 128.2, 127.2, 69.1, 68.5, 65.7, 56.1, 52.5, 49.3, 44.7, 36.3, 24.8, 23.0; HRMS (ESI+) Calcd. C\(_{24}\)H\(_{24}\)ClINaO\(_3\)^+ ([M+Na]^+): 432.1337, found: 432.1337. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AS-H,
i-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.56 and 15.95 min.

Methyl (1S,2R,2'S,4R,4'R,5'R) -4',5'-bis(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5t): Yield (49%); yellow solid; m.p. 145-147 °C; \([\alpha]\)\(^{30}\)D = +21.5 (c 0.67, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.43 (m, 2H), 7.26 (d, \(J = 8.4\) Hz, 2H), 7.19 – 6.83 (m, 4H), 4.57 (d, \(J = 11.2\) Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.72 (d, \(J = 11.2\) Hz, 1H), 2.83 – 2.78 (m, 1H), 2.67 – 2.62 (m, 1H), 2.26 – 2.18 (m, 1H), 1.71 – 1.61 (m, 1H), 1.59 – 1.52 (m, 1H), 1.22 – 1.10 (m, 1H), 1.05 – 0.94 (m, 1H), 0.86 – 0.76 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 217.7, 173.0, 138.0, 136.1, 133.8, 131.4, 129.1, 128.9, 128.5, 69.1, 68.5, 65.8, 55.6, 52.6, 49.3, 44.8, 36.4, 24.8, 23.2.; HRMS (ESI+) Calcd. For C\(_{24}\)H\(_{23}\)Cl\(_2\)NNaO\(_3\)\(^+\) ([M+Na]\(^+\)): 466.0947, found: 466.0949. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, i-propanol / hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.35 and 16.73 min.

Methyl (1S,2R,2'S,4R,4'R,5'R) -4'-(4-bromophenyl)-5'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5u): Yield (50%); yellow solid; m.p. 148-150 °C; \([\alpha]\)\(^{30}\)D = +15.3 (c 0.17, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.43 (m, 2H), 7.27 (m, 4H), 6.99 (s, 2H), 4.57 (d, \(J = 11.2\) Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.70 (d, \(J = 11.2\) Hz, 1H), 2.82 – 2.78 (m, 1H), 2.67 – 2.63 (m, 1H), 2.26 – 2.18 (m, 1H), 1.71 – 1.60 (m, 1H), 1.59 – 1.52 (m, 1H), 1.22 – 1.11 (m, 1H), 1.05 – 0.94 (m, 1H), 0.86 – 0.76 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 217.7, 173.0, 138.0, 136.1, 133.8, 131.4, 129.1, 129.0, 121.2, 69.1, 68.5, 65.8, 55.6, 52.6, 49.3, 44.8, 36.4, 24.8, 23.2.; HRMS (ESI+) Calcd. For C\(_{24}\)H\(_{23}\)BrCl\(_2\)NNaO\(_3\)\(^+\) ([M+Na]\(^+\)): 510.0442, found: 510.0446. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, i-propanol / hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.58 and 16.81 min.
Methyl (1S,2R,2'S,4R,4'R,5'R) -4'-(3-chlorophenyl)-5'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5v): Yield (48%); white solid; m.p. 123-125 °C; [α]30D = +39.0 (c 0.41, CH2Cl2); 1H NMR (400 MHz, CDCl3) δ 7.46 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.21 – 6.85 (m, 4H), 4.62 (d, J = 10.8 Hz, 1H), 3.93 (s, 1H), 3.72 (s, 3H), 3.72 (d, J = 10.8 Hz, 1H), 3.24 (s, 1H), 2.87 – 2.78 (m, 1H), 2.72 – 2.61 (m, 1H), 2.23 – 2.17 (m, 1H), 1.72 – 1.60 (m, 1H), 1.59 – 1.52 (m, 1H), 1.23 – 1.13 (m, 1H), 1.01 (d, J = 6.4 Hz, 1H), 0.79 (d, J = 10.0 Hz, 1H). 13C NMR (100 MHz, CDCl3) δ 217.4, 172.7, 139.1, 137.7, 134.2, 133.8, 129.5, 129.2, 129.0, 127.5, 68.9, 68.4, 65.6, 55.6, 52.6, 49.2, 44.7, 36.3, 24.7, 23.1.; HRMS (ESI+) Calcd. For C24H23Cl2NNaO3+: [M + Na]+: 466.0947, found: 466.0953. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, i-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); tR = 6.91 and 16.93 min.

Methyl (1S,2R,2'S,4R,4'R,5'R) -5'-(4-chlorophenyl)-4'-(2-fluorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5w): Yield (51%); yellow liquid; [α]30D = +48.6 (c 0.66, CH2Cl2); Major (5w): 1H NMR (400 MHz, CDCl3) δ 7.41 (d, J = 8.4 Hz, 3H), 7.27 – 7.21 (m, 3H), 6.93 – 6.86 (m, 2H), 4.60 (d, J = 10.0 Hz, 1H), 4.14 (s, 1H), 3.76 (s, 3H), 3.46 (d, J = 10.0 Hz, 1H), 2.91– 2.84 (m, 1H), 2.68– 2.64 (m, 1H), 2.54 (brs, 1H), 2.14– 2.60 (m, 1H), 1.76 – 1.63 (m, 1H), 1.54– 1.48 (m, 1H), 1.33 – 1.07 (m, 3H). 13C NMR (100 MHz, CDCl3) δ 219.0, 172.5, 161.1 (d, J = 244 Hz), 138.4, 133.5, 132.9, 128.81, 128.75, 125.4 (d, J = 14 Hz), 124.5 (d, J = 4 Hz), 116.2 (d, J = 22 Hz), 70.4, 68.0, 66.7, 58.3, 52.6, 49.4, 44.3 (d, J = 2 Hz), 36.1, 25.7, 23.6. Minor (3w): 1H NMR (400 MHz, CDCl3) δ 7.39 – 7.28 (m, 3H), 7.21 – 7.15 (m, 3H), 7.02 – 6.96 (m, 2H), 4.35 (d, J = 9.2 Hz, 1H), 4.03 (s, 1H), 3.99 (d, J = 9.2 Hz, 1H), 3.77 (s, 3H), 2.74 – 2.67 (m, 1H), 2.65 – 2.55 (m, 1H), 2.09 – 2.00 (m, 1H), 1.76 – 1.63 (m, 1H), 1.52 – 1.47 (m, 1H), 1.33 – 1.07 (m, 3H). 13C NMR
(100 MHz, CDCl₃) δ 217.75, 171.75, 161.1 (d, J = 15 Hz), 124.3 (d, J = 3 Hz), 115.7 (d, J = 23 Hz), 69.0 (d, J = 4 Hz), 67.52, 66.6, 58.3, 52.7, 49.6, 43.57, 35.8, 25.6, 23.9.; HRMS (ESI+) Calcd. For C₂₄H₂₃ClFNNaO₃⁺ ([M+Na⁺]): 450.1243, found: 450.1243. The product was analyzed by HPLC to determine the enantiomeric excess: 83% ee (Chiralpak AS-H, i-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); tᵣ = 7.47 and 13.42 min.

Methyl (1S,2R,2'S,4R,4'R,5'R) -5'-(4-chlorophenyl)-3-oxo-4'-p-tolyl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5x): Yield (47%); yellow solid; m.p. 124-126 °C; [α]³⁰ D = +40.8 (c 0.66, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.43 (m, 2H), 7.24 (m, 2H), 6.97 (m, 4H), 4.59 (d, J = 11.2 Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.72 (d, J = 11.2 Hz, 1H), 2.80 – 2.76 (m, 1H), 2.64 – 2.60 (m, 1H), 2.24 (s, 3H), 2.22 – 2.17 (m, 1H), 1.67 – 1.57 (m, 1H), 1.57 – 1.49 (m, 1H), 1.16 – 0.98 (m, 2H), 0.89 – 0.80 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 218.1, 173.1, 138.5, 136.8, 133.9, 133.5, 129.2, 129.0, 128.8, 69.3, 68.5, 65.9, 55.9, 52.5, 49.4, 44.9, 36.4, 24.9, 23.1, 21.0.; HRMS (ESI+) Calcd. For C₂₅H₂₆ClINaO₃⁺ ([M+Na⁺]): 446.1493, found: 446.1497. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, i-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); tᵣ = 5.70 and 12.29 min.

Methyl (1S,2R,2'S,4R,4'R,5'R) -5'-(4-chlorophenyl)-3-oxo-4'-(m-tolyl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5y): Yield (46%); white to yellow solid; m.p. 118-120 °C; [α]³⁰ D = +45.1 (c 0.90, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.10 – 6.71 (m, 4H), 4.62 (d, J = 11.2 Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.71 (d, J = 11.2 Hz, 1H), 2.81 – 2.78 (m, 1H), 2.65 – 2.62 (m, 1H), 2.22 (s, 3H), 2.21 – 2.12 (m, 1H), 1.69 – 1.57 (m, 1H), 1.56 – 1.48 (m, 1H), 1.16 – 0.97 (m, 2H),
$0.85 - 0.71$ (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 218.0, 173.0, 138.4, 133.5, 129.2, 128.8, 128.1, 128.0, 69.3, 68.5, 65.8, 56.2, 52.5, 49.4, 44.8, 36.4, 24.9, 23.1, 21.2.; HRMS (ESI+) Calcd. For C$_{25}$H$_{26}$ClNNaO$_3^+$ ([M+Na]$^+$): 446.1493, found: 446.1493. The product was analyzed by HPLC to determine the enantiomeric excess: 93% ee (Chiralpak AS-H, $i$-propanol/hexane = 10/90, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 5.49$ and 11.77 min.

![Methyl (1S,2R,2'S,4R,4'R,5'R) -5'-(4-chlorophenyl)-4'-(4-methoxyphenyl)-3-oxospiro[bicycle [2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5z): Yield (42%); yellow solid; m.p. 140-141 °C; $[\alpha]^{30}_D = +36.0$ (c 0.42, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 – 7.42 (m, 2H), 7.26 – 7.22 (m, 2H), 7.00 (s, 2H), 6.70 (d, $J = 7.6$ Hz, 2H), 4.58 (d, $J = 11.6$ Hz, 1H), 3.95 (s, 1H), 3.73 (s, 3H), 3.721 (s, 3H), 3.719 (d, $J = 11.6$ Hz, 1H), 2.81 – 2.75 (m, 1H), 2.65 – 2.60 (m, 1H), 2.24 – 2.19 (m, 1H), 1.67 – 1.58 (m, 1H), 1.56 – 1.51 (m, 1H), 1.18 – 1.07 (m, 1H), 1.05 – 0.96 (m, 1H), 0.86 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 218.1, 173.2, 158.6, 138.5, 133.5, 129.2, 128.8, 128.7, 113.6, 69.2, 68.4, 65.7, 55.4, 55.0, 52.5, 49.4, 44.9, 36.4, 24.9, 23.1.; HRMS (ESI+) Calcd. For C$_{25}$H$_{26}$ClNNaO$_4^+$ ([M+Na]$^+$): 462.1443, found: 462.1443. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AS-H, $i$-propanol /hexane = 10/90, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 8.61$ and 19.50 min.

![Methyl (1S,2R,2'S,4R,4'R,5'R) -5'-(4-chlorophenyl)-4'-(napthalen-2-yl)-3-oxospiro[bicyclo[2.2.1] heptane-2,3'-pyrrolidine]-2'-carboxylate (5A): Yield (46%); white solid; m.p. 140-142 °C; $[\alpha]^{30}_D = +10.5$ (c 0.75, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.80 – 7.34 (m, 9H), 7.22 (d, $J = 8.4$ Hz, 2H), 4.73 (d, $J = 11.2$ Hz, 1H), 4.03 (s, 1H), 3.91 (d, $J = 11.2$ Hz, 1H), 3.76 (s, 3H), 2.90 – 2.85 (m, 1H), 2.66 – 2.63 (m, 1H), 2.24 –](image-url)
2.19 (m, 1H), 1.59 – 1.48 (m, 2H), 1.10 – 0.73 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 218.1, 173.1, 153.5, 138.3, 133.6, 133.0, 132.4, 129.2, 128.8, 127.9, 127.7, 127.5, 126.2, 125.9, 69.4, 68.7, 66.4, 56.9, 52.6, 49.3, 44.8, 36.3, 24.9, 23.3.; HRMS (ESI+) Calcd. For C$_{28}$H$_{26}$ClNNaO$_3$+ ([M+Na]$^+$): 482.1493, found: 482.1493. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AS-H, $i$-propanol /hexane = 20/80, flow rate 1.0 mL/min, $\lambda$ = 220 nm); $t_r$ = 5.79 and 11.80 min.

Methyl (1S,2R,2'S,4R,4'R,5'R) -5'-(4-chlorophenyl)-3-oxo-4'-(thiophen-2-yl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5B): Yield (45%); yellow solid; m.p. 157-159 °C; $[\alpha]_{D}^{30} = +82.6$ (c 0.35, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, $J = 8.4$ Hz, 2H), 7.79 (d, $J = 8.8$ Hz, 2H), 7.10 (dd, $J = 4.8$, 0.8 Hz, 1H), 6.82 (dd, $J = 4.8$, 3.6 Hz, 1H), 6.70 (d, $J = 3.6$ Hz, 1H), 4.52 (d, $J = 11.2$ Hz, 1H), 4.08 (d, $J = 11.2$ Hz, 1H), 3.98 (s, 1H), 3.73 (s, 3H), 2.85 – 2.80 (m, 1H), 2.68 – 2.64 (m, 1H), 2.28 – 2.22 (m, 1H), 1.76 – 1.66 (m, 1H), 1.61 – 1.55 (m, 1H), 1.25 – 1.16 (m, 2H), 0.79 – 0.67 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 217.5, 173.3, 139.2, 138.5, 133.8, 129.4, 128.8, 126.8, 126.0, 124.4, 68.8, 68.7, 66.9, 52.5, 51.7, 49.4, 45.0, 36.7, 25.8, 22.6.; HRMS (ESI+) Calcd. For C$_{22}$H$_{22}$ClNNaO$_3$S$^+$ ([M+Na]$^+$): 416.1082, found: 416.1085. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AS-H, $i$-propanol /hexane = 10/90, flow rate 1.0 mL/min, $\lambda$ = 220 nm); $t_r$ = 7.61 and 15.38 min.

Methyl (1S,2R,2'S,4R,4'R,5'R) -5'-(4-chlorophenyl)-3-oxo-4'-(pyridin-2-yl)spiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-2'-carboxylate (5C): Yield (46%); yellow solid; m.p. 162-164 °C; $[\alpha]_{D}^{30} = +15.0$ (c 0.24, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.51 (dd, $J = 4.8$, 0.8 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.45 (td, $J = 8.0$, 2.0 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.08 (ddd, $J = 7.2$, 4.8, 0.8 Hz, 1H), 6.92 (d, $J = 7.6$ Hz, 1H), 4.90 (d, $J =
10.0 Hz, 1H), 4.16 (s, 1H), 3.75 (s, 3H), 3.71 (d, J = 10.0 Hz, 1H), 2.93 – 2.86 (m, 1H), 2.66 – 2.62 (m, 1H),
2.17 – 2.12 (m, 1H), 1.69 – 1.60 (m, 1H), 1.55 – 1.49 (m, 1H), 1.22 – 1.13 (m, 1H), 1.08 – 1.00 (m, 1H), 0.49 –
0.40 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 218.3, 173.0, 158.1, 149.2, 139.3, 136.1, 133.2, 129.2, 128.5,
124.5, 122.2, 69.4, 69.2, 66.3, 59.1, 52.4, 49.5, 44.3, 36.2, 25.2, 23.4.; HRMS (ESI+) Calcd. For
C23H23ClN2NaO3+ ([M+Na]+): 433.1289, found: 433.1287. The product was analyzed by HPLC to determine
the enantiomeric excess: 97% ee (Chiralpak AS-H, i-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220
nm); t_r = 9.05 and 15.24 min.

Methyl \((2S,3S,3a'R,4'R,5R,7'S,7a'S)-5-(4-chlorophenyl)-6'-oxooctahydrospiro[pyrrolidine-3,5'-[4,7]
methanoindene]-2-carboxylate (5D): Yield (48%); yellow liquid; \(\alpha\)\(^{30}_{\text{D}}\) = -37.8 (c 0.27, CH2Cl2); 1H NMR
(400 MHz, CDCl3) δ 7.48 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.15 (dd, J = 12.0, 4.8 Hz, 1H), 3.82 (s,
1H), 3.67 (s, 3H), 2.52 (brs, 1H), 2.46 – 2.41 (m, 2H), 2.38 – 2.30 (m, 1H), 2.13 – 1.79 (m, 8H), 1.40 – 1.29 (m,
1H), 1.23 – 1.11 (m, 2H). 13C NMR (100 MHz, CDCl3) δ 217.4, 173.2, 139.9, 133.3, 128.7, 128.4, 68.7, 64.2,
62.0, 53.7, 52.3, 49.1, 42.9, 41.9, 39.6, 32.1, 31.9, 28.9, 27.8.; HRMS (ESI+) Calcd. For C21H25ClNO3+
([M+H]+): 374.1517, found: 374.1517. The product was analyzed by HPLC to determine the enantiomeric
excess: 96% ee (Chiralpak IA, i-propanol /hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 11.25 and
25.54 min.

Methyl \((2S,3S,3a'R,4'R,5R,7'S,7a'R)-5-(4-chlorophenyl)-6'-oxooctahydrospiro[pyrrolidine-3,5'-[4,7]
methanoindene]-2-carboxylate (5E): Yield (45%); white liquid; \(\alpha\)\(^{30}_{\text{D}}\) = +2.1 (c 0.33, CH2Cl2); 1H NMR
(400 MHz, CDCl3) δ 7.47 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.21 (dd, J = 12.0, 4.4 Hz, 1H), 3.90 (s,
1H), 3.67 (s, 3H), 2.90 – 2.82 (m, 2H), 2.70 – 2.66 (m, 1H), 2.58 – 2.54 (m, 1H), 2.43 – 2.33 (m, 2H), 2.11 – 2.03 (m,
1H), 1.85 – 1.78 (m, 2H), 1.63 – 1.47 (m, 4H), 1.38 – 1.29 (m, 1H). $^1$C NMR (100 MHz, CDCl$_3$) δ 217.2, 173.1, 139.9, 133.4, 128.7, 128.5, 70.6, 67.0, 62.3, 54.5, 52.3, 47.4, 47.1, 45.7, 40.2, 39.3, 27.5, 27.2, 26.8.; HRMS (ESI+) Calcd. For C$_{21}$H$_{24}$ClNaO$_3$ $^+$ ([M+Na$^+$]): 396.1337, found: 396.1337. The product was analyzed by HPLC to determine the enantiomeric excess: 85% ee (Chiralpak AD-H, $i$-propanol /hexane = 10/90, flow rate 1.0 mL/min, $\lambda$ = 220 nm); $t_r$ = 15.47 and 25.34 min.

![Chemical Structure](5F)

Methyl (1'R,2'S,3'S,4'S,5'R)-5-(4-chlorophenyl)-3'-oxo-3',4'-dihydro-1'H-spiro[pyrrolidine-3,2']-[1,4]methanonaphthalene]-2-carboxylate (5F): Yield (47%); yellow solid; m.p. 166-167 °C; $[\alpha]_{30}^D = -183.8$ (c 0.40, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.40 (d, $J = 8.4$ Hz, 2H), 7.32 – 7.28 (m, 2H), 7.27 – 7.25 (m, 2H), 7.19 – 7.12 (m, 2H), 4.28 (dd, $J = 12.0$, 4.8 Hz, 1H), 3.96 (s, 1H), 3.73 (s, 3H), 3.65 – 3.58 (m, 2H), 2.82 – 2.76 (m, 1H), 2.68 (brs, 1H), 2.61 – 2.55 (m, 1H), 1.90 – 1.80 (m, 1H), 1.36 – 1.29 (m, 1H). $^1$C NMR (100 MHz, CDCl$_3$) δ 213.0, 172.9, 146.3, 140.0, 139.5, 133.3, 128.6, 128.3, 127.4, 127.3, 123.5, 123.1, 68.7, 61.9, 60.9, 56.6, 52.5, 51.6, 47.2, 44.8.; HRMS (ESI+) Calcd. For C$_{22}$H$_{20}$ClNaO$_3$ $^+$ ([M+H$^+$]): 404.1024, found: 404.1024. The product was analyzed by HPLC to determine the enantiomeric excess: 92% ee (Chiralpak AS-H, $i$-propanol /hexane = 10/90, flow rate 1.0 mL/min, $\lambda$ = 220 nm); $t_r$ = 9.30 and 16.81 min.
Cu(I)/L3-Catalyzed Kinetic Resolution of 3-Methylene-2-Norcamphor

(S)-TF-BiphamPhos $L_3$ (20.1 mg, 0.022 mmol) and Cu(CH$_3$CN)$_4$BF$_4$ (6.3 mg, 0.020 mmol) were dissolved in 2.0 mL CH$_2$Cl$_2$, and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -60 °C and the imino ester $2a$ (0.40 mmol), Et$_3$N (0.060 mmol) were added sequentially. Then 3-methylene-2-norcamphor $1a$ (0.40 mmol) was added. After the reaction completed in 1 h (monitored by chiral-phase GC and HPLC), the reaction mixture was quenched by silica-gel. The organic solvent was removed and the residue was purified by column chromatography to give the recovered $1a$ and the cycloadduct $3a$, which were then directly analyzed by chiral-phase GC and HPLC to determine the enantiomeric excess, respectively.

Methyl (1S,2S,2'R,4R,5'R)-2'-(4-chlorophenyl)-3-oxospiro[bicyclo[2.2.1]heptane-2,3'-pyrrolidine]-5'-carboxylate (3a): Yield (46%); yellow liquid; [α]$^D_{24} = +3.5$ (c 0.31, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.27 (s, 4H), 4.17 (s, 1H), 3.94 (t, $J = 8.0$ Hz, 1H), 3.82 (s, 3H), 2.94 (s, 1H), 2.55 – 2.48 (m, 1H), 2.32 – 2.25 (m, 3H), 1.84 – 1.64 (m, 3H), 1.54 – 1.40 (m, 2H), 1.35 – 1.30 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 219.0, 173.6, 138.6, 133.7, 129.4, 128.6, 71.5, 63.5, 58.5, 52.3, 49.7, 45.2, 38.1, 34.5, 26.0, 24.7.; HRMS (ESI+) Caled. For C$_{18}$H$_{20}$ClNNaO$_3$ ([M+Na]$^+$): 356.1024, found: 356.1022. The product was analyzed by HPLC to determine the enantiomeric excess: 90% ee (Chiralpak AD-H, i-propanol /hexane = 10/90, flow rate 1.0 mL/min, $\lambda = 220$ nm); $t_r = 17.61$ and 27.76 min.
Gram Scales and Synthetic Transformations

![Chemical Structure](image)

(S)-TF-BiphamPhos L5 (79.0 mg, 0.099 mmol) and Cu(CH3CN)4BF4 (28.3 mg, 0.090 mmol) were dissolved in 9.0 mL CH2Cl2, and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -60 °C and the imino ester 2a (1.90 g, 9.00 mmol), Et3N (0.14 g, 1.35 mmol) were added sequentially. Then 3-methylene-2-norcamphor 1a (1.10 g, 9.00 mmol) was added. After the reaction completed (monitored by chiral-phase GC and HPLC), the reaction mixture without quenched and the residue was purified by column chromatography rapidly to give the recovered 1a and the cycloadduct 5a, which were then directly analyzed by chiral-phase GC and HPLC to determine the enantiomeric excess, respectively. Meanwhile, nearly 80% yield of chiral ligand L5 could be recovered, which can be reused in the model reaction in Table 1 under standard reaction condition without loss of yield and enantioselectivity control.

![Chemical Structure](image)

(S)-TF-BiphamPhos L5 (46.3 mg, 0.058 mmol) and Cu(CH3CN)4BF4 (16.7 mg, 0.053 mmol) were dissolved in 5.0 mL CH2Cl2, and stirred at room temperature for about 30 min. Then, the reaction temperature was dropped to -20 °C and the imino ester 2a (0.74 g, 3.50 mmol), Et3N (0.08 g, 0.80 mmol) were added sequentially. Then 3-benzylidene-2-norcamphor 1b (1.05 g, 5.30 mmol) was added. After the reaction completed (monitored by chiral-phase GC and HPLC), the reaction mixture without quenched and the residue was purified by column chromatography rapidly to give the recovered 1a and the cycloadduct 5q, which were then directly analyzed by chiral-phase GC and HPLC to determine the enantiomeric excess, respectively. Meanwhile, nearly 80% yield of chiral ligand L5 could be recovered, which can be reused in the model reaction in Table 1 under standard reaction condition without loss of yield and enantioselectivity control.
To a suspension of NaBH₄ (2.0 mmol, 75.7 mg) in THF (6 mL) was added in one portion Ca(OTf)₂ (0.5 mmol, 169.1 mg) and (1S,4R)-1b (0.80 mmol, 158.6 mg, 95% ee) in MeOH (0.5 mL). The reaction mixture was stirred for 30 min at rt until consumption of the starting material (monitored by TLC). The reaction mixture was quenched with H₂O (3 mL) and the aqueous phase was extracted with Et₂O (3 × 4 mL). The combined organic layers were washed with brine, dried over MgSO₄ and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography (EtOAc:hex ane = 1:10 to 1:5) to give 6 in 88% yield which was then directly analyzed by HPLC to determine the enantiomeric excess.

\[\text{(1S,2S,4R)-3-((E)-benzylidene)bicyclo[2.2.1]heptan-2-ol (6):}\]

Yield (88%); white solid; m.p. 108-110 °C; [\(\alpha\)]$_{D}^{30}$ = −300.8 (c 0.41, CH₂Cl₂); $^1$H NMR (400 MHz, CDCl₃) δ 7.35 – 7.29 (m, 4H), 7.23 – 7.17 (m, 1H), 6.37 (s, 1H), 4.52 (brs, 1H), 3.26 (d, $J$ = 3.2 Hz, 1H), 2.49 – 2.41 (m, 1H), 1.91 – 1.79 (m, 3H), 1.63 – 1.52 (m, 2H), 1.45 – 1.41 (m, 2H). $^{13}$C NMR (100 MHz, CDCl₃) δ 150.9, 137.8, 128.3, 128.0, 126.3, 120.9, 77.0, 41.9, 41.6, 36.2, 29.5, 19.4. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak AS-H, i-propanol/hexane = 5/95, flow rate 1.0 mL/min, $\lambda$ = 254 nm); $t_r$ = 7.20 and 8.05 min.

A solution of (1S,4R)-1b (0.80 mmol, 158.6 mg, 95% ee) in 4 mL MeOH was added 16 mg Pd/C (10%).
The reaction mixture was stirred at room temperature under hydrogen atmosphere (1 bar) for 4 h. The reaction mixture was filtered through a short plug of silica (eluted with EtOAc) and the solvent was removed by rotary evaporation and the crude product was purified by column chromatography (EtOAc:hexane = 1:20) to give (1S,3R,4R)-3-benzylbicyclo[2.2.1]heptan-2-one 7 in 81% yield which was then directly analyzed by HPLC to determine the enantiomeric excess.

To a solution of m-CPBA (0.22 mmol) and NaHCO₃ (0.22 mmol) in DCM (6 mL) at 0-5 °C, was added 7 (0.2 mmol) in DCM (1 mL) dropwise over 10 min, the reaction was allowed to warm to rt. After 6 h the reaction was filtrated, the residue was washed with DCM. The organic filtrate was washed with sat. NaHCO₃, sat. NaCl, dried over Na₂SO₄ and concentrated in vacuum. The concentrate was directly purified by column chromatography (EtOAc:hexane = 1:10 to 1:3) to give 8 in 98% yield which was then directly analyzed by HPLC to determine the enantiomeric excess.

(1S,3R,4R)-3-benzylbicyclo[2.2.1]heptan-2-one (7): Yield (81%); colorless liquid; [α]_{30}^{D} = -35.3 (c 0.37, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.17 (m, 3H), 3.13 (dd, J = 14.0, 3.6 Hz, 1H), 2.70 – 2.65 (m, 1H), 2.49 – 2.46 (m, 1H), 2.42 (dd, J = 14.0, 2.4 Hz, 1H), 2.36 – 2.29 (m, 1H), 1.91 – 1.76 (m, 2H), 1.68 – 1.62 (m, 2H), 1.58 – 1.53 (m, 1H), 1.52 – 1.44 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 218.8, 140.3, 128.48, 128.47, 126.1, 55.9, 50.5, 37.9, 36.9, 32.0, 25.4, 21.2.; HRMS (ESI+) Calcd. For C₁₄H₁₆NaO⁺ ([M+Na⁺]): 223.1093, found: 223.1093. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak OJ-H, i-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); tᵣ = 11.08 and 11.86 min.

(1S,3R,4R)-4-benzyl-3-oxabicyclo[3.2.1]octan-2-one (8): Yield (98%); white solid; m.p. 70-72 °C; [α]_{30}^{D} = +20.7 (c 0.15, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.28 (m, 2H), 7.26 – 7.23 (m, 1H), 7.22 – 7.19 (m,
2H), 4.52 (ddd, $J = 8.4, 6.4, 2.4$ Hz, 1H), 3.06 (dd, $J = 13.6, 6.4$ Hz, 1H), 2.94 – 2.88 (m, 1H), 2.83 (dd, $J = 13.6, 8.4$ Hz, 1H), 2.29 – 2.22 (m, 1H), 2.13 – 2.05 (m, 1H), 1.99 – 1.87 (m, 3H), 1.79 – 1.69 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.5, 136.6, 129.3, 128.6, 126.7, 85.9, 41.8, 39.0, 35.9, 33.2, 29.4, 21.0.; HRMS (ESI+) Calcd. For C$_{14}$H$_{16}$NaO$_2^+$ ([M+Na]$^+$): 239.1043, found: 239.1043. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, $i$-propanol/hexane = 10/90, flow rate 1.0 mL/min, $\lambda$ = 210 nm); $t_r$ = 27.92 and 44.25 min.

A solution of (1$R$,4$S$)-1a (2.50 mmol, 305 mg, $>99$% ee) in 5 mL MeOH was added 50 mg 10% Pd/C. The reaction mixture was stirred at room temperature under hydrogen atmosphere (1 bar) for 2 h. The reaction mixture was filtered through a short plug of silica (eluted with Et$_2$O) and the solvent was removed by rotary evaporation and the crude product was purified by column chromatography (Et$_2$O:hexane = 1:20) to give (1$R$,3$S$,4$S$)-3-methylbicyclo[2.2.1]heptan-2-one 9 in 99% yield which was then directly analyzed by GC to determine the enantiomeric excess.

A 2.5 M solution of $n$-butyllithium in hexane (0.60 mL, 1.50 mmol) was added dropwise to a solution of THF (2 mL) and diisopropylamine (161.9 mg, 1.60 mmol) at 0 ºC and let stir under argon for 10 min. And (1$R$,3$S$,4$S$)-3-methylbicyclo[2.2.1] heptan-2-one 9 (124.2 mg, 1.00 mmol) was added. After 30 min, 2-(2-iodoethyl)-1,3-dioxolane 10 (342 mg, 1.50 mmol) was added dropwise. The mixture was refluxed for 20 hours and cooled down to room temperature. The reaction mixture was quenched with saturated NaHCO$_3$ and extracted with EtOAc then the organic was dried over Na$_2$SO$_4$ and concentrated to give an oil. The crude product was purified by column chromatography (Et$_2$O:hexane = 1:20) to give (1$R$,3$R$,4$S$)-3-(2-(1,3-dioxolan-2-yl) ethyl)-3-methylbicyclo[2.2.1]heptan-2-one 11 in 70% yield.
(1R,3S,4S)-3-methylbicyclo[2.2.1]heptan-2-one (9): Yield (99%); colorless liquid; $[\alpha]^{30}_D = -46.1$ (c 0.54, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.63 – 2.58 (m, 1H), 2.57 – 2.50 (m, 1H), 2.17 – 2.07 (m, 1H), 1.88 – 1.78 (m, 1H), 1.70 (m, 1H), 1.66 – 1.54 (m, 3H), 1.44 – 1.35 (m, 1H), 1.02 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 220.8, 50.3, 48.3, 40.4, 37.2, 25.3, 20.9, 10.7.; HRMS (ESI+) Calcd. For C$_8$H$_{12}$NaO$^+$ ([M+Na]$^+$): 147.0780, found: 147.0780. The product was analyzed by GC to determine the enantiomeric excess: >99% ee (Chiral Select-1000, 30 m × 0.25 mm, column temperature: 150 °C, carrier gas: N$_2$, 1.0 mL/min); $t_r$ = 8.88 and 9.42 min.

(1R,3R,4S)-3-(2-(1,3-dioxolan-2-yl)ethyl)-3-methylbicyclo[2.2.1]heptan-2-one (11): Yield (70%); $[\alpha]^{22}_D = -79.3$ (c 3.10, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.83 (t, $J = 4.4$ Hz, 1H), 4.00 – 3.93 (m, 2H), 3.87 – 3.78 (m, 2H), 2.59 – 2.54 (m, 1H), 2.37 – 2.30 (m, 1H), 2.01 (d, $J = 10.4$ Hz, 1H), 1.86 – 1.81 (m, 1H), 1.79 – 1.70 (m, 2H), 1.69 – 1.56 (m, 2H), 1.54 – 1.42 (m, 4H), 0.99 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 222.1, 104.4, 64.9, 50.0, 49.2, 43.4, 34.8, 28.6, 28.4, 25.0, 23.1, 18.3.;

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