Nickel-Catalyzed Asymmetric Domino Ring Opening/Cross-Coupling Reaction of Cyclobutanones via a Reductive Strategy

Decai Ding, Haiyan Dong, Chuan Wang
chuanw@ustc.edu.cn

HIGHLIGHTS
- Asymmetric ring opening of prochiral cyclobutanones via reductive Nickel-catalysis
- Merger of electrophilic ring opening and cross-electrophile coupling
- Chiral indanones were synthesized in highly enantioselective manner

High Enantioselectivities
No Use of Organometallics
Quaternary Stereocenter
High Functionality Tolerance
Article

Nickel-Catalyzed Asymmetric Domino Ring Opening/Cross-Coupling Reaction of Cyclobutanones via a Reductive Strategy

Decai Ding,1 Haiyan Dong,1 and Chuan Wang1,2,*

SUMMARY
Herein we demonstrate the successful application of reductive strategy in the asymmetric domino ring opening/cross-coupling reaction of prochiral cyclobutanones. Under the catalysis of a chiral nickel complex, various aryl iodide-tethered cyclobutanones were reacted with alkyl bromides as the electrophilic coupling partner, providing a variety of chiral indanones bearing a quaternary stereogenic center in highly enantioselective manner, which can be further converted to diverse benzene-fused cyclic compounds including indane, indene, dihydrocoumarin, and dihydroquinolinone. The preliminary mechanistic investigations support a mechanism involving Ni(I)-mediated enantiotopic C–C σ-bond activation of cyclobutanones as key elementary step in the catalytic cycle.

INTRODUCTION
Enantioselective ring opening of small strained molecules is one of the cornerstone reactions in organic synthesis, providing a convenient access to diverse chiral compounds. However, the main progresses in this domain are limited to small heterocycles, eg, epoxides and aziridines (Jacobsen, 2000; Meninno and Lattanzi, 2016; Pastor and Yus, 2005; Schneider, 2006; Wang et al., 2016a, 2016b). Furthermore, significant advances have been made in the Ti-mediated radical-type regiodivergent ring opening of epoxides in recent years (Funken et al., 2016, 2017; Mühlhaus et al., 2019). In contrast, the development of asymmetric ring opening of small carbocycles (Schneider et al., 2014; Grover et al., 2015; Fumagalli et al., 2017) lags behind due to the challenging C–C σ-bond cleavage (Dong, 2014; Marek et al., 2015; Souillart and Cramer, 2015; Nairoukh et al., 2017). Cyclobutanones have proved to be versatile precursors for ring opening or ring expansion reaction involving C–C σ-bond activation (Murakami et al., 1994, 2002, 2005a, 2005b; Matsuda et al., 2008; Xu and Dong, 2012; Ishida et al., 2012, 2014; Ko and Dong, 2014; Chen et al., 2014; Zhou and Dong, 2015; Juliá-Hernández et al., 2015), but only a few transition-metal-catalyzed asymmetric variants were reported in the last two decades, which are constrained to the following three strategies (Sietmann and Wiest, 2019): (1) In the pioneering work of Murakami, a method with an Rh-promoted enantioselective nucleophilic ring opening of prochiral cyclobutanones as key step followed by protonation was accomplished, in which a tethered aryl boronate or phenol can serve as the nucleophile (Scheme 1A) (Matsuda et al., 2006, 2007); (2) Dong, Cramer, and Murakami developed a variety of Rh- or Ni-catalyzed enantioselective intramolecular cycloadditions of cyclobutanones with various pendant unsaturated units, such as alkynes (Liu et al., 2012; Xu et al., 2012; Souillart et al., 2014; Deng et al., 2019), allenes (Zhou and Dong, 2016), aldehydes (Souillart and Cramer, 2014; Parker and Cramer, 2014), and oximes (Deng et al., 2016), affording an array of bridged bicyclic compounds with high enantiocontrol (Scheme 1B); (3) Cao, Xu, and coworkers achieved Pd-catalyzed enantioselective electrophilic ring opening of cyclobutanones with the appended aryl halide, and the resultant chiral alkyl Pd(II) species containing an indanone scaffold can be successfully trapped by different nucleophiles including aryl boronic acids, iodide, and alkynes (Scheme 1C) (Cao et al., 2019; Sun et al., 2019a, 2019b). Moreover, metallic Lewis acid- or organo-catalyzed asymmetric Baeyer-Villiger oxidation of prochiral cyclobutanones has also been established by Bolm (Bolm and Beckmann, 2000), Imada (Murashashi et al., 2002), Feng (Zhou et al., 2012), and Miller (Featherston et al., 2019). To expand the scope of asymmetric ring opening of cyclobutanones, a conceptionally new reaction pathway is still highly desired.

On the other side, Ni-catalyzed reductive cross-electrophile coupling has emerged as a powerful tool for step-economical C–C bond formation with high functionality tolerance through bypassing the use of organometallics as the coupling partner (Everson and Weix, 2014; Gu et al., 2015; Moragas et al., 2014; Richmond and Moran, 2018; Wang et al., 2016a, 2016; Weix, 2015). Herein we envisaged a Ni-catalyzed cascade
consisting of enantioselective electrophilic ring opening of aryl-iodide-tethered cyclobutanones and the following termination of the generated alkyl Ni intermediate using electrophilic alkyl bromides via reductive strategy, providing a new entry to chiral indanones in asymmetric fashion, which is featured as a characteristic motif in numerous compounds of pharmaceutical interest (DeSolms et al., 1978; Li, et al., 1995; Inoue et al., 1996; Ito et al., 2004; Huang et al., 2012; Peauger et al., 2017) (Scheme 1D).

RESULTS AND DISCUSSION

Optimization of the Reaction Conditions

For optimization of the reaction conditions, we chose the prochiral cyclobutanone 1a incorporating an aryl iodide unit and n-octyl bromide (2a) as model substrates (Table 1). Initially, various types of chiral ligands including BOX, Pyrox, PHOX, BINAP, DIOP, DuPhos, phosphoamidates etc. were investigated in this Ni-catalyzed reaction. However, all these reactions failed to deliver the desired product. To our delight, the reaction employing the Trost ligand L1 with chiral 1,2-cyclohexanediamine scaffold provided a promising result in terms of both efficiency and enantioselectivity (entry 1). Encouraged by this result, two additional Trost ligands with different backbones (L2 and L3) were tested for our reaction, giving only inferior results (entries 2 and 3). Moreover, the Trost ligand with naphthyl as linker (L4) turned out to be unsuitable for the studied reaction (entry 4). Tuning the substitution on the phenyl ring of L1 revealed that introduction of the bulky and electron-donating tert-butyl could improve the performance of the ligand (L5) concerning both reactivity and selectivity (entry 5). In sharp contrast, the desired reaction was completely shut down when the electron-withdrawing CF3 was installed on the phenyl substituent of the phosphine ligand (L6, entry 6).

Next, a brief solvent screening was undertaken (entries 7–11). In general, moderate to good results were obtained in polar solvents (entries 7–9) wherein the best outcome was achieved in the case of
Table 1. Optimization of the Reaction Conditions

Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the cyclobutanone 1a using 2.0 equiv of n-octyl bromide (2a), 10 mol% Ni-precatalyst, 12 mol% ligand and 2 equiv of Mn in 1.0 mL solvent at 40 °C for 12 h.

| Entry | Ligands | Ni-Salts  | Solvent | Yield (%)a | ee (%)b |
|-------|---------|-----------|---------|------------|---------|
| 1     | L1      | NiBr₂•glyme | DMA     | 66         | 54      |
| 2     | L2      | NiBr₂•glyme | DMA     | 15         | 13      |
| 3     | L3      | NiBr₂•glyme | DMA     | 21         | 19      |
| 4     | L4      | NiBr₂•glyme | DMA     | 0          | –       |
| 5     | L5      | NiBr₂•glyme | DMA     | 69         | 76      |
| 6     | L6      | NiBr₂•glyme | DMA     | 0          | –       |
| 7     | L5      | NiBr₂•glyme | DMSO    | 81         | 34      |
| 8     | L5      | NiBr₂•glyme | DMF     | 53         | 73      |
| 9     | L5      | NiBr₂•glyme | DMI     | 76         | 87      |
| 10    | L5      | NiBr₂•glyme | THF     | 0          | –       |
| 11    | L5      | NiBr₂•glyme | MeCN    | 0          | –       |
| 12    | L5      | NiBr₂   | DMI     | trace      | NDc     |
| 13    | L5      | NiCl₂   | DMI     | 56         | 85      |
| 14    | L5      | Ni(acac)₂ | DMI     | 0          | –       |
| 15    | L5      | Ni(COD)₂ | DMI     | 73         | 89      |
| 16    | L5      | NiCl₂•glyme | DMI     | 83         | 94      |
| 17d   | L5      | NiCl₂•glyme | DMI     | 23         | 70      |
| 18e   | L5      | NiCl₂•glyme | DMI     | 0          | –       |

Table 1. Optimization of the Reaction Conditions

aYields of the isolated product after column chromatography.

bDetermined by HPLC-analysis on chiral stationary phase.

cNot determined.

dZn was used as reductant instead of Mn.

eThe bromo analogue of 1a was used instead of 1a.
1,3-dimethyl-2-imidazolidinone (DMI, entry 9). In less polar solvents such as THF and MeCN, the formation of the product 3a was not observed (entries 10 and 11). Subsequently, a series of Ni-precatalysts were examined for this reaction (entries 12–16). Gratifyingly, both efficiency and asymmetric induction could be elevated to a high level when NiCl$_2$, glyme was utilized (entry 16). Replacing Mn by Zn as the reducing agent gave rise to a diminished yield and enantiocontrol (entry 17). In addition, we also employed the bromo analogue of 1a as precursor in this domino ring opening/cross-coupling reaction, but the conversion of 1a was not observed in this case (entry 18).

**Substrate Scope**

After establishing the optimal reaction conditions, we started to evaluate the substrate spectrum of this Ni-catalyzed reaction (Scheme 2). First, an array of primary alkyl bromides reacted with the cyclobutanones 1 using 2.0 equiv of alkyl bromides 2, 10 mol% NiCl$_2$-glyme, 12 mol% ligand L5, and 2 equiv of Mn in 1.0 mL DMI at 40 °C for 12 h. Yields of the isolated products after column chromatography. The ee or de were determined by HPLC-analysis on chiral stationary phase. The reaction was performed on a 10 mmol scale. Enantiopure precursors were employed.

1,3-dimethyl-2-imidazolidinone (DMI, entry 9). In less polar solvents such as THF and MeCN, the formation of the product 3a was not observed (entries 10 and 11). Subsequently, a series of Ni-precatalysts were examined for this reaction (entries 12–16). Gratifyingly, both efficiency and asymmetric induction could be elevated to a high level when NiCl$_2$-glyme was utilized (entry 16). Replacing Mn by Zn as the reducing agent gave rise to a diminished yield and enantiocontrol (entry 17). In addition, we also employed the bromo analogue of 1a as precursor in this domino ring opening/cross-coupling reaction, but the conversion of 1a was not observed in this case (entry 18).
(3k), and carbamate (3q) were well tolerated. Furthermore, the alkyl bromides containing a menthol or epiandrosterone subunit posed no problem, providing the products 3r and 3s in good efficiency and high diastereomeric excesses. Moreover, sterically more demanding secondary alkyl bromides also turned out to be competitive substrates for this reaction, and the corresponding products 3t-x were obtained in moderate to good yields and good to high enantiocontrol. Unfortunately, no desired product was formed when tertiary alkyl and benzyl halides were employed as precursors. Next, the impact of geminal substitution on the β-position of the prochiral cyclobutanones was examined. In the case of ethyl and n-propyl substituent comparable results were achieved (3y-aa), whereas no desired reaction occurred in the case of phenyl substitution. The use of mono-substituted cyclobutanone (R1=H) as a precursor also failed to deliver the cross-coupling product. Subsequently, we continued to study the scope of this reaction through introduction of either electron-donating or withdrawing groups to the tethered phenyl ring (3ab-ag), and in all these cases the products were afforded in good yields and good to high enantiomeric excesses. Notably, a 10-mmol-scale reaction for synthesis of 3i was carried out providing a similar result.

Derivatization of the Products

In order to demonstrate synthetic value of this method, some derivatizations of the cross-coupling product 3i were conducted (Scheme 3). First, Clemmensen reduction of the keto-moiety afforded a chiral indane 4 in an excellent yield. Compound 3i was also successfully subjected to Wittig olefination, providing a geminal disubstituted alkene 5 in a moderate yield. Moreover, the conversion of the indanone 3i into the corresponding oxime using hydroxyl amine followed by PCl5-mediated Beckmann rearrangement delivered a dihydroquinolinone 6 in 56% yield over two steps. In addition, the framework of dihydrocoumarin (7) or 3-aryl indene (8) can be constructed starting from the indanone 3i according to the known procedure in the literature (Jin and Wang, 2017).

Mechanistic Studies

A series of control experiments were designed to uncover the mechanism of this Ni-catalyzed reaction (Scheme 4). First, we performed the stoichiometric reaction between the cyclobutanone 1a and Ni(COD)2 in the presence of the ligand L5. After quenching with water, the formation of the indanone 9 was not observed, whereas the deiodinated product 10 was obtained in 89% yield (Scheme 4A). Considering that MnI2 is present in the catalytic reaction and can serve as Lewis acid to activate the carbonyl group,
we performed this stoichiometric reaction with 1 equiv of MnI₂. Again, only the deiodinated product 10 was generated (83% yield). This result confirms the feasibility of oxidative addition of the incorporated aryl iodide to the Ni(0) species, but the generated Ni(II) complex 11 is not able to further react with the Cyclobutanone to approach the indanone motif. When the reductant Mn (2 equiv) was added to the stoichiometric reaction mentioned earlier, the indanone 9 was furnished in 84% yield (Scheme 4B).

In this case, the aryl Ni(II) intermediate 11 is probably reduced to the corresponding Ni(I) species 12, which can subsequently undergo two possible reaction pathways: (1) oxidative addition with the cyclobutanone moiety followed by facile reductive elimination from the bridged bicyclic Ni(II) species 13; (2) migratory insertion into the carbonyl moiety followed by β-carbon-elimination from the Ni(I) complex 14. In both cases, the Ni(I) intermediate 15 with the indanone scaffold could be approached, which upon protonation leads to the compound 9. Moreover, the stoichiometric reaction employing the aryl

Scheme 4. Control Experiments
(A) Stoichiometric Reaction of 1a with Ni(COD)₂.
(B) Stoichiometric Reaction of 1a with Ni(COD)₂ in the Presence of Mn.
(C) Stoichiometric Reaction of 16 with Ni(COD)₂.
(D) Sequential Stoichiometric Reaction.
(E) Radical Clock Experiment.
iodide 16 tethering a linear ketone failed to deliver the addition product 17, arguing against the mechanism involving a Ni(I)-mediated migratory insertion step (Scheme 4C). Next, the sequential stoichiometric reaction with the addition of n-octyl bromide (2a) in the second stage provided the coupling product 3a in 88% ee, which is similar to one of the catalytic reactions (Scheme 4D). This result suggests that the enantiotopic C-C bond activation is probably the enantiodetermining step with generation of the Ni-complex 15, which can further react with n-octyl bromide to reach the product 3a. Moreover, an alkyl bromide with a pendant olefinic unit (2z) was employed as a precursor in the Ni-catalyzed reaction with cyclobutanone under the standard conditions, which resulted in cyclization of the alkyl bromide prior to the cross-coupling reaction (Scheme 4E). The corresponding product 3ah was yielded in a diastereomeric ratio of 1:1, which indicates a free-radical-mediated ring closure for the formation of the cyclopentane ring.

**Proposed Catalytic Cycle**

On the basis of the results of the control experiments, we proposed a plausible reaction mechanism for this Ni-catalyzed ring opening/cross-coupling reaction (Scheme 5). Initially, a Ni(0) species is generated under the reductive condition, which undergoes oxidative addition with the tethered aryl iodide 1. Next, the resultant Ni(II) complex I is reduced by Mn to the Ni(I) intermediate II, which in turn performs enantioselective insertion into one of the two C(sp²)-C(sp³) σ-bonds of the cyclobutanone to give the bicyclic Ni(III) complex III. The subsequent C(sp²)-C(sp³) reductive elimination affords the alkyl Ni(II) species IV with the indanone scaffold. In the next step, alkyl bromides 3 conduct oxidative addition to the complex IV via the formation of a cage V consisting of an alkyl radical and a Ni(III) species. Upon reductive elimination
from the intermediate VI, the indanone products 3 are furnished. Finally, the Ni(0) species is regenerated for the next catalytic cycle via the Mn-mediated reduction of Ni(0)Br.

**Conclusion**

In summary, we developed a reductive strategy for ring opening of prochiral cyclobutanones via sequential C–C bond cleavage and electrophilic trapping. Under the catalysis of a chiral Ni-complex in assistance of Mn as reducing agent, various cyclobutanones tethering an aryl iodide were reacted with both primary and secondary alkyl bromides, furnishing a variety of chiral indanones containing a quaternary stereogenic center in good to high enantioselectivities. According to the preliminary mechanistic studies, this tandem reaction proceeds with selective insertion of Ni(I) into the C–C σ-bond of cyclobutanones as the enantio-determining step, and the subsequent cage-bound oxidative addition with alkyl bromides and reductive elimination can afford the ring opening/cross-coupling products.

**Limitation of the Study**

Tertiary alkyl and benzyl bromides are not applicable in this methodology.

**METHODS**

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

**DATA AND CODE AVAILABILITY**

All data and methods can be found in the Supplemental Information.

**SUPPLEMENTAL INFORMATION**

Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.101017.

**ACKNOWLEDGMENTS**

This work is supported by National Natural Science Foundation of China (Grant No. 21772183), Fundamental Research Funds for the Central Universities (WK2060190086), “1000-Youth Talents Plan” start-up funding as well as University of Science and Technology of China.

**AUTHOR CONTRIBUTIONS**

C.W. and D.D. conceived and designed the experiments. D.D. and H.D. performed experiments and prepared the Supplementary Information. C.W. directed the project and wrote the paper. All authors discussed the results and commented on the manuscript.

**DECLARATION OF INTERESTS**

The authors declare no competing financial interests.

Received: February 10, 2020

Revised: March 6, 2020

Accepted: March 23, 2020

Published: April 24, 2020

**REFERENCES**

Bolm, C., and Beckmann, O. (2000). Zirconium-mediated asymmetric baeyer-villiger oxidation. Chirality 12, 523–525.

Cao, J., Chen, L., Sun, F.-N., Sun, Y.-L., Jiang, K.-Z., Yang, K.-F., Xu, Z., and Xu, L.-W. (2019). Pd-catalyzed enantioselective ring opening/cross-coupling and cyclopropanation of cyclobutanones. Angew. Chem. Int. Ed. 53, 1674–1678.

Chen, P.-h., Xu, T., and Dong, G. (2014). Divergent syntheses of fused β-naphthol and indene scaffolds by rhodium-catalyzed direct and decarbonylative alkyne-benzocyclobutenone couplings. Angew. Chem. Int. Ed. 53, 897–901.

DeSolms, S.J., Woltersdorf, O.W., Jr., Cragoe, E.J., Jr., Watson, L.S., and Fanelli, G.M., Jr. (1978). (Acylaryloxy)acetic acid diuretics. 2. (2-Alkyl-2-aryl-1-oxo-5-indanyloxy)acetic acids. J. Med. Chem. 21, 437–443.

Deng, L., Xu, T., Li, H., and Dong, G. (2016). Enantioselective Rh-catalyzed carboacylation of C=N bonds via C=C activation of benzocyclobutenones. J. Am. Chem. Soc. 138, 369–374.

Deng, L., Fu, Y., Lee, S.Y., Wang, C., Liu, P., and Dong, G. (2019). Kinetic resolution via Rh-catalyzed C–C activation of cyclobutanones at room temperature. J. Am. Chem. Soc. 141, 16260–16265.

G. Dong, ed. (2014). Top. Curr. Chem (Springer-Verlag), p. 346.
Everson, D.A., and Weix, D.J. (2014). Cross-electrolyte coupling: Principles of reactivity and selectivity. J. Org. Chem. 79, 4793–4798.

Featherston, A.L., Shugrue, C.R., Mercado, B.Q., and Miller, S.J. (2019). Asymmetric Bayeyer–Villiger reaction with hydrogen peroxide catalyzed by a novel planar-chiral bisflavin. ACS Catal. 9, 242–252.

Fumagalli, G., Stanton, S., and Bower, J.-F. (2017). Recent methodologies that exploit C–C single-bond cleavage of strained ring systems by transition metal complexes. Chem. Rev. 117, 9404–9432.

Funken, N., Mühlhaus, F., and Gansauer, A. (2016). General, highly selective synthesis of 1,3- and 1,4-difunctionalized building blocks by regiodivergent epoxide opening. Angew. Chem. Int. Ed. 55, 12030–12034.

Funken, N., Zhang, Y.-Q., and Gansauer, A. (2017). Regiodivergent catalysis: a powerful tool for selective catalysis. Chem. Eur. J. 23, 19–32.

Grover, H.K., Emmett, M.R., and Kerr, M.A. (2015). Carbocycles from donor–acceptor cyclopropanes. Org. Biomol. Chem. 13, 655–671.

Gu, J.; Wang, X.; Xue, W., and Gong, H. (2015). Nickel-catalyzed reductive coupling of alky halides with other electrophiles: concept and mechanistic considerations. Org. Chem. Front. 2, 1411–1421.

Huang, L., Lu, C., Sun, Y., Mao, F., Luo, Z., Su, T., Jiang, H., Shan, W., and Li, X. (2012). Asymmetric Baeyer–Villiger reaction with hydrogen peroxide catalyzed by a novel planar-chiral bisflavin. ACS Catal. 9, 242–252.

Jacobsen, E.N. (2000). Asymmetric catalysis of epoxide ring-opening reactions. Acc. Chem. Res. 33, 421–431.

Jin, Y., and Wang, C. (2017). Nickel-catalyzed asymmetric reductive alylation of unactivated alkenes. Angew. Chem. Int. Ed. 58, 6722–6726.

Julii-Hernández, F., Zaidi, A., Nishimura, A., and Martin, R. (2015). Nickel-catalyzed chemo- regio- and diastereoselective bond formation through proximal C–C cleavage of benzoxyclobuteneones. Angew. Chem. Int. Ed. 54, 9637–9641.

Ko, H.M., and Dong, G. (2014). Cooperative activation of cyclobutanones and olefins leads to bridged ring systems by a catalytic (A + 2) coupling. Nat. Chem. 6, 739–744.

Li, C.S., Black, W.C., Chan, C.-C., Ford-Hutchinson, A.W., Gauthier, J.Y., Gordon, R., Guay, D., Kargman, L., Lau, C.K., Mancini, J., et al. (1995). Cyclooxygenase-2 inhibitors syntheses and pharmacological activities of 5-methanesulphonamido-1-indane derivatives. J. Med. Chem. 38, 4897–4905.

Liu, L., Ishida, N., and Murakami, M. (2012). Atom- and step-economic catalytic benzylobicyclo[2.2.2]octenones through carbon-carbon bond cleavage. Angew. Chem. Int. Ed. 51, 2485–2488.

Marek, I., Masarwa, A., Delaye, P.-O., and Leibeling, M. (2015). Selective carbon–carbon bond cleavage for the stereoselective synthesis of acyclic systems. Angew. Chem. Int. Ed. 54, 414–429.

Matsuda, T., Shigeno, M., and Murakami, M. (2006). Enantioselective C–C bond cleavage creating chiral quaternary carbon centers. Org. Lett. 8, 3379–3381.

Matsuda, T., Shigeno, M., and Murakami, M. (2007). Asymmetric synthesis of 3,4-dihydrocoumarins by rhodium(I)-catalyzed reaction of 3-(2-hydroxyphenyl)cyclobutanones. J. Am. Chem. Soc. 129, 12066–12067.

Matsuda, T., Shigeno, M., and Murakami, M. (2008). Palladium-catalyzed sequential carbon–carbon bond cleavage/formation producing arylatedbenzolactones. Org. Lett. 10, 5219–5222.

Meninno, S., and Lattanzi, A. (2016). Organo-catalytic cyclopropane reactions of epoxides: recent progress. Chem. Eur. J. 22, 3632–3642.

Moragas, T., Correa, A., and Martin, R. (2014). Metal-catalyzed reductive coupling reactions of organic halides with carbonyl-type compounds. Chem. Eur. J. 20, 8242–8258.

Mühlhaus, F., Weilbarch, H., Dahmen, T., Schnakenburg, G., and Gansauer, A. (2019). Merging regiodivergent catalysis with atom-economic radical arylation. Angew. Chem. Int. Ed. 58, 14208–14212.

Murahashi, S.-I., Ono, S., and Imada, Y. (2002). Merging regiodivergent catalysis with atom-economic radical arylation. Angew. Chem. Int. Ed. 41, 2366–2368.

Murakami, M., Amii, H., and Ito, Y. (1994). Selective activation of carbon-carbon bonds next to a carboxylgroup. Nature 370, 540–541.

Murakami, M., Ishibashi, T., and Ito, Y. (2002). Catalytic intramolecular olefin insertion into a carbon–carbon single bond. J. Am. Chem. Soc. 124, 13976–13977.

Murakami, M., Kadokawa, S., Fujimoto, A., Ishibashi, M., and Matsuda, T. (2000a). Acids direct 2-styrylcyclobutane into two distinctly different reaction pathways. Org. Lett. 7, 2059–2061.

Murakami, M., Ashida, S., and Matsuda, T. (2005b). Nickel-catalyzed intermolecular alkyl insertion into cyclobutanones. J. Am. Chem. Soc. 127, 6932–6933.

Nairoukh, Z., Cormier, M., and Marek, I. (2017). Merging C–H and C–C bond cleavage in organic synthesis. Nat. Chem. Rev. 1, 35.

Parker, E., and Cramer, N. (2014). Asymmetric rhodium(II)-catalyzed C–C activations with zwitterionic bis-phospholane ligands. Organometallics 33, 780–787.

Pastor, M.I., and Yus, M. (2005). Asymmetric ring opening of epoxides. Curr. Org. Chem. 9, 1–29.

Peauger, L., Azzouz, R., Gembus, V., Tıntaş, M.-L., Santos, J.S.O., Bohn, P., Papamicaél, C., and Levecher, V. (2017). Donepezil-based central acetylcholinesterase inhibitors by means of a “bio-oxidizable” prodrug strategy: design, synthesis, and in vitro biological evaluation. J. Med. Chem. 60, 5909–5926.

Richmond, E., and Moran, J. (2018). Recent advances in nickel catalysis enabled by stoichiometric metallic reducing agents. Synthesis 50, 699–713.

Schneider, C. (2006). Synthesis of 1,2-difunctionalized fine chemicals through catalytic, enantioselective ring-opening reactions of epoxides. Synthesis 38, 3919–3944.

Schneider, T.F., Kaschel, J., and Weiz, D.B. (2014). A new golden age for donor-acceptor cyclopropanes. Angew. Chem. Int. Ed. 53, 5504–5523.

Sietmann, J., and Wiest, J.M. (2019). Enantioselective desymmetrization of cyclobutanones: a roadway to molecular complexity. Angew. Chem. Int. Ed. 58, https://doi.org/10.1002/anie.201910767.

Souillat, L., and Cramer, N. (2014). Highly enantioselectiveverhoudim(II)-catalyzed carbonyl carboacylations initiated by C–C bond activation. Angew. Chem. Int. Ed. 53, 9640–9644.

Souillat, L., and Cramer, N. (2015). Catalytic C–C bond activations via oxidative addition to transition metals. Chem. Rev. 115, 9410–9464.

Souillat, L., Parker, E., and Cramer, N. (2014). Highly enantioselectiveverhoudim(II)-catalyzed activation of enantiotopiccyclobutaneC–C bonds. Angew. Chem. Int. Ed. 53, 3001–3005.

Sun, Y.-L., Wang, X.-B., Sun, F.-N., Chen, Q.-Q., Cao, J., Xu, X., and Xu, L.-W. (2019a). Asymmetric biomimetic desymmetrization of bicyclo[2.2.1]heptanes: a new approach for the synthesis of 2-styrylcyclobutane. J. Org. Chem. 84, 6747–6751.

Sun, F.-N., Yang, W.-C., Chen, X.-B., Sun, Y.-L., Cao, J., Xu, Z., and Xu, L.-W. (2019). Asymmetric biomimetic desymmetrization of bicyclo[2.2.1]heptanes: a new approach for the synthesis of 2-styrylcyclobutane. J. Org. Chem. 84, 6747–6751.
type C(sp³)–C(sp) cross-coupling alkylation. Chem. Sci. 10, 7579–7583.
Wang, C., Luo, L., and Yamamoto, H. (2016a). Metal-catalyzed directed regio- and enantioselective ring-opening of epoxides. Acc. Chem. Res. 49, 193–204.
Wang, X., Dai, Y., and Gong, H. (2016b). Nickel-catalyzed reductive couplings. Top.Curr. Chem. 374, 43.
Weix, D.J. (2015). Methods and mechanisms for cross-electrophile coupling of Csp2 halides with alkyl electrophiles. Acc. Chem. Res. 48, 1767–1775.
Xu, T., and Dong, G. (2012). Rhodium-catalyzed regioselective carboacylation of olefins: a C–C bond activation approach for accessing fused-ring systems. Angew.Chem. Int. Ed. 51, 7567–7571.
Xu, T., Ko, H.M., Savage, N.A., and Dong, G. (2012). Highly enantioselectively-catalyzed carboacylation of olefins: efficient syntheses of chiral poly-fused rings. J. Am. Chem. Soc. 134, 20005–20008.
Zhou, X., and Dong, G. (2015). (4+1) vs (4+2): catalytic intramolecular coupling between cyclobutanones and trisubstituted allenes via C–C activation. J. Am. Chem. Soc. 137, 13715–13721.
Zhou, X., and Dong, G. (2016). Nickel-catalyzed chemo- and enantioselective coupling between cyclobutanones and allenes: rapid synthesis of [3.2.2] bicycles. Angew.Chem. Int. Ed. 55, 15091–15095.
Zhou, L., Liu, X., Li, J., Zhang, Y., Hu, X., Lin, L., and Feng, X. (2012). Kinetic resolution via Rh-catalyzed C–C activation of cyclobutanones at room temperature. J. Am. Chem. Soc. 134, 17023–17026.
Supplemental Information

Nickel-Catalyzed Asymmetric Domino Ring Opening/Cross-Coupling Reaction of Cyclobutanones via a Reductive Strategy

Decai Ding, Haiyan Dong, and Chuan Wang
Figure S1 $^1$H NMR Spectrum of 1c, related to Scheme 2
Figure S2 $^{13}$C NMR Spectrum of 1c, related to Scheme 2
Figure S3 $^1$H NMR Spectrum of 2k, related to Scheme 2
Figure S4 $^{13}$C NMR Spectrum of 2k, related to Scheme 2
Figure S5 $^1$H NMR Spectrum of 2l, related to Scheme 2
Figure S6 $^{13}$C NMR Spectrum of 2l, related to Scheme 2
Figure S7 $^1$H NMR Spectrum of 2o, related to Scheme 2
Figure S8 $^{13}$C NMR Spectrum of 2o, related to Scheme 2
Figure S9 $^1$H NMR Spectrum of 2q, related to Scheme 2
Figure S10 $^{13}$C NMR Spectrum of 2q, related to Scheme 2
Figure S11 $^1$H NMR Spectrum of 2r, related to Scheme 2
Figure S12 $^{13}$C NMR Spectrum of 2r, related to Scheme 2
Figure S13 $^1$H NMR Spectrum of 2t, related to Scheme 2
Figure S14 $^{13}$C NMR Spectrum of 12t, related to Scheme 2
Figure S15 $^1$H NMR Spectrum of 3a, related to Scheme 2
Figure S16 $^{13}$C NMR Spectrum of 3a, related to Scheme 2

![NMR Spectrum of 3a](image)
Figure S17 $^1$H NMR Spectrum of 3b, related to Scheme 2
Figure S18 $^{13}$C NMR Spectrum of 3b, related to Scheme 2
Figure S19 $^1$H NMR Spectrum of 3c, related to Scheme 2
Figure S20 $^{13}$C NMR Spectrum of 3c, related to Scheme 2
Figure S21 $^{19}$F NMR Spectrum of 3c, related to Scheme 2
Figure S22 $^1$H NMR Spectrum of 3d, related to Scheme 2
Figure S23 $^{13}$C NMR Spectrum of 3d, related to Scheme 2
Figure S24 $^1$H NMR Spectrum of 3e, related to Scheme 2
Figure S25 $^{13}$C NMR Spectrum of 3e, related to Scheme 2

![C NMR Spectrum of 3e](image)
Figure S26 $^1$H NMR Spectrum of 3f, related to Scheme 2
Figure S27 $^{13}$C NMR Spectrum of 3f, related to Scheme 2
Figure S28 $^1$H NMR Spectrum of 3g, related to Scheme 2
Figure S29 $^{13}$C NMR Spectrum of 3g, related to Scheme 2
Figure S30 $^1$H NMR Spectrum of 3h, related to Scheme 2

3h
Figure S31 $^{13}$C NMR Spectrum of 3h, related to Scheme 2
Figure S32 $^1$H NMR Spectrum of 3i, related to Scheme 2

3i
Figure S33 $^{13}$C NMR Spectrum of 3i, related to Scheme 2
Figure S34 $^1$H NMR Spectrum of 3j, related to Scheme 2
Figure S35 $^{13}$C NMR Spectrum of 3j, related to Scheme 2
Figure S36 $^1$H NMR Spectrum of 3k, related to Scheme 2
Figure S37 $^{13}$C NMR Spectrum of 3k, related to Scheme 2
Figure S38 $^1$H NMR Spectrum of 3l, related to Scheme 2
Figure S39 $^{13}$C NMR Spectrum of 3l, related to Scheme 2
Figure S40 $^1$H NMR Spectrum of 3m, related to Scheme 2
Figure S41 $^{13}$C NMR Spectrum of 3m, related to Scheme 2
Figure S42 $^1$H NMR Spectrum of 3n, related to Scheme 2
Figure S43 $^{13}$C NMR Spectrum of 3n, related to Scheme 2
Figure S44 $^1$H NMR Spectrum of 3o, related to Scheme 2

3o
Figure S45 $^{13}$C NMR Spectrum of 3o, related to Scheme 2
Figure S46 $^{19}$F NMR Spectrum of 3o, related to Scheme 2
Figure S47 $^1$H NMR Spectrum of 3p, related to Scheme 2
Figure S48 $^{13}$C NMR Spectrum of 3p, related to Scheme 2
Figure S49 $^1$H NMR Spectrum of 3q, related to Scheme 2
Figure S50 $^{13}$C NMR Spectrum of 3q, related to Scheme 2
Figure S51 $^1$H NMR Spectrum of 3r, related to Scheme 2

[Image: H NMR Spectrum of 3r]
Figure S52 $^{13}$C NMR Spectrum of 3r, related to Scheme 2
Figure S53 $^1$H NMR Spectrum of 3s, related to Scheme 2
Figure S54 $^{13}$C NMR Spectrum of 3a, related to Scheme 2
Figure S55 $^1$H NMR Spectrum of 3t, related to Scheme 2
Figure S56 $^{13}$C NMR Spectrum of 3t, related to Scheme 2
Figure S57 $^1$H NMR Spectrum of 3u, related to Scheme 2
Figure S58 $^{13}$C NMR Spectrum of 3u, related to Scheme 2
Figure S59 $^1$H NMR Spectrum of 3v, related to Scheme 2
Figure S60 $^{13}$C NMR Spectrum of 3v, related to Scheme 2
Figure S61 $^1$H NMR Spectrum of 3w, related to Scheme 2

![NMR Spectrum of 3w](image-url)
Figure S62 $^{13}$C NMR Spectrum of 3w, related to Scheme 2
Figure S63 $^1$H NMR Spectrum of 3w, related to Scheme 2
Figure S64 $^{13}$C NMR Spectrum of 3w, related to Scheme 2
Figure S65 $^1$H NMR Spectrum of 3y, related to Scheme 2
Figure S66 $^{13}$C NMR Spectrum of 3y, related to Scheme 2

3y
Figure S67 $^1$H NMR Spectrum of 3z, related to Scheme 2
Figure S68 $^{13}$C NMR Spectrum of 3z, related to Scheme 2
Figure S69 $^1$H NMR Spectrum of 3aa, related to Scheme 2
Figure S70 $^{13}$C NMR Spectrum of 3aa, related to Scheme 2
Figure S71 $^1$H NMR Spectrum of 3ab, related to Scheme 2
Figure S72 $^1$H NMR Spectrum of 3ab, related to Scheme 2
Figure S73 $^1$H NMR Spectrum of 3ac, related to Scheme 2
Figure S74 $^{13}$C NMR Spectrum of 3ac, related to Scheme 2
Figure S75 $^1$H NMR Spectrum of 3ad, related to Scheme 2
Figure S76 $^{13}$C NMR Spectrum of 3ad, related to Scheme 2
Figure S77 $^1$H NMR Spectrum of 3ae, related to Scheme 2
Figure S78 $^{13}$C NMR Spectrum of 3ae, related to Scheme 2
Figure S79 $^1$H NMR Spectrum of 3af, related to Scheme 2
Figure S80 $^{13}$C NMR Spectrum of 3af, related to Scheme 2
Figure S81 $^{19}$F NMR Spectrum of 3af, related to Scheme 2
Figure S82 $^1$H NMR Spectrum of 3ag, related to Scheme 2
Figure S83 $^{13}$C NMR Spectrum of 3ag, related to Scheme 2
Figure S84 $^1$H NMR Spectrum of 9, related to Scheme 4
Figure S85 $^{13}$C NMR Spectrum of 9, related to Scheme 4
Figure S86 $^1$H NMR Spectrum of 10, related to Scheme 4
Figure S87 $^{13}$C NMR Spectrum of 10, related to Scheme 4
Figure S88 $^1$H NMR Spectrum of 18, related to Scheme 4
Figure S89 $^{13}$C NMR Spectrum of 18, related to Scheme 4
Figure S90 $^1$H NMR Spectrum of 3ah, related to Scheme 4
Figure S91 $^{13}$C NMR Spectrum of 3ah, related to Scheme 4
Figure S92 $^1$H NMR Spectrum of 4, related to Scheme 3
Figure S93 $^{13}$C NMR Spectrum of 4, related to Scheme 3
Figure S94 $^1$H NMR Spectrum of 5, related to Scheme 3

5, 50%
Figure S9 $^{13}$C NMR Spectrum of 5, related to Scheme 3
Figure S96 $^1$H NMR Spectrum of 6, related to Scheme 3
Figure S97 $^{13}$C NMR Spectrum of 6, related to Scheme 3
Figure S98 HPLC Data and Chromatograms of 3a, related to Scheme 2

HPLC (Chiralpak IC): $t_R = 13.7$ (minor), 15.3 (major)
Condition: 95:5 n-Hexane: $i$-PrOH, flow rate 0.5 mL/min, 25°C.
254nm.

| No. | Peak Name | Retention Time (min) | Area (mAU*min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount |
|-----|-----------|----------------------|----------------|--------------|-------------------|---------------------|--------|
| 1   |           | 13.670               | 139.655        | 528.405      | 49.73             | 52.45               | n.a.   |
| 2   |           | 15.287               | 140.650        | 479.038      | 50.27             | 47.55               | n.a.   |

Total:

Costs: 279.606 1007.442 100.00 100.00
Figure S99 HPLC Data and Chromatograms of 3b, related to Scheme 2

HPLC (Chiralpak IC): $t_R = 15.9$ (minor), 18.4 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
Figure S10 HPLC Data and Chromatograms of 3c, related to Scheme 2

HPLC (Chiralpak IC): $t_R = 32.0$ (minor), 32.6 (major)
Condition: 95:5 n-Hexane: $i$-PrOH, flow rate 0.5 mL/min, 25°C.
254nm

3c
Figure S101 HPLC Data and Chromatograms of 3d, related to Scheme 2

HPLC (Chiralpak IC): \( t_R = 29.0 \) (minor), 30.2 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C, 254nm

3d
Figure S102 HPLC Data and Chromatograms of 3e, related to Scheme 2

HPLC (Chiralpak ADH): $t_R$ = 12.6 (minor), 11.7 (major)
Condition: 80:20 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C, 254nm
Figure S103 HPLC Data and Chromatograms of 3f, related to Scheme 2

HPLC (Chiralcel OJH): $t_R$ = 12.6 (minor), 12.0 (major)
Condition: 90:10 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
Figure S104 HPLC Data and Chromatograms of 3g, related to Scheme 2

HPLC (Chiralcel ODH): t_R = 27.6 (minor), 25.4 (major)
Condition: 85:15 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
Figure S105 HPLC Data and Chromatograms of 3h, related to Scheme 2

HPLC (Chiralpak ADH): t_R = 30.2 (minor), 31.4 (major)
Condition: 85:15 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
Figure S106 HPLC Data and Chromatograms of 3i, related to Scheme 2

HPLC (Chiralpak IB): $t_R = 26.0$ (minor), 22.4 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.4 mL/min, 25°C, 254 nm

3i
Figure S107 HPLC Data and Chromatograms of 3j, related to Scheme 2

HPLC (Chiralpak ADH): $t_R$ = 19.8 (minor), 18.4 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
Figure S108 HPLC Data and Chromatograms of 3k, related to Scheme 2

HPLC (Chiralpak ADH): $t_R = 31.7$ (minor), 29.3 (major)
Condition: 90:10 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm

3K
**Figure S109 HPLC Data and Chromatograms of 3l, related to Scheme 2**

HPLC (Chiralpak IB): $t_R = 17.8$ (minor), 15.1 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm

![Chromatogram](image)

**Integration Results**

| No. | Peak Name | Retention Time min | Area mAU/ min | Height mAU | Relative Area % | Relative Height % | Amount n.a. |
|-----|-----------|--------------------|---------------|-------------|----------------|-------------------|-------------|
| 1   |           | 16.287             | 197.812       | 621.560     | 49.05          | 54.80             | n.a.        |
| 2   |           | 17.903             | 205.499       | 512.688     | 50.95          | 45.20             | n.a.        |
| Total |          |                    | 403.362       | 1134.247    | 100.00         | 100.00            |             |

![Chromatogram](image)

**Integration Results**

| No. | Peak Name | Retention Time min | Area mAU/ min | Height mAU | Relative Area % | Relative Height % | Amount n.a. |
|-----|-----------|--------------------|---------------|-------------|----------------|-------------------|-------------|
| 1   |           | 16.127             | 192.862       | 615.429     | 94.67          | 94.52             | n.a.        |
| 2   |           | 17.803             | 10861         | 32934       | 5.33           | 5.88              | n.a.        |
| Total |          |                    | 203.722       | 648.363     | 100.00         | 100.00            |             |
HPLC (Chiralpak ADH): $t_R = 24.4$ (minor), 21.2 (major)
Condition: 90:10 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C, 254 nm

Integration Results

| No. | Peak Name | Retention Time (min) | Area (mAU.min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount (n.a.) |
|-----|-----------|----------------------|----------------|--------------|-------------------|---------------------|--------------|
| 1   |           | 21.187               | 374.013        | 798.876      | 92.31             | 92.59               | n.a.         |
| 2   |           | 24.403               | 31.172         | 63.179       | 7.69              | 7.41                | n.a.         |

Total: 405.185 852.055 100.00 100.00
Figure S11 HPLC Data and Chromatograms of 3n, related to Scheme 2

HPLC (Chiralpak ADH): $t_R = 23.0$ (minor), 20.5 (major)
Condition: 90:10 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
Figure S112 HPLC Data and Chromatograms of 3o, related to Scheme 2

HPLC (Chiralpak IB): t_R = 16.1 (minor), 14.2 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm
Figure S113 HPLC Data and Chromatograms of 3p, related to Scheme 2

HPLC (Chiralpak IB): $t_R = 14.8$ (minor), 13.2 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm

![HPLC Chromatogram of 3p](image_url)

| No. | Peak Name | Retention Time (min) | Area (mAU)*min | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount (n.a.) |
|-----|-----------|---------------------|----------------|--------------|-------------------|--------------------|---------------|
| 1   |           | 13.157              | 179.572        | 678.452      | 49.26             | 53.68              | n.a           |
| 2   |           | 14.530              | 184.943        | 585.604      | 50.74             | 46.32              | n.a           |
| Total|           | 364.515             | 1263.956       | 100.00       | 100.00            |                    |               |

![Integration Results Table](image_url)
Figure S114 HPLC Data and Chromatograms of 3q, related to Scheme 2

HPLC (Chiralpak ADH): $t_R = 28.7$ (minor), 23.3 (major)
Condition: 90:10 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm
Figure S115 HPLC Data and Chromatograms of 3r, related to Scheme 2

HPLC (Chiralpak ADH): $t_R = 21.2$ (minor), 19.0 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm
Figure S116 HPLC Data and Chromatograms of 3s, related to Scheme 2

HPLC (Chiralpak IB): $t_R = 25.7$ (minor), 22.1 (major)
Condition: 85:15 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm
Figure S117 HPLC Data and Chromatograms of 3t, related to Scheme 2

HPLC (Chiralpak IC): $t_R = 12.7$ (minor), 11.4 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm

3t
Figure S118 HPLC Data and Chromatograms of 3u, related to Scheme 2

HPLC (Chiralpak IC): $t_R = 17.4$ (minor), 19.7 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
Figure S119 HPLC Data and Chromatograms of 3v, related to Scheme 2

HPLC (Chiralpak IC): $t_R = 15.9$ (minor), 18.0 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm.
Figure S120 HPLC Data and Chromatograms of 3w, related to Scheme 2

HPLC (Chiralpak IB): $t_R = 12.7$ (minor), 13.8 (major)
Condition: 85:15 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm

![Chromatogram](image1)

**Integration Results**

| No. | Peak Name | Retention Time (min) | Area (mAU*min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount (n.a.) |
|-----|-----------|----------------------|----------------|--------------|-------------------|---------------------|---------------|
| 1   |           | 12.400               | 43.216         | 192.976      | 50.00             | 52.70               | n.a.          |
| 2   |           | 13.077               | 43.216         | 177.392      | 50.00             | 47.90               | n.a.          |
| Total: |       |                      | 86.427         | 370.398      | 100.00            | 100.00              |               |

![Chromatogram](image2)

**Integration Results**

| No. | Peak Name | Retention Time (min) | Area (mAU*min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount (n.a.) |
|-----|-----------|----------------------|----------------|--------------|-------------------|---------------------|---------------|
| 1   |           | 12.700               | 3.114          | 13.399       | 4.17              | 4.45                | n.a.          |
| 2   |           | 13.833               | 71.621         | 286.691      | 95.83             | 95.56               | n.a.          |
| Total: |       |                      | 74.735         | 299.430      | 100.00            | 100.00              |               |
Figure S121 HPLC Data and Chromatograms of 3x, related to Scheme 2

HPLC (Chiralpak IC): $t_R = 15.9$ (minor), 18.1 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
Figure S122 HPLC Data and Chromatograms of 3y, related to Scheme 2

HPLC (Chiralpak IB): $t_R = 12.8$ (minor), 11.7 (major)
Condition: 90:10 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm
Figure S123 HPLC Data and Chromatograms of 3z, related to Scheme 2

HPLC (Chiralpak IB): $t_R$ = 11.6 (minor), 12.4 (major)
Condition: 85:15 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
HPLC (Chiralcel OJH): $t_R = 9.8$ (minor), 10.8 (major)
Condition: 95:5 n-Hexane: i-PrOH, flow rate 1.0 mL/min, 25°C. 254nm
HPLC Data and Chromatograms of 3ab, related to Scheme 2

HPLC (Chiralpak IB): $t_R = 16.2$ (minor), 15.3 (major)
Condition: 92.5:7.5 n-Hexane: i-PrOH, flow rate 0.4 mL/min, 25°C, 254nm

3ab

![Chromatogram and Integration Results]

Integration Results

| No. | Peak Name | Retention Time (min) | Area (mAU*min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount (n.a.) |
|-----|-----------|----------------------|----------------|-------------|-------------------|---------------------|--------------|
| 1   |           | 15.300               | 60.854         | 238.738     | 48.20             | 50.69               | n.a.         |
| 2   |           | 16.143               | 65.396         | 232.250     | 51.00             | 49.31               | n.a.         |
| Total|           | 126.242              | 470.988        | 100.00      | 100.00            |                     |              |
Figure S126 HPLC Data and Chromatograms of 3ac, related to Scheme 2

HPLC (Chiralpak IB): $t_R = 17.5$ (minor), 15.6 (major)
Condition: 92.5:7.5 n-Hexane: i-PrOH, flow rate 0.4 mL/min, 25°C. 254nm

| No. | Peak Name | Retention Time (min) | Area (mAU*min) | Height (mAU) | Relative Area % | Relative Height % | Amount n.a. |
|-----|-----------|----------------------|----------------|-------------|-----------------|------------------|-------------|
| 1   |           | 16.607               | 166.728        | 603.656     | 49.95           | 51.70            | n.a.        |
| 2   |           | 17.433               | 166.966        | 563.969     | 50.04           | 48.30            | n.a.        |
| Total: |          | 333.694              | 1167.625       |              | 100.00          | 100.00           |             |

Integration Results
Figure S127 HPLC Data and Chromatograms of 3ad, related to Scheme 2

HPLC (Chiralpak ADH): $t_R = 17.1$ (minor), 19.9 (major)
Condition: 80:20 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm
Figure S128 HPLC Data and Chromatograms of 3ae, related to Scheme 2

HPLC (Chiralpak IB): $t_R = 10.8$ (minor), 10.3 (major)
Condition: 80:20 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C. 254nm
Figure S129 HPLC Data and Chromatograms of 3af, related to Scheme 2

HPLC (Chiralpak ADH): $t_R = 22.2$ (minor), 23.1 (major)
Condition: 97:3 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm
Figure S130 HPLC Data and Chromatograms of 3ag, related to Scheme 2

HPLC (Chiralpak ADH): $t_R = 23.7$ (minor), 25.3 (major)
Condition: 97:3 n-Hexane: i-PrOH, flow rate 0.5 mL/min, 25°C.
254nm

3ag
Figure S131 HPLC Data and Chromatograms of 4, related to Scheme 3

HPLC (ChiralpakIB): $t_R = 11.6$ (minor), $13.2$ (major)
Condition: 98:2 n-Hexane:i-PrOH, flow rate 0.5 mL/min, 25°C.
254 nm

Integration Results

| No. | Peak Name | Retention Time (min) | Area (mAU*min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount (n.a.) |
|-----|-----------|----------------------|----------------|-------------|-------------------|-------------------|--------------|
| 1   |           | 10.183               | 23 874         | 143 321     | 47.71             | 55.18             | n.a.         |
| 2   |           | 11.756               | 26 182         | 116 403     | 52.29             | 44.82             | n.a.         |
| Total: |          |                      | 50 036         | 259 724     | 100.00            | 100.00            | n.a.         |

Integration Results

| No. | Peak Name | Retention Time (min) | Area (mAU*min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount (n.a.) |
|-----|-----------|----------------------|----------------|-------------|-------------------|-------------------|--------------|
| 1   |           | 10.280               | 250 985        | 1289 300    | 95.49             | 96.09             | n.a.         |
| 2   |           | 11.933               | 11 823         | 52 438      | 4.51              | 3.91              | n.a.         |
| Total: |          |                      | 261 307        | 1341 138    | 100.00            | 100.00            | n.a.         |
Transparent Method

General Methods and Materials

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Advance 400M and 500M NMR spectrometers at ambient temperature in CDCl$_3$ at 400 and 101 MHz. The chemical shifts are given in ppm relative to tetramethylsilane [$^1$H: δ= (SiMe$_4$)= 0.00 ppm] as an internal standard or relative to the resonance of the solvent [$^1$H: δ=(CDCl$_3$)= 7.26,$^{13}$C: δ= (CDCl$_3$)= 77.16 ppm]. Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); dt (doublet of triplets); m (multiplets), etc. Coupling constants are reported as $J$ values in Hz. High resolution mass spectral analysis (HRMS) was performed on Waters XEVO G2 Q-TOF. HPLC was performed on ThermoUltiMate 3000. Flash chromatography was performed using 300-400 mesh silica gel with the indicated solvent system.

All reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

Preparation of Cyclobutanones

Scheme S1. Cyclobutanones Employed, Related to Scheme 2

Successful Substrates for the Ni-Catalyzed Reactions:

![Successful Substrates Diagram]

Unsuccessful Substrates for the Ni-Catalyzed Reactions:

![Unsuccessful Substrates Diagram]

Cyclobutanones $1a$, $1b$ and $1d$-k are known compounds in the literature procedures (Sun et al., 2019).
Triflic anhydride (3.95 g, 14 mmol, 1.4 equiv) was added dropwise to a solution of \( N,N \)-dimethylacetamide (1.05 g, 12 mmol, 1.2 equiv) in 14 mL of 1,2-dichloroethane under stirring at 5 °C. The mixture was stirred at 5°C for 30 min, and then a mixture of 1-iodo-2-(pent-1-en-2-yl)benzene (2.72 g, 10 mmol, 1.0 equiv) and 2,4,6-collidine (1.69 g, 14 mmol, 1.4 equiv) in 2 mL of 1,2-dichloroethane was added dropwise. After the reaction mixture was refluxed for 18 h, 1,2 dichloromethane was removed in vacuum and the residue was treated with 4 mL H\(_2\)O and CCl\(_4\) (1:1). The obtained mixture was refluxed for 18 h, and then the aqueous layer was extracted with CCl\(_4\) (3 × 50 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and filtered. Concentration of the solution by rotary evaporation under reduced pressure gave a residue, which was purified by silica gel (petroleum ether: EtOAc= 25:1) to afford \( 3- \text{(2-iodophenyl)-3-propylcyclobutan-1-one} \) (1c) as yellow solid (2.13 g, 68% yield). \(^1\)H NMR (500 MHz, Chloroform-\( d \)) \( \delta = 7.92 \) (dd, \( J = 7.9, 1.3 \) Hz, 1H), 7.34 (td, \( J = 7.5, 1.4 \) Hz, 1H), 7.20 (dd, \( J = 7.8, 1.7 \) Hz, 1H), 6.93 (td, \( J = 7.6, 1.6 \) Hz, 1H), 3.61-3.16 (m, 4H), 2.39-1.56 (m, 2H), 1.18-0.96 (m, 2H), 0.84 (t, \( J = 7.2 \) Hz, 3H) ppm. \(^{13}\)C NMR (126 MHz, Chloroform-\( d \)) \( \delta = 206.2, 146.8, 141.6, 129.5, 128.3, 127.7, 95.4, 57.6, 41.4, 40.9 \) (2C), 18.9, 14.2 ppm. HRMS (ESI): calcd. for C\(_{13}\)H\(_{15}\)IONa [M+Na]\(^+\): 337.0060, found: 337.0065.
Preparation of Alkyl Bromides

Scheme S3. Alkyl Bromides Employed, Related to Scheme 2

2a-j, 2m and 2u-y are commercially available. 2n, 2p, 2s and 2z are known compounds in the literature (Nicotrat et al., 1990; Zhang et al., 2004; Narayan et al., 2015; Burkhart et al., 2012). 2k, 2l, 2o, 2q, 2r and 2t were prepared according to the following general procedure.
Scheme S4. Preparation of Alkyl Bromides 2k, 2l, 2o, 2q, 2r and 2t, Related to Scheme 2

A mixture of acids (12 mmol, 1.2 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.16 g, 12 mmol, 1.2 equiv), 4-dimethylaminopyridine (0.25g, 2 mmol, 0.2 equiv) and alcohols (10 mmol, 1.0 equiv) in DCM (0.2 M, 50 mL) was stirred at room temperature for 12 hours, before it was quenched by adding water. The aqueous phase was then extracted with DCM (3 × 25 mL). The combined organic phases were washed with water and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with EtOAc–petroleum ether as an eluent to give the corresponding esters.

6-Bromohexyl 3-cyclohexylpropanoate (2k) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a colorless oil (3.02g, 95%). ¹H NMR (500 MHz, Chloroform-d) δ= 4.00 (t, J = 6.6, 2H), 3.34 (t, J = 6.9, 2H), 2.27-2.18 (m, 2H), 1.85-1.76 (m, 2H), 1.67-1.54 (m, 7H), 1.51-1.38 (m, 4H), 1.36-1.28 (m, 2H), 1.22-1.01 (m, 4H), 0.89-0.76 (m, 2H) ppm. ¹³C NMR (126 MHz, Chloroform-d) δ= 173.1, 63.1, 36.2, 32.6, 32.0 (2C), 31.6, 31.4, 30.9, 27.5, 26.8, 25.5, 25.2 (2C), 24.2 ppm. HRMS (ESI): calcd. for C₁₅H₂₇BrO₂Na [M+Na]⁺: 341.1087, found: 341.1082.

6-Bromohexyl 3-oxocyclobutane-1-carboxylate (2l) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 15:1) as a colorless oil (2.62g, 95%). ¹H NMR (500 MHz, Chloroform-d) δ= 4.16 (t, J = 6.7 Hz, 2H), 3.46-3.37 (m, 4H), 3.34-3.16 (m, 3H), 1.87 (dt, J= 8.3, 6.8 Hz, 2H), 1.74-1.62 (m, 2H), 1.56-1.34 (m, 4H) ppm. ¹³C NMR (126 MHz, Chloroform-d) δ= 203.7, 174.1, 65.2, 51.6 (2C), 33.7, 32.5, 28.4, 27.7, 27.4, 25.1 ppm. HRMS (ESI): calcd. for C₁₁H₁₇BrO₂Na [M+Na]⁺: 299.0253, found: 299.0256.

3-Chlorophenyl 6-bromohexanoate (2o) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a colorless oil (2.70g, 90%). ¹H NMR (400 MHz, Chloroform-d) δ= 7.28 (t, J = 8.1 Hz, 1H), 7.23-7.16 (m, 1H), 7.12 (t, J = 2.2 Hz, 1H), 7.02-6.95 (m, 1H), 3.41 (t, J = 6.7 Hz, 2H), 2.55 (t, J = 7.4 Hz, 2H), 1.96-1.84 (m, 2H), 1.79-1.70 (m, 2H), 1.60-1.49 (m, 2H) ppm. ¹³C NMR (101 MHz, Chloroform-d) δ= 171.5, 151.2, 134.6, 130.2, 126.1, 122.3, 120.1, 134.0, 33.6, 32.4, 27.6, 24.0 ppm. HRMS (ESI): calcd. for C₁₂H₁₄BrClO₂Na [M+Na]⁺: 326.9761, found: 326.9761.

Adamantan-2-yl 6-bromohexanoate (2q) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a colorless oil (2.79g, 85%). ¹H NMR (400 MHz, Chloroform-d) δ= 4.90 (t, J = 2.4 Hz, 1H), 3.41 (t, J = 6.8 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 2.04-1.96 (m, 4H), 1.94-1.81 (m, 6H), 1.80-1.72 (m, 4H), 1.71-1.63 (m, 2H), 1.59-1.44 (m, 4H) ppm. ¹³C NMR (101 MHz, Chloroform-d) δ= 172.9, 76.9, 37.4, 36.3 (2C), 34.6, 33.6, 32.5, 31.9 (2C), 31.8 (2C), 27.7, 27.2, 27.0, 24.3 ppm. HRMS (ESI): calcd. for C₁₆H₂₅BrO₂Na [M+Na]⁺: 351.0930, found: 351.0935.
Tert-butyl 4-((6-bromohexanoyl)oxy)piperidine-1-carboxylate (2r) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 10:1) as a white solid (3.39g, 90%). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$= 4.99-4.86 (m, 1H), 3.79-3.65 (m, 2H), 3.48 (t, $J$= 6.7 Hz, 2H), 3.29-3.11 (m, 2H), 2.33 (t, $J$= 7.4 Hz, 2H), 1.99-1.75 (m, 4H), 1.70-1.55 (m, 4H), 1.53-1.47 (m, 2H), 1.46 (s, 9H) ppm. $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$= 172.6, 154.6, 79.5, 69.6, 44.7, 40.9, 34.2, 33.4, 32.3, 30.5, 28.4 (3C), 27.5, 26.2, 24.1 ppm. HRMS (ESI): calcd. for C$_{16}$H$_{29}$BrO$_2$ [M+H]$^+$: 378.1274, found: 378.1283.

(3S,5S,8R,9S,10S,13S,14S)-10,13-Dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl 6-bromohexanoate (2t) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 10:1) as a white solid (3.7g, 80%). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$= 4.70 (tt, $J$= 10.8, 4.6 Hz, 1H), 3.4 (t, $J$= 6.7, 2H), 2.43 (dd, $J$= 19.2, 8.8 Hz, 1H), 2.29 (t, $J$= 7.4 Hz, 2H), 2.06 (dt, $J$= 18.8, 9.0 Hz, 1H), 1.99-1.73 (m, 7H), 1.70-1.57 (m, 4H), 1.59-1.43 (m, 5H), 1.41-1.15 (m, 7H), 1.10-0.92 (m, 2H), 0.86 (s, 6H), 0.72 (td, $J$= 11.1, 3.9 Hz, 1H) ppm. $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$= 73.3, 54.3, 51.3, 47.7, 44.6, 36.7, 35.8, 35.6, 35.0, 34.4, 34.0, 33.6, 32.4, 32.2, 31.5, 30.8, 28.3, 27.6, 27.4, 26.3, 24.2, 21.8, 20.5, 13.8, 12.2 ppm. HRMS (ESI): calcd. for C$_{25}$H$_{39}$BrO$_2$Na [M+Na]$^+$: 489.1975, found: 489.1980.

**Experimental Procedures for Nickel-Catalyzed Asymmetric Domino Ring Opening/Cross-Coupling Reaction**

**Scheme S5. Nickel-Catalyzed Asymmetric Domino Ring Opening/Cross-Coupling Reaction, Related to Scheme 2**

A dry test tube equipped with a stirring bar was charged with NiCl$_2$•glyme (4.4 mg, 0.02 mmol, 10 mol%), ligand L5 (30.2 mg, 0.024 mmol, 12 mol %), Mn (22 mg, 0.4 mmol, 2.0 equiv) and anhydrous 1,3-dimethyl-2-imidazolidinone (1 mL) under N$_2$. The mixture was heated to 40° C, before cyclobutanones 1 (0.2 mmol, 1.0 equiv) and alkyl bromides 2 (0.4 mmol, 2.0 equiv) were added. After stirring for 12 h at 40 °C, the reaction mixture was cooled to room temperature. The mixture was purified through column chromatography on silica gel, affording the corresponding products 3.

(R)-3-Methyl-3-nonyl-2,3-dihydro-1H-inden-1-one (3a) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a yellow oil (45 mg, 83%, 93% ee). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$= 7.70 (d, $J$= 7.7 Hz, 1H), 7.60 (td, $J$= 7.5, 1.3 Hz, 1H), 7.45 (d, $J$= 7.7 Hz, 1H), 7.35 (t, $J$= 7.4 Hz, 1H), 2.67 (d, $J$= 18.8 Hz, 1H), 2.44 (d, $J$= 18.8 Hz, 1H), 1.79-1.57 (m, 2H), 1.40 (s, 3H), 1.30-1.17 (m, 14H), 0.86 (t, $J$ = 6.9 Hz, 3H). $^{13}$C
NMR (101 MHz, Chloroform-d) δ = 206.0, 163.0, 136.0, 134.8, 127.3, 123.8, 123.2, 50.2, 42.3, 42.0, 31.8, 30.0, 29.5, 29.4, 29.3, 28.4, 25.0, 22.6, 14.1 ppm. HRMS (ESI): calcd. for C_{19}H_{20}O [M+H]^+: 273.2213, found: 273.2214. The ee was determined by HPLC analysis (Chiralpak IC column, λ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): t_{R(minor)} = 13.7 min, t_{R(major)} = 15.3 min.

(R)-3-(2-Cyclohexyl)ethyl)-3-methyl-2,3-dihydro-1H-inden-1-one (3b) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a yellow oil (43 mg, 83%, 94% ee). ^1H NMR (400 MHz, Chloroform-d) δ = 7.70 (dt, J = 7.7, 1.1 Hz, 1H), 7.63-7.58 (m, 1H), 7.44 (dt, J = 7.8, 0.9 Hz, 1H), 7.36 (td, J = 7.3, 1.0 Hz, 1H), 2.66 (d, J = 18.9 Hz, 1H), 2.43 (d, J = 18.9 Hz, 1H), 1.79-1.57 (m, 7H), 1.40 (s, 3H), 1.20-1.04 (m, 5H), 0.88-0.72 (m, 3H) ppm. ^13C NMR (101 MHz, Chloroform-d) δ = 206.2, 163.0, 136.0, 134.8, 127.4, 123.8, 123.3, 50.1, 42.3, 42.0, 31.8, (2C), 32.6, 28.5, 26.6, 26.31, 26.30 ppm. HRMS (ESI): calcd. for C_{19}H_{22}ONa [M+Na]^+: 279.1719, found: 279.1711. The ee was determined by HPLC analysis (Chiralpak IC column, λ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): t_{R(minor)} = 15.9 min, t_{R(major)} = 18.4 min.

(R)-3-(6-Fluorohexyl)-3-methyl-2,3-dihydro-1H-inden-1-one (3c) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a yellow oil (39 mg, 79%, 94% ee). ^1H NMR (400 MHz, Chloroform-d) δ = 7.70 (dt, J = 7.6, 1.0 Hz, 1H), 7.61 (td, J = 7.5, 1.2 Hz, 1H), 7.45 (dt, J = 7.8, 0.9 Hz, 1H), 7.37 (td, J = 7.4, 1.0 Hz, 1H), 4.39 (d, J = 47.3, 6.1 Hz, 2H), 2.66 (d, J = 18.8 Hz, 1H), 2.45 (d, J = 18.8 Hz, 1H), 1.82-1.53 (m, 4H), 1.41 (s, 3H), 1.38-1.16 (m, 6H) ppm. ^13C NMR (101 MHz, Chloroform-d) δ = 206.1, 162.8, 136.0, 134.9, 127.4, 123.8, 123.3, 84.1 (d, J = 164.2 Hz), 50.2, 42.2, 42.0, 30.3 (d, J = 19.4 Hz), 29.6, 28.4, 25.0 (d, J = 5.3 Hz), 24.9 ppm. ^19F NMR (471 MHz, Chloroform-d) δ = -218.19 (s, 1F) ppm. HRMS (ESI): calcd. for C_{16}H_{23}FONa [M+Na]^+: 271.1469, found: 271.1473. The ee was determined by HPLC analysis (Chiralpak IC column, λ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): t_{R(minor)} = 32.0 min, t_{R(major)} = 32.6 min.

(R)-3-(7-Chloroheptyl)-3-methyl-2,3-dihydro-1H-inden-1-one (3d) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a yellow oil (45 mg, 81%, 92% ee). ^1H NMR (400 MHz, Chloroform-d) δ = 7.63 (dt, J = 7.6, 1.0 Hz, 1H), 7.54 (td, J = 7.5, 1.2 Hz, 1H), 7.38 (dt, J = 7.8, 0.9 Hz, 1H), 7.29 (td, J = 7.4, 1.0 Hz, 1H), 3.42 (t, J = 6.7 Hz, 2H), 2.59 (d, J = 18.8 Hz, 1H), 2.37 (d, J = 18.8 Hz, 1H), 1.71-1.48 (m, 4H), 1.34 (s, 3H), 1.34-1.22 (m, 2H), 1.21-1.09 (m, 6H) ppm. ^13C NMR (101 MHz, Chloroform-d) δ = 206.2, 162.9, 136.0, 134.9, 127.4, 123.8, 123.3, 50.2, 45.1, 42.2, 42.0, 32.5, 29.8, 28.7, 28.4, 26.8, 24.9 ppm. HRMS (ESI): calcd. for C_{17}H_{25}FClONa [M+Na]^+: 301.1330, found: 301.1327. The ee was determined by HPLC analysis (Chiralpak IC column, λ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): t_{R(minor)} = 29.0 min, t_{R(major)} = 30.2 min.

(R)-3-(7-Hydroxyheptyl)-3-methyl-2,3-dihydro-1H-inden-1-one (3e) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a yellow oil (41 mg, 78%, 90% ee). ^1H NMR (400 MHz, Chloroform-d) δ = 7.70 (dt, J = 7.7, 1.0 Hz, 1H), 7.61 (td, J = 7.5, 1.3 Hz, 1H), 7.45 (dd, J = 7.8, 1.0 Hz, 1H), 7.36 (td, J = 7.5, 1.0 Hz, 1H), 3.60 (t, J = 6.6 Hz, 2H), 2.67 (d, J = 18.8 Hz, 1H), 2.44 (d, J = 18.8 Hz, 1H), 1.81 (s, 1H), 1.77-1.58 (m, 2H), 1.57-1.47 (m, 2H), 1.41 (s, 3H), 1.35-1.16 (m, 6H) ppm. ^13C NMR (101 MHz, Chloroform-d) δ = 206.3, 162.9, 136.0, 134.9, 127.4, 123.8, 123.3, 62.9, 50.2, 42.3, 42.0, 32.7, 30.0, 29.2, 28.4, 25.7, 25.0 ppm. HRMS (ESI): calcd.
for C$_{17}$H$_{24}$O$_2$Na [M+Na]$^+$: 283.1669, found: 283.1666. The ee was determined by HPLC analysis (Chiralpak AD-H column, $\lambda = 254$ nm, hexane/isopropanol = 80/20, flow rate = 0.5 mL/min): $t_R$(minor) = 12.6 min, $t_R$(major) = 11.7 min.

(R)-3-(3-Methoxypropyl)-3-methyl-2,3-dihydro-1H-inden-1-one (3f) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 15:1) as a yellow oil (30 mg, 68%, 90% ee). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ = 7.63 (d, $J$ = 7.7 Hz, 1H), 7.53 (d, $J$ = 7.5 Hz, 1H), 7.40 (d, $J$ = 7.8 Hz, 1H), 7.30 (t, $J$ = 7.5 Hz, 1H), 3.24 (t, $J$ = 6.7 Hz, 2H), 3.20 (s, 3H), 2.60 (d, $J$ = 18.7 Hz, 1H), 2.40 (d, $J$ = 18.8 Hz, 1H), 1.79-1.61 (m, 2H), 1.51-1.38 (m, 2H), 1.36 (s, 3H) ppm. $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ = 204.9, 161.5, 135.0, 133.9, 126.5, 122.8, 122.3, 71.7, 57.5, 49.1, 40.7, 37.6, 27.3, 24.4 ppm. HRMS (ESI): calcd. for C$_{14}$H$_{18}$O$_2$Na [M+Na]$^+$: 241.1199, found: 241.1196. The ee was determined by HPLC analysis (Chiralcel OJ-H column, $\lambda = 254$ nm, hexane/isopropanol = 90/10, flow rate = 0.5 mL/min): $t_R$(minor) = 12.7 min, $t_R$(major) = 12.0 min.

(R)-6-(1-Methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)hexanenitrile (3g) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 10:1) as a yellow oil (34 mg, 71%, 92% ee). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ = 7.62 (d, $J$ = 7.6 Hz, 1H), 7.55 (t, $J$ = 7.5 Hz, 1H), 7.38 (d, $J$ = 7.7 Hz, 1H), 7.30 (t, $J$ = 7.5 Hz, 1H), 2.57 (d, $J$ = 18.8 Hz, 1H), 2.38 (d, $J$ = 18.9 Hz, 1H), 2.20 (t, $J$ = 7.1 Hz, 2H), 1.71-1.54 (m, 2H), 1.73-1.43 (m, 2H), 1.34 (s, 3H), 1.32-1.24 (m, 2H), 1.24-1.09 (m, 2H) ppm. $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ = 205.9, 162.4, 136.0, 135.0, 127.6, 123.8, 123.3, 119.7, 50.1, 41.92, 41.89, 29.0, 28.4, 25.2, 24.3, 17.1 ppm. HRMS (ESI): calcd. for C$_{16}$H$_{19}$NONA [M+Na]$^+$: 264.1359, found: 264.1363. The ee was determined by HPLC analysis (Chiralcel OD-H column, $\lambda = 254$ nm, hexane/isopropanol = 85/15, flow rate = 0.5 mL/min): $t_R$(minor) = 27.6 min, $t_R$(major) = 25.4 min.

(R)-2-(5-(1-Methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)pentyl)isoindoline-1,3-dione (3h) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 3:1) as a yellow oil (60 mg, 84%, 92% ee). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ = 7.87-7.79 (m, 2H), 7.74-7.65 (m, 3H), 7.60 (t, $J$ = 7.5 Hz, 1H), 7.45 (d, $J$ = 7.7 Hz, 1H), 7.35 (t, $J$ = 7.4 Hz, 1H), 3.62 (t, $J$ = 7.1 Hz, 2H), 2.66 (d, $J$ = 18.9 Hz, 1H), 2.45 (d, $J$ = 18.9 Hz, 1H), 1.79-1.54 (m, 4H), 1.40 (s, 3H), 1.36-1.15 (m, 4H) ppm. $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ = 206.0, 168.4 (2C), 162.7, 135.9, 134.9 (2C), 133.9 (2C), 132.1, 127.4, 123.8, 123.3, 123.1 (2C), 50.1, 42.0, 41.9, 37.8, 28.4, 28.3, 27.2, 24.6 ppm. HRMS (ESI): calcd. for C$_{23}$H$_{26}$NO$_3$Na [M+Na]$^+$: 384.1570, found: 384.1571. The ee was determined by HPLC analysis (Chiralpak AD-H column, $\lambda = 254$ nm, hexane/isopropanol = 85/15, flow rate = 0.5 mL/min): $t_R$(minor) = 30.2 min, $t_R$(major) = 31.4 min.

(R)-5-(1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)pentyl acetate (3i) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 10:1) as a yellow oil (38 mg, 70%, 90% ee). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ = 7.63 (d, $J$ = 7.6 Hz, 1H), 7.54 (t, $J$ = 7.5 Hz, 1H), 7.38 (d, $J$ = 7.7 Hz, 1H), 7.31 (t, 1H), 3.92 (t, $J$ = 6.7 Hz, 2H), 2.59 (d, $J$ = 18.9 Hz, 1H), 2.39 (d, $J$ = 18.8 Hz, 1H), 1.95 (s, 3H), 1.73-1.42 (m, 4H), 1.34 (s, 3H), 1.25-1.13 (m, 4H) ppm. $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ = 206.1, 171.2, 162.7, 136.0, 135.0, 127.5, 123.8, 123.4, 64.4, 50.2, 42.2, 42.0, 28.44, 28.39, 26.4, 24.8, 21.0 ppm. HRMS (ESI): calcd. for C$_{19}$H$_{22}$O$_2$Na [M+Na]$^+$: 297.1461, found: 297.1460. The ee was determined by HPLC analysis (Chiralpak IB column, $\lambda = 254$ nm,
hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): t<sub>r</sub>(minor) = 17.8 min, t<sub>r</sub>(major) = 15.1 min.

(R)-7-(1-Methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptyl 3-cyclohexylpropanoate (3j) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 10:1) as a yellow oil (60 mg, 76%, 91% ee). <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ= 7.63 (d, J = 7.7 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 3.94 (t, J = 6.8 Hz, 2H), 2.59 (d, J = 18.8 Hz, 1H), 2.37 (d, J = 18.8 Hz, 1H), 2.22 (t, J = 7.9 Hz, 2H), 1.75-1.39 (m, 13H), 1.34 (s, 3H), 1.24-1.05 (m, 12H) ppm. <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ= 206.2, 174.3, 162.9, 136.0, 134.9, 127.4, 123.8, 123.3, 64.3, 50.2, 42.3, 42.0, 37.2, 33.0 (2C), 32.4, 32.0, 29.9, 29.1, 28.6, 28.4, 26.5, 26.2 (2C), 25.9, 25.0 ppm. HRMS (ESI): calcd. for C<sub>26</sub>H<sub>38</sub>O<sub>3</sub>Na [M+Na]<sup>+</sup>: 421.2713, found: 421.2713. The ee was determined by HPLC analysis (Chiralpak AD-H column, λ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): t<sub>r</sub>(minor) = 19.8 min, t<sub>r</sub>(major) = 18.4 min.

(R)-7-(1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptyl 3-oxocyclobutane-1-carboxylate (3k) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 5:1) as a yellow oil (56 mg, 78%, 94% ee). <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ= 7.76-7.67 (m, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 4.11 (t, J = 6.7 Hz, 2H), 3.46-3.34 (m, 2H), 3.33-3.16 (m, 3H), 2.64 (d, J = 18.8 Hz, 1H), 2.47 (d, J = 18.8 Hz, 1H), 1.79-1.53 (m, 4H), 1.41 (s, 3H), 1.34-1.18 (m, 8H). <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ= 206.1, 203.8, 174.1, 162.8, 136.0, 134.9, 127.4, 123.8, 123.3, 65.4, 51.6 (2C), 50.2, 42.3, 42.0, 29.9, 29.0, 28.5, 28.4, 27.4, 25.8, 24.9 ppm. HRMS (ESI): calcd. for C<sub>23</sub>H<sub>20</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup>: 379.1880, found: 379.1883. The ee was determined by HPLC analysis (Chiralpak AD-H column, λ = 254 nm, hexane/isopropanol = 90/10, flow rate = 0.5 mL/min): t<sub>r</sub>(minor) = 31.7 min, t<sub>r</sub>(major) = 29.3 min.

Methyl (R)-7-(1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3l) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 10:1) as a yellow oil (49 mg, 85%, 89% ee). <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ= 7.70 (dt, J = 7.7, 1.0 Hz, 1H), 7.61 (ddd, J = 7.7, 7.2, 1.2 Hz, 1H), 7.45 (dt, J = 7.7, 0.9 Hz, 1H), 7.37 (td, J = 7.4, 1.0 Hz, 1H), 3.65 (s, 3H), 2.66 (d, J = 18.8 Hz, 1H), 2.45 (d, J = 18.9 Hz, 1H), 2.26 (t, J = 7.5 Hz, 2H), 1.73-1.61 (m, 2H), 1.60-1.52 (m, 2H), 1.41 (s, 3H), 1.31-1.22 (m, 6H) ppm. <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ= 206.1, 174.2, 162.8, 136.0, 134.9, 127.4, 123.8, 123.3, 51.5, 50.2, 42.2, 42.0, 34.0, 29.7, 28.9, 28.4, 24.9, 24.8 ppm. HRMS (ESI): calcd. for C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup>: 311.1616, found: 311.1616. The ee was determined by HPLC analysis (Chiralpak AD-H column, λ = 254 nm, hexane/isopropanol = 90/10, flow rate = 0.5 mL/min): t<sub>r</sub>(minor) = 24.4 min, t<sub>r</sub>(major) = 21.2 min.

Phenyl (R)-7-(1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3m) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 10:1) as a yellow oil (54 mg, 77%, 84% ee). <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ= 7.70 (dt, J = 7.7, 1.0 Hz, 1H), 7.61 (td, J = 7.5, 1.2 Hz, 1H), 7.45 (dt, J = 7.8, 0.9 Hz, 1H), 7.40-7.34 (m, 3H), 7.24-7.19 (m, 1H), 7.08-7.04 (m, 2H), 2.67 (d, J = 18.8 Hz, 1H), 2.51 (t, J = 7.5 Hz, 2H), 2.45 (d, J = 18.8 Hz, 1H), 1.79-1.61 (m, 4H), 1.41 (s, 3H), 1.37-1.26 (m, 6H) ppm. <sup>13</sup>C NMR (126
3-Chlorophenyl (R)-7-(1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3n) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 10:1) as a yellow oil (53 mg, 69%, 94% ee). \(^{1}\)H NMR (400 MHz, Chloroform-d) δ = 7.11 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 8.2 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 2.67 (d, J = 18.9 Hz, 1H), 2.55-2.41 (m, 3H), 1.81-1.60 (m, 4H), 1.41 (s, 3H), 1.38-1.23 (m, 6H) ppm. \(^{13}\)C NMR (101 MHz, Chloroform-d) δ = 206.3, 171.8, 162.8, 151.2, 136.0, 134.6, 130.2, 127.5, 126.1, 123.8, 123.4, 122.3, 120.0, 50.2, 42.2, 42.0, 34.2, 29.7, 28.9, 28.4, 24.9, 24.7 ppm. HRMS (ESI): calcd. for C\(_{23}\)H\(_{23}\)ClO\(_3\)Na [M+Na]: 407.1384, found: 407.1396. The ee was determined by HPLC analysis (Chiralpak AD-H column, λ = 254 nm, hexane/isopropanol = 90/10, flow rate = 0.5 mL/min): t\(_{R}\) (minor) = 24.4 min, t\(_{R}\) (major) = 21.2 min.

2,2,2-Trifluoroethyl (R)-7-(1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3o) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 10:1) as a yellow oil (58 mg, 82%, 89% ee). \(^{1}\)H NMR (400 MHz, Chloroform-d) δ = 7.70 (ddd, J = 7.7, 1.3, 0.8 Hz, 1H), 7.61 (ddd, J = 7.7, 7.1, 1.2 Hz, 1H), 7.45 (dt, J = 7.7, 0.9 Hz, 1H), 7.37 (td, J = 7.5, 1.0 Hz, 1H), 4.45 (q, J = 8.5 Hz, 2H), 2.66 (d, J = 18.8 Hz, 1H), 2.45 (d, J = 18.8 Hz, 1H), 2.37 (t, J = 7.4 Hz, 2H), 1.78-1.52 (m, 4H), 1.41 (s, 3H), 1.33-1.21 (m, 6H) ppm. \(^{13}\)C NMR (101 MHz, Chloroform-d) δ = 206.1, 172.0, 162.8, 136.0, 134.9, 127.4, 123.8, 123.3, 123.0 (q, J = 277.2 Hz), 60.1 (q, J = 36.4 Hz), 50.2, 42.1, 42.0, 33.5, 29.6, 28.7, 28.4, 24.8, 24.5 ppm. \(^{19}\)F NMR (376 MHz, Chloroform-d) δ = -73.85 (s, 3F) ppm. HRMS (ESI): calcd. for C\(_{19}\)H\(_{23}\)F\(_3\)O\(_3\)Na [M+Na]: 379.1492, found: 379.1498. The ee was determined by HPLC analysis (Chiralpak IB column, λ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): t\(_{R}\) (minor) = 16.1 min, t\(_{R}\) (major) = 14.2 min.

Adamantan-2-yl (R)-7-(1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3p) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 15:1) as a yellow oil (60 mg, 73%, 91% ee). \(^{1}\)H NMR (400 MHz, Chloroform-d) δ = 7.70 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 4.91 (d, J = 3.4 Hz, 1H), 2.66 (d, J = 18.9 Hz, 1H), 2.44 (d, J = 18.9 Hz, 1H), 2.28 (t, J = 7.4 Hz, 2H), 2.03-1.94 (m, 5H), 1.85-1.79 (m, 4H), 1.77-1.71 (m, 4H), 1.62-1.53 (m, 6H), 1.40 (s, 3H), 1.31-1.22 (m, 5H) ppm. \(^{13}\)C NMR (101 MHz, Chloroform-d) δ = 206.2, 173.2, 162.9, 136.0, 134.9, 127.4, 123.8, 123.3, 50.2, 42.2, 42.0, 37.4, 36.3 (3C), 34.8, 31.9 (2C), 31.8 (2C), 29.7, 29.0, 28.4, 27.2, 27.0, 25.1, 24.9 ppm. HRMS (ESI): calcd. for C\(_{27}\)H\(_{39}\)O\(_3\)Na [M+Na]: 431.2557, found: 431.2562. The ee was determined by HPLC analysis (Chiralpak IB column, λ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): t\(_{R}\) (minor) = 14.8 min, t\(_{R}\) (major) = 13.2 min.
Tert-butyl (R)-4-((7-(1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoyl)oxy)piperidine-1-carboxylate (3q) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 10:1) as a yellow oil (73mg, 85%, 94% ee). $^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.70 (dd, $J$ = 7.7 Hz, 1H), 7.61 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.45 (dd, $J$ = 7.8, 1.0 Hz, 1H), 7.37 (td, $J$ = 7.4, 0.9 Hz, 1H), 4.98-4.86 (m, 1H), 3.75-3.63 (m, 2H), 3.27-3.16 (m, 2H), 2.66 (d, $J$ = 18.8 Hz, 1H), 2.45 (d, $J$ = 18.8 Hz, 1H), 2.25 (t, $J$ = 7.5 Hz, 2H), 1.86-1.77 (m, 3H), 1.62-1.55 (m, 5H), 1.46 (s, 9H), 1.41 (s, 3H), 1.29-1.26 (m, 6H) ppm. $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ (mixture of two rotamers) = 206.1, 173.0, 162.8, 154.7, 136.0, 134.9, 127.4, 123.8, 123.3, 79.7, 69.5, 50.2, 42.2, 42.0, 41.0, 34.6, 34.5, 30.6, 29.4, 29.2, 29.1, 28.9, 28.4, 25.0, 24.9 ppm. HRMS (ESI): calcd. for C$_{27}$H$_{39}$NO$_3$Na [M+Na]$^+$: 480.2720, found: 480.2726. The ee was determined by HPLC analysis (Chiralpak AD-H column, $\lambda$ = 254 nm, hexane/isopropanol = 90/10, flow rate = 0.5 mL/min): $t_R$(minor) = 28.7 min, $t_R$(major) = 23.3 min.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 7-((R)-1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3r) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 10:1) as a yellow oil (66mg, 80%, 93% de). $^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.70 (d, $J$ = 7.6 Hz, 1H), 7.61 (td, $J$ = 7.5, 1.3 Hz, 1H), 7.45 (d, $J$ = 7.7 Hz, 1H), 7.36 (t, $J$ = 7.4 Hz, 1H), 4.66 (td, $J$ = 10.9, 4.4 Hz, 1H), 2.66 (d, $J$ = 18.8 Hz, 1H), 2.45 (d, $J$ = 18.8 Hz, 1H), 2.23 (t, $J$ = 7.4 Hz, 2H), 2.02-1.91 (m, 1H), 1.89-1.76 (m, 1H), 1.76-1.61 (m, 5H), 1.60-1.49 (m, 3H), 1.40 (s, 3H), 1.38-1.29 (m, 2H), 1.26-1.20 (m, 5H), 1.12-0.97 (m, 2H), 0.89 (d, $J$ = 6.6 Hz, 3H), 0.87 (d, $J$ = 7.7 Hz, 3H), 0.73 (d, $J$ = 6.9 Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ = 203.6, 170.8, 160.3, 133.5, 132.3, 124.9, 121.3, 120.8, 71.4, 47.7, 44.5, 39.7, 39.4, 38.4, 32.1, 31.7, 28.8, 27.2, 26.4, 25.8, 23.7, 22.5, 22.4, 20.9, 19.5, 18.2, 13.8 ppm. HRMS (ESI): calcd. for C$_{27}$H$_{40}$O$_3$Na [M+Na]$^+$: 435.2870, found: 435.2769. The de was determined by HPLC analysis (Chiralpak AD-H column, $\lambda$ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): $t_R$(minor) = 21.2 min, $t_R$(major) = 19.0 min.

(3S,5S,8R,9S,10S,13S,14S)-10,13-Dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl 7-((R)-1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3s) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 5:1) as a yellow oil (78mg, 71%, 94% de). $^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.62 (dd, $J$ = 7.8, 1.1 Hz, 1H), 7.54 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.38 (d, $J$ = 7.7 Hz, 1H), 7.29 (t, $J$ = 7.4 Hz, 1H), 4.67-4.52 (m, 1H), 2.59 (d, $J$ = 18.8 Hz, 1H), 2.37 (d, $J$ = 18.8 Hz, 1H), 2.31 (t, $J$ = 17.1 Hz, 1H), 2.14 (t, $J$ = 7.5 Hz, 2H), 2.06-1.93 (m, 1H), 1.91-1.80 (m, 1H), 1.78-1.36 (m, 15H), 1.33 (s, 3H), 1.29-1.08 (m, 14H), 0.78 (s, 3H), 0.77 (s, 3H) ppm. $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ = 221.3, 206.2, 173.3, 162.9, 136.0, 134.9, 127.4, 123.8, 123.3, 73.2, 54.3, 51.4, 50.2, 47.8, 44.6, 42.2, 42.0, 36.7, 35.9, 35.7, 35.0, 34.6, 34.0, 31.5, 30.8, 29.7, 28.9, 28.4, 28.3, 27.5, 25.0, 24.9, 21.8, 20.5, 13.8, 12.2 ppm. HRMS (ESI): calcd. for C$_{36}$H$_{50}$O$_4$Na [M+Na]$^+$: 569.3601, found: 569.3600. The de was determined by HPLC analysis (Chiralpak IB column, $\lambda$ = 254 nm, hexane/isopropanol = 85/15, flow rate = 0.5 mL/min): $t_R$(minor) = 25.7 min, $t_R$(major) = 22.1 min.
(R)-3-(2-Butylhexyl)-3-methyl-2,3-dihydro-1H-inden-1-one (3t) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a yellow oil (31mg, 68%, 84% ee). 1H NMR (400 MHz, Chloroform-d) δ = 7.70 (dt, J = 7.7, 1.1 Hz, 1H), 7.60 (dd, J = 7.8, 7.2, 1.3 Hz, 1H), 7.48 (dt, J = 7.8 Hz, 1H), 7.36 (dd, J = 8.1, 7.2, 1.0 Hz, 1H), 7.24 (d, J = 18.9 Hz, 1H), 2.47 (d, J = 18.9 Hz, 1H), 1.70 (dd, J = 14.1, 4.3 Hz, 1H), 1.64-1.47 (m, 6H), 1.39 (s, 3H), 1.23-1.11 (m, 2H), 1.11-0.94 (m, 3H), 0.87-0.69 (m, 1H) ppm. 13C NMR (101 MHz, Chloroform-d) δ = 206.4, 163.6, 135.8, 134.7, 127.4, 127.4, 124.1, 123.3, 50.7, 49.4, 42.0, 35.6, 34.9, 34.6, 29.3, 26.3, 26.2, 26.1 ppm. HRMS (ESI): calcd. for C16H19ONa [M+Na]+: 265.1406, found: 265.1410. The ee was determined by HPLC analysis (Chiralpak IC column, λ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): tr(minor) = 17.4 min, tr(major) = 19.7 min.

(R)-3-(Cyclopentylmethyl)-3-methyl-2,3-dihydro-1H-inden-1-one (3u) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) as a yellow oil (31mg, 68%, 84% ee). 1H NMR (400 MHz, Chloroform-d) δ = 7.70 (dt, J = 7.7, 1.1 Hz, 1H), 7.60 (dd, J = 7.8, 7.2, 1.3 Hz, 1H), 7.48 (dt, J = 7.8 Hz, 1H), 7.36 (dd, J = 8.1, 7.2, 1.0 Hz, 1H), 7.24 (d, J = 18.9 Hz, 1H), 2.47 (d, J = 18.9 Hz, 1H), 1.70 (dd, J = 14.1, 4.3 Hz, 1H), 1.64-1.47 (m, 6H), 1.39 (s, 3H), 1.23-1.11 (m, 2H), 1.11-0.94 (m, 3H), 0.87-0.69 (m, 1H) ppm. 13C NMR (101 MHz, Chloroform-d) δ = 206.4, 163.6, 135.8, 134.7, 127.4, 127.4, 124.1, 123.3, 50.7, 49.4, 42.0, 35.6, 34.9, 34.6, 29.3, 26.3, 26.2, 26.1 ppm. HRMS (ESI): calcd. for C16H20ONa [M+Na]+: 265.1563, found: 265.1566. The ee was determined by HPLC analysis (Chiralpak IC column, λ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): tr(minor) = 15.9 min, tr(major) = 18.0 min.

(R)-3-Methyl-3-((tetrahydro-2-pyran-4-yl)methyl)-2,3-dihydro-1H-inden-1-one (3w) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 5:1) as a yellow oil (40mg, 83%, 91% ee). 1H NMR (500 MHz, Chloroform-d) δ = 7.71 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.1 Hz, 1H), 3.94-3.61 (m, 2H), 3.36-3.09 (m, 2H), 2.73 (d, J = 18.9 Hz, 1H), 2.50 (d, J = 18.9 Hz, 1H), 1.77 (dd, J = 14.3, 4.1 Hz, 1H), 1.67 (dd, J = 14.2, 6.7 Hz, 1H), 1.54-1.46 (m, 1H), 1.42 (s, 3H), 1.41-1.32 (m, 2H), 1.17-1.05 (m, 1H), 1.03-0.95 (m, 1H) ppm. 13C NMR (126 MHz, Chloroform-d) δ = 205.9, 162.9, 135.9, 134.9, 127.6, 124.1, 123.4, 67.9, 67.7, 50.6, 49.0, 41.8, 34.9, 34.3, 32.3, 29.6 ppm. HRMS (ESI): calcd. for C16H20O2Na [M+Na]+: 267.1356, found: 267.1355. The ee was determined by HPLC analysis (Chiralpak IB column, λ = 254 nm, hexane/isopropanol = 85/15, flow rate = 0.5 mL/min): tr(minor) = 12.7 min, tr(major) = 13.8 min.
(R)-3-(Adamantan-2-ylmethyl)-3-methyl-2,3-dihydro-1H-inden-1-one (3x) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 5:1) as a yellow oil (35mg, 59%, 92% ee). $^1$H NMR (400 MHz, Chloroform-d) $\delta$= 7.71 (dt, $J$= 7.6, 1.0 Hz, 1H), 7.60 (td, $J$= 7.5, 1.3 Hz, 1H), 7.48 (dd, $J$= 7.8, 1.0 Hz, 1H), 7.36 (td, $J$= 7.4, 1.1 Hz, 1H), 2.66 (d, $J$= 18.9 Hz, 1H), 2.45 (d, $J$= 18.9 Hz, 1H), 1.88-1.72 (m, 8H), 1.68-1.50 (m, 9H), 1.41 (s, 3H) ppm. $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$= 206.4, 163.2, 136.1, 134.7, 127.4, 124.0, 123.3, 50.1, 45.5, 42.6, 41.3, 39.03, 38.95, 38.0, 34.4, 33.2, 32.0, 31.8, 28.8, 27.5 (2C). HRMS (ESI): calcd. for C$_{21}$H$_{29}$ONa [M+Na]+: 317.1876, found: 317.1875. The ee was determined by HPLC analysis (Chiralpak IC column, $\lambda$ = 254 nm, hexane/isopropanol = 95/5, flow rate = 0.5 mL/min): $t_{R}(\text{minor})$ = 15.9 min, $t_{R}(\text{major})$ = 18.1 min.

Methyl (R)-7-(1-ethyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3y) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 5:1) as a yellow oil (43mg, 71%, 87% ee). $^1$H NMR (400 MHz, Chloroform-d) $\delta$= 7.70 (ddd, $J$= 7.6, 1.3, 0.7 Hz, 1H), 7.60 (ddd, $J$= 7.8, 7.2, 1.3 Hz, 1H), 7.40 (dt, $J$= 7.8, 0.9 Hz, 1H), 7.36 (ddd, $J$= 7.7, 7.2, 1.0 Hz, 1H), 3.65 (s, 3H), 2.52 (s, 2H), 2.25 (t, $J$= 7.5 Hz, 2H), 1.84-1.65 (m, 3H), 1.59-1.47 (m, 2H), 1.31-1.17 (m, 6H), 0.97-0.82 (m, 1H), 0.70 (t, $J$= 7.4 Hz, 3H) ppm. $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$= 206.4, 174.2, 161.2, 137.1, 134.7, 127.4, 124.2, 123.3, 51.5, 47.0, 46.0, 40.4, 34.0, 33.2, 29.8, 29.0, 24.9, 24.5, 8.9 ppm. HRMS (ESI): calcd. for C$_{19}$H$_{26}$O$_3$Na [M+Na]+: 325.1774, found: 325.1777. The ee was determined by HPLC analysis (Chiralpak IB column, $\lambda$ = 254 nm, hexane/isopropanol = 90/10, flow rate = 0.5 mL/min): $t_{R}(\text{minor})$ = 12.8 min, $t_{R}(\text{major})$ = 11.7 min.

(R)-3-Ethyl-3-((tetrahydro-2H-pyran-4-yl)methyl)-2,3-dihydro-1H-inden-1-one (3z) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 5:1) as a yellow oil (38mg, 74%, 85% ee). $^1$H NMR (400 MHz, Chloroform-d) $\delta$= 7.71 (dt, $J$= 7.6, 1.1 Hz, 1H), 7.61 (td, $J$= 7.5, 1.3 Hz, 1H), 7.44 (dd, $J$= 7.8, 0.9 Hz, 1H), 7.38 (td, $J$= 7.5, 1.0 Hz, 1H), 3.91-3.65 (m, 2H), 3.35-3.03 (m, 2H), 2.58 (s, 2H), 1.86-1.61 (m, 4H), 1.51-1.31 (m, 3H), 1.18-1.03 (m, 1H), 1.00-0.90 (m, 1H), 0.66 (t, $J$= 7.4 Hz, 3H) ppm. $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$= 206.1, 161.1, 137.0, 134.8, 127.6, 124.4, 123.4, 67.9, 67.7, 47.6, 47.2, 45.7, 35.0, 34.5, 34.2, 31.9, 8.7 ppm. HRMS (ESI): calcd. for C$_{19}$H$_{26}$O$_2$Na [M+Na]+: 281.1512, found: 285.1516. The ee was determined by HPLC analysis (Chiralpak IB column, $\lambda$ = 254 nm, hexane/isopropanol = 85/15, flow rate = 0.5 mL/min): $t_{R}(\text{minor})$ = 11.6 min, $t_{R}(\text{major})$ = 12.4 min.

(R)-7-(3-Oxo-1-propyl-2,3-dihydro-1H-inden-1-yl)heptyl acetate (3aa) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 5:1) as a yellow oil (42mg, 64%, 93% ee). $^1$H NMR (500 MHz, Chloroform-d) $\delta$= 7.70 (d, $J$= 7.6 Hz, 1H), 7.60 (t, $J$= 7.5 Hz, 1H), 7.42 (d, $J$= 7.7 Hz, 1H), 7.36 (t, $J$= 7.4 Hz, 1H), 4.02 (t, $J$= 6.8 Hz, 2H), 2.54 (s, 2H), 2.03 (s, 3H), 1.81-1.50 (m, 7H), 1.30-1.14 (m, 7H), 0.97-0.87 (m, 2H), 0.84 (t, $J$= 7.0 Hz, 3H) ppm. $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$= 206.4, 171.2, 161.6, 136.9, 134.7, 127.4, 124.1, 123.3, 64.5, 47.6, 45.7, 43.2, 40.8, 30.0, 29.0, 28.5, 25.8, 24.5, 21.0, 17.9, 14.6. HRMS (ESI): calcd. for C$_{21}$H$_{26}$O$_3$Na [M+Na]+: 353.2087, found: 353.2083. The ee was determined by HPLC analysis (Chiralcel OJ-H column, $\lambda$ = 254 nm, hexane/isopropanol = 95/5, flow rate = 1.0 mL/min): $t_{R}(\text{minor})$ = 9.8 min, $t_{R}(\text{major})$ = 10.8 min.
Methyl (R)-7-(1,6-dimethyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3ab) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 5:1) as a yellow oil (50mg, 84%, 90% ee). $^1$H NMR (500 MHz, Chloroform-d) $\delta$= 7.49 (s, 1H), 7.43 (dd, $J$= 7.9, 1.7 Hz, 1H), 7.33 (d, $J$= 7.8 Hz, 1H), 3.65 (s, 3H), 2.64 (d, $J$= 18.8 Hz, 1H), 2.43 (d, $J$= 18.8 Hz, 1H), 2.40 (s, 3H), 2.26 (t, $J$= 7.5 Hz, 2H), 1.79-1.48 (m, 5H), 1.38 (s, 3H), 1.30-1.17 (m, 5H) ppm. $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$= 206.2, 174.2, 160.3, 137.3, 136.2, 136.1, 123.5, 123.2, 51.5, 50.5, 42.2, 41.6, 34.0, 29.7, 29.0, 28.5, 24.9, 21.1 ppm. HRMS (ESI): calcd. for C$_{19}$H$_{26}$O$_2$Na [M+Na]$^+$: 325.1774, found: 325.1776. The $ee$ was determined by HPLC analysis (Chiralpak IB column, $\lambda$ = 254 nm, hexane/isopropanol = 92.5/7.5, flow rate = 0.4 mL/min): $t_{R}$(minor) = 16.2 min, $t_{R}$(major) = 15.3 min.

Methyl (R)-7-(1,5-dimethyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3ac) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 5:1) as a yellow oil (47mg, 79%, 89% ee). $^1$H NMR (500 MHz, Chloroform-d) $\delta$= 7.59 (d, $J$= 7.8 Hz, 1H), 7.23 (s, 1H), 7.17 (dd, $J$= 7.7, 1.4 Hz, 1H), 3.65 (s, 3H), 2.64 (d, $J$= 18.7 Hz, 1H), 2.46 (s, 3H), 2.42 (d, $J$= 18.7 Hz, 1H), 2.26 (t, $J$= 7.5 Hz, 2H), 1.78-1.52 (m, 5H), 1.38 (s, 3H), 1.34-1.14 (m, 5H) ppm. $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$= 205.6, 174.2, 163.4, 146.0, 133.8, 128.7, 124.1, 123.2, 51.5, 50.4, 42.2, 41.8, 34.0, 29.7, 29.0, 28.4, 24.88, 24.85, 22.3 ppm. HRMS (ESI): calcd. for C$_{19}$H$_{26}$O$_2$Na [M+Na]$^+$: 325.1774, found: 325.1773. The $ee$ was determined by HPLC analysis (Chiralpak IB column, $\lambda$ = 254 nm, hexane/isopropanol = 92.5/7.5, flow rate = 0.4 mL/min): $t_{R}$(minor) = 17.5 min, $t_{R}$(major) = 15.6 min.

Methyl (R)-7-(5,6-dimethoxy-1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3ad) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 3:1) as a yellow oil (48mg, 69%, 78% ee). $^1$H NMR (400 MHz, Chloroform-d) $\delta$= 7.13 (s, 1H), 6.82 (s, 1H), 4.00 (s, 3H), 3.91 (s, 3H), 3.65 (s, 3H), 2.63 (d, $J$= 18.7 Hz, 1H), 2.42 (d, $J$= 18.7 Hz, 1H), 2.27 (t, $J$= 7.5 Hz, 2H), 1.78-1.51 (m, 5H), 1.39 (s, 3H), 1.30-1.20 (m, 5H) ppm. $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$= 204.5, 174.2, 158.1, 155.6, 149.4, 128.9, 104.5, 103.7, 56.2, 56.1, 51.4, 50.1, 42.0, 41.6, 33.9, 29.6, 28.9, 28.4, 24.84, 24.80 ppm. HRMS (ESI): calcd. for C$_{20}$H$_{28}$O$_3$Na [M+Na]$^+$: 371.1829, found: 370.1833. The $ee$ was determined by HPLC analysis (Chiralpak AD-H column, $\lambda$ = 254 nm, hexane/isopropanol = 80/20, flow rate = 0.5 mL/min): $t_{R}$(minor) = 17.1 min, $t_{R}$(major) = 19.9 min.

Methyl (R)-7-(6-methoxy-1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptanoate (3ae) was isolated through column chromatography on silica gel (petroleum ether: EtOAc= 5:1) as a yellow oil (48mg, 70%, 84% ee). $^1$H NMR (400 MHz, Chloroform-d) $\delta$= 7.34 (dd, $J$= 8.4, 0.6 Hz, 1H), 7.20 (dd, $J$= 8.4, 2.6 Hz, 1H), 7.13 (dd, $J$= 2.6, 0.6 Hz, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 2.67 (d, $J$= 18.8 Hz, 1H), 2.46 (d, $J$= 18.8 Hz, 1H), 2.26 (t, $J$= 7.5 Hz, 2H), 1.76-1.49 (m, 4H), 1.38 (s, 3H), 1.31-1.12 (m, 6H) ppm. $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$= 205.9, 174.1, 159.4, 155.7, 137.2, 124.6, 124.1, 104.4, 55.6, 51.4, 50.7, 42.2, 41.4, 33.9, 29.6, 28.9, 28.4, 24.9, 24.8 ppm. HRMS (ESI): calcd. for C$_{19}$H$_{26}$O$_2$Na [M+Na]$^+$: 341.1723, found: 341.1726. The $ee$ was determined by HPLC analysis (Chiralpak IB column, $\lambda$ = 254 nm, hexane/isopropanol = 80/20, flow rate = 0.5 mL/min): $t_{R}$(minor) = 10.8 min, $t_{R}$(major) = 10.3 min.
(R)-7-(6-fluoro-1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptyl acetate (3af) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 5:1) as a yellow oil (49 mg, 76%, 93% ee). 1H NMR (500 MHz, Chloroform-d) δ = 7.45-7.38 (m, 1H), 7.36-7.30 (m, 2H), 4.02 (t, J = 6.5 Hz, 2H), 2.70 (d, J = 18.9 Hz, 1H), 2.49 (d, J = 18.9 Hz, 1H), 2.04 (s, 3H), 1.76-1.51 (m, 5H), 1.40 (s, 3H), 1.33-1.13 (m, 7H) ppm. 13C NMR (126 MHz, Chloroform-d) δ = 204.9, 171.2, 162.3 (d, J = 247.8 Hz), 158.3 (d, J = 8.0 Hz), 122.5 (d, J = 23.8 Hz), 109.1 (d, J = 21.6 Hz), 64.5, 50.6, 42.3, 41.7, 29.9, 29.0, 28.5, 28.46, 25.8, 25.0, 21.0 ppm. 19F NMR (471 MHz, Chloroform-d) δ = -114.7 (s, 1F) ppm. HRMS (ESI): calcd. for C_{19}H_{25}FO_3Na [M+Na]^+: 343.1680, found: 343.1675. The ee was determined by HPLC analysis (Chiralpak AD-H column, λ = 254 nm, hexane/isopropanol = 97/3, flow rate = 0.5 mL/min): t_R(minor) = 22.2 min, t_R(major) = 23.1 min.

(R)-7-(6-chloro-1-methyl-3-oxo-2,3-dihydro-1H-inden-1-yl)heptyl acetate (3ag) was isolated through column chromatography on silica gel (petroleum ether: EtOAc = 5:1) as a yellow oil (49 mg, 73%, 93% ee). 1H NMR (500 MHz, Chloroform-d) δ = 7.65 (s, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 4.02 (td, J = 6.8, 1.4 Hz, 2H), 2.68 (d, J = 18.9 Hz, 1H), 2.47 (d, J = 18.9 Hz, 1H), 2.04 (s, 3H), 1.74-1.52 (m, 5H), 1.40 (s, 3H), 1.36-1.18 (m, 7H). 13C NMR (126 MHz, Chloroform-d) δ = 204.6, 171.2, 160.9, 137.6, 134.9, 133.8, 125.2, 123.2, 64.5, 50.4, 42.2, 41.9, 29.9, 29.0, 28.5, 28.3, 25.8, 25.0, 21.0 ppm. HRMS (ESI): calcd. for C_{19}H_{25}ClO_3Na [M+Na]^+: 359.1384, found: 359.1386. The ee was determined by HPLC analysis (Chiralpak AD-H column, λ = 254 nm, hexane/isopropanol = 97/3, flow rate = 0.5 mL/min): t_R(minor) = 23.7 min, t_R(major) = 25.3 min.

Scheme S6. Procedure for the 10-mmol-Scale Reaction for the Synthesis of 3i, Related to Scheme 2

A dry flask equipped with a stirring bar was charged with NiCl_2·glyme (220 mg, 1.0 mmol, 10 mol%), ligand L5 (1.51 g, 1.2 mmol, 12 mol%), Mn (1.10 g, 20 mmol, 2.0 equiv) and anhydrous 1,3-dimethyl-2-imidazolidinone (50 mL) under N_2. The mixture was heated to 40°C, before the cyclobutanone 1a (2.86 g, 10 mmol, 1.0 equiv) and the alkyl bromides 2i (3.90 g, 20 mmol, 2.0 equiv) were added. After stirring for 12 h at 40°C, the reaction mixture was cooled to room temperature and quenched by adding water. The aqueous phase were extracted by EtOAc 3 times, and the combined organic phases were washed with brine, dried out over MgSO_4, filtered and removed under reduced pressure. The residue was purified through column chromatography on silica gel (petroleum ether: EtOAc = 10:1), affording the corresponding product 3i as a yellow oil (2.02 g, 74%, 90%ee).
Control Experiments

Scheme S7. Stoichiometric Reaction of 1a with Ni(COD)₂, Related to Scheme 4

A dry test tube equipped with a stirring bar was charged with Ni(COD)₂ (55 mg, 0.2 mmol, 1.0 equiv), ligand L₅ (250 mg, 0.2 mmol, 1.0 equiv), and anhydrous 1,3-dimethyl-2-imidazolidinone (1 mL) under N₂. The mixture was heated to 40 °C, and then the cyclobutanone 1a (57 mg, 0.2 mmol, 1.0 equiv) was added. After stirring for 3 h at 40 °C, the reaction mixture was cooled to room temperature and then quenched with H₂O. The aqueous phase was then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) affording 3-methyl-3-phenylcyclobut-1-ene (10) as a yellow oil (28 mg, 89%). ¹H NMR (400 MHz, Chloroform-d) δ= 7.29-7.16 (m, 4H), 7.16-7.08 (m, 1H), 3.38-3.27 (m, 2H), 3.04-2.90 (m, 2H), 1.48 (s, 3H) ppm. ¹³C NMR (126 MHz, Chloroform-d) δ= 206.7, 148.3, 128.6 (2C), 126.3, 125.7 (2C), 59.3 (2C), 34.0, 31.1 ppm.

Scheme S8. Stoichiometric Reaction of 1a with Ni(COD)₂ in the Presence of MnI₂, Related to Scheme 4

A dry test tube equipped with a stirring bar was charged with Ni(COD)₂ (55 mg, 0.2 mmol, 1.0 equiv), ligand L₅ (250 mg, 0.2 mmol, 1.0 equiv), MnI₂ (62 mg, 0.2 mmol, 1.0 equiv) and anhydrous 1,3-dimethyl-2-imidazolidinone (1 mL) under N₂. The mixture was heated to 40 °C, and then the cyclobutanone 1a (57 mg, 0.2 mmol, 1.0 equiv) was added. After stirring for 3 h at 40 °C, the reaction mixture was cooled to room temperature and then quenched with H₂O. The aqueous phase was then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified through column chromatography on silica gel (petroleum ether: EtOAc= 25:1) affording 3-methyl-3-phenylcyclobut-1-ene (10) as a yellow oil (26 mg, 83%).

Scheme S9. Stoichiometric Reaction of 1a with Ni(COD)₂ in the Presence of Mn, Related to Scheme 4

A dry test tube equipped with a stirring bar was charged with Ni(COD)₂ (55 mg, 0.2 mmol, 1.0 equiv), ligand
L5 (250 mg, 0.2 mmol, 1.0 equiv), Mn (22 mg, 0.4 mmol, 2.0 equiv) and anhydrous 1,3-dimethyl-2-imidazolidinone (1 mL) under N₂. The mixture was heated to 40 °C, and then the cyclobutane 1a (57 mg, 0.2 mmol, 1.0 equiv) was added. After stirring for 3 h at 40 °C, the reaction mixture was cooled to room temperature, and then quenched with H₂O. The aqueous phase was then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified through column chromatography on silica gel (petroleum ether: EtOAc=25:1) affording 3,3-dimethyl-2,3-dihydro-1H-inden-1-one (9) as a yellow oil (27 mg, 84%). ¹H NMR (500 MHz, Chloroform-d) δ= 7.70 (dt, J = 7.7, 1.0 Hz, 1H), 7.62 (td, J = 7.5, 1.2 Hz, 1H), 7.51 (dd, J = 7.8, 0.9 Hz, 1H), 7.37 (td, J = 7.5, 1.0 Hz, 1H), 2.60 (s, 2H), 1.43 (s, 6H) ppm. ¹³C NMR (126 MHz, Chloroform-d) δ= 206.0, 163.9, 135.3, 135.0, 127.4, 123.5, 123.4, 53.0, 38.6, 30.0 (2C).

Scheme S10. Stoichiometric Reaction of 16 with Ni(COD)₂ in the Presence of Mn, Related to Scheme 4

A dry test tube equipped with a stirring bar was charged with Ni(COD)₂ (55 mg, 0.2 mmol, 1.0 equiv), ligand L5 (250 mg, 0.2 mmol, 1.0 equiv), Mn (22 mg, 0.4 mmol, 2.0 equiv) and anhydrous 1,3-dimethyl-2-imidazolidinone (1 mL) under N₂. The mixture was heated to 40°C, before the 4-(2-iodophenyl)butan-2-one (16) (55 mg, 0.2 mmol, 1.0 equiv) was added. After stirring for 3 h at 40 °C, the reaction mixture was cooled to room temperature. The mixture was purified through column chromatography on silica gel (petroleum ether: EtOAc=5:1) affording 3-(3-oxobutyl)benzene-1-ylium (18) as a yellow oil (23 mg, 78%). ¹H NMR (500 MHz, Chloroform-d) δ= 7.27 (dd, J = 8.6, 6.6 Hz, 2H), 7.20-7.15 (m, 3H), 2.88 (t, J = 7.7 Hz, 2H), 2.75 (dd, J = 8.4, 6.9 Hz, 2H), 2.12 (s, 3H) ppm. ¹³C NMR (126 MHz, Chloroform-d) δ= 208.1, 141.0, 128.6 (2C), 128.4, 126.2 (2C), 45.2, 30.2, 29.7 ppm.

Scheme S11. Sequential Stoichiometric Reaction, Related to Scheme 4

A dry test tube equipped with a stirring bar was charged with Ni(COD)₂ (55 mg, 0.2 mmol, 1.0 equiv), ligand L5 (250 mg, 0.2 mmol, 1.0 equiv), Mn (22 mg, 0.4 mmol, 2.0 equiv) and anhydrous 1,3-dimethyl-2-imidazolidinone (1 mL) under N₂. The mixture was heated to 40 °C, and then the cyclobutane 1a (57 mg, 0.2 mmol, 1.0 equiv) was added. After stirring for 3 h at 40 °C, n-octyl bromide 2a (77 mg, 0.4 mmol, 2.0 equiv) was added to the reaction mixture. The mixture was stirred for 12h at 40 °C and then quenched with H₂O. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified through column chromatography on silica gel (petroleum ether: EtOAc=25:1) affording 3a as a yellow oil (26 mg, 48%).
Scheme S12. Radical Clock Experiment, Related to Scheme 4

![Chemical structure](image)

A dry test tube equipped with a stirring bar was charged with NiCl₂(dme) (4.4 mg, 0.02 mmol, 10 mol %), ligand L₅ (30.1 mg, 0.024 mmol, 12 mol %), Mn (22 mg, 0.4 mmol, 2 equiv) and anhydrous 1,3-dimethyl-2-imidazolidinone (1 mL) under N₂. The mixture was heated to 40°C, before the cycloketone 1a (57 mg, 0.2 mmol, 1 equiv) and the alkyl bromide 2z (130 mg, 0.4 mmol, 2 equiv) were added. After stirring for 12 h at 40°C, the reaction mixture was cooled to room temperature. The mixture was purified through column chromatography on silica gel (petroleum ether: EtOAc = 5:1) affording 3ah as a yellow oil (56 mg, 73%).

**1H NMR (400 MHz, Chloroform-d)** δ = 7.70 (dt, J = 7.6, 1.0 Hz, 1H), 7.66-7.57 (m, 1H), 7.48-7.40 (m, 1H), 7.37 (td, J = 7.4, 0.9 Hz, 1H), 4.21-4.09 (m, 4H), 2.65 (d, J = 18.9 Hz, 1H), 2.44 (d, J = 18.9 Hz, 1H), 2.43-2.33 (m, 1H), 2.31-2.19 (m, 1H), 2.13-2.04 (m, 1H), 1.88-1.52 (m, 6H), 1.40 (s, 3H), 1.31-1.13 (m, 8H) ppm.

**13C NMR (101 MHz, Chloroform-d)** δ (mixture of two diastereomers) = 205.9, 172.64, 172.58, 162.62, 162.57, 136.0, 134.9, 127.5, 123.8, 123.7, 123.3, 61.3, 59.87, 59.85, 50.1, 50.0, 41.9, 41.1, 41.0, 40.60, 40.58, 40.1, 40.0, 33.63, 33.61, 32.0, 30.49, 30.48, 28.41, 28.43, 14.0 ppm. HRMS (ESI): calcd. for C₂₃H₃₀O₅Na [M+Na]⁺: 409.1958, found: 409.1988.

**Derivatization of the Cross-Coupling Product**

Scheme S13. Clemmensen Reduction of the Indanone 3i, Related to Scheme 3

5 g of zinc powder was washed with HCl (6 M in water, 2 × 4.45 mL). Then HgCl₂ (214.5 mg, 0.79 mmol, 4.0 equiv), water (3.4 mL), and concentrated HCl (0.6 mL) were added to the washed Zn dust, and the resulting mixture was stirred vigorously for 1 h at room temperature. To this mixture was added the indanone 3i (55 mg, 0.2 mmol, 1.0 equiv) in toluene (2.0 mL) followed by addition of concentrated HCl (3.2 mL). After stirring overnight at room temperature, it was filtered through a pad of Celite to remove the solid and washed with EtOAc. The organic layer was sperated, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether) to (R)-5-((1-methyl-2,3-dihydro-1H-inden-1-yl)pentyl acetate (4) afford as a colorless oil (50 mg, 96%, 91% ee). **1H NMR: (400 MHz, Chloroform-d)** δ = 7.23-7.00 (m, 4H), 4.02 (t, J = 6.7 Hz, 2H), 2.96-2.79 (m, 2H), 2.10-1.94 (m, 1H), 2.03 (s, 3H), 1.87-1.76 (m, 1H), 1.66-1.54 (m, 3H), 1.53-1.42 (m, 1H), 1.39-1.15 (m, 4H), 1.23 (s, 3H) ppm. **13CNMR (101 MHz, Chloroform-d)** δ = 171.3, 151.5, 143.2, 126.2, 126.1, 124.5, 122.6, 64.7, 47.3, 41.3, 38.6, 30.3, 28.6, 26.8, 26.7, 24.6, 21.0 ppm.
Scheme S14. Wittig Olefination of the Indanone 3i, Related to Scheme 3

To a 10-mL flame-dried flask charged with Ph₃P*CH₂Br⁻ (79 mg, 0.22 mmol, 1.1 equiv) and dry THF (1 mL), iBuOK (33 mg, 0.3 mmol, 1.5 equiv) was added slowly at 0 °C over 10 minutes. After stirring at room temperature for 2 h, the indanone 3i (32 mg, 0.2 mmol, 1.0 equiv) was added. Then the mixture was stirred at room temperature overnight, before water (5.0 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 5mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was then purified by flash column chromatography (petroleum ether:EtOAc= 5:1) to give product (R)-5-(1-methyl-3-methylene-2,3-dihydro-1H-inden-1-yl)pentan-1-ol (5) as colorless oil (23 mg, 50% yield). ¹H NMR (400 MHz, Chloroform-d) δ= 7.48-7.42 (m, 1H), 7.26-7.13 (m, 3H), 5.43 (t, J= 2.5 Hz, 1H), 5.01 (t, J= 2.1 Hz, 1H), 3.57 (t, J= 6.6 Hz, 2H), 2.72 (dt, J= 16.2, 2.2 Hz, 1H), 2.53 (dt, J= 16.3, 2.4 Hz, 1H), 1.61-1.46 (m, 4H), 1.33-1.27 (m, 4H), 1.25 (s, 3H) ppm. ¹³C NMR (126 MHz, Chloroform-d) δ= 154.1, 148.8, 140.1, 128.4, 126.7, 123.2, 120.5, 102.8, 63.0, 45.7, 45.2, 42.4, 32.7, 28.0, 26.3, 24.7 ppm. HRMS (ESI): calcd. for C₁₆H₂₃O [M+H]⁺: 231.1743, found: 231.1749.

Scheme S15. Beckmann Rearrangement of the Indanone 3i, Related to Scheme 3

Step 1: To a 10-mL flame-dried flask charged with 3i (137 mg, 0.5 mmol, 1.0 equiv), hydroxylaminium chloride (39.0 mg, 0.55 mmol, 1.1 equiv) and dry EtOH (1.0 mL), sodium acetate (82.0 mg, 1.0 mmol, 2.0 equiv) was added slowly at 0 °C. Then the mixture was heated to 60 °C and stirred at this temperature for 2 h, before water (5.0 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 5mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was then used without further purification.

Step 2: Phosphorus pentachloride (105 mg, 0.5 mmol, 1.0 equiv) was added in one portion to the residue in THF (4 mL). The reaction mixture was then heated to 60 °C and stirred at this temperature for 1.5 h, before it was quenched with sat. aq. NH₂OH solution (10mL). The aqueous phase was extracted with EtOAc (2×10 mL) and the combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc= 1:1) to give (R)-5-(4-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl)pentyl acetate (6) as a colorless oil (81 mg, 56 % yield). ¹H NMR (500 MHz, Chloroform-d) δ= 8.79 (s, 1H), 7.17-7.07 (m, 2H), 6.97 (td, J= 7.6, 1.3 Hz, 1H), 6.76 (dd, J= 7.8, 1.3 Hz, 1H), 3.92 (t, J= 6.6 Hz, 2H), 2.51-2.37 (m, 2H), 1.95 (s, 3H), 1.57-1.45 (m, 4H), 1.26 (s, 3H), 1.24-1.18 (m, 4H). ¹³C NMR (126 MHz, Chloroform-d) δ= 171.28, 171.31, 136.2, 131.0, 127.5, 125.5, 123.4, 116.0, 64.5, 43.4, 39.7, 36.9, 28.5, 26.4, 25.4, 23.9, 21.0 ppm. HRMS (ESI): calcd. for C₁₇H₂₃NO₃ [M+H]⁺: 290.1751, found: 290.1748.
Determination of the Absolute Configuration

Scheme S16. Preparation the Indane 4 with a Known Absolute Configuration, Related to Scheme 2

\[ \text{Me} \quad \overset{\text{OAc}}{\text{O}} \quad \text{Zn-Hg, HCl} \quad \overset{\text{Toluene, RT}}{\text{4, 96%, 91%ee}} \]

The ee of 4 (91%) was determined by HPLC analysis: Chiralpak IB column, \( \lambda = 254 \text{ nm} \), hexane/isopropanol = 97/3, flow rate = 0.5 mL/min): \( t_R(\text{major}) = 11.6 \text{ min} \), \( t_R(\text{minor}) = 13.2 \text{ min} \). (For HPLC-chromatograms, see: Page S152)

The HPLC data for ent-4 ((S)-5-(1-methyl-2,3-dihydro-1H-inden-1-yl)pentyl acetate) reported in the literature (Jin and Wang, 2019): Chiralpak IB column, \( \lambda = 254 \text{ nm} \), hexane/isopropanol = 97/3, flow rate = 0.5 mL/min): \( t_R(\text{minor}) = 11.6 \text{ min} \), \( t_R(\text{major}) = 13.2 \text{ min} \).

Relying on the comparison of the HPLC data, the absolute configuration of 4 was determined to be \( R \). Accordingly, the stereochemistry of 3i was determined to be \( R \). The absolute configuration of all the other ring opening/cross-coupling products was assigned to be \( R \) assuming a common reaction pathway.
Supplementary References

Sun, Y.-L., Wang, X.-B., Sun, F.-N., Chen, Q.-Q., Cao, J., Xu, Z., and Xu, L.-W. (2019). Enantioselective cross-exchange between C-I and C-C σ bonds. Angew. Chem. Int. Ed. 58, 6747-6751.

Guo, J.-W., Xu, X.-M., Xing, Q.-Z., Gao, Z.-W., Gou, J., and Yu, B.-X. (2018). Furfuryl cation induced cascade formal [3 + 2] cycloaddition/double ring-opening/chlorination: an approach to chlorine-containing complex triazoles. Org. Lett. 20, 7410-7414.

Nicotrat, F., Riva, S., Secundo, F., and Zucchelli, L. ω-Functionalized esters by enzymatic acylation. (1990). Synth. Commun. 20, 679-685.

Zhang, M.-J., Vedantham, P., Flynn, D. L., and Hanson, P. R. (2004). High-load, soluble oligomeric carbodiimide: synthesis and application in coupling reactions. J. Org. Chem. 69, 8340-8344.

Narayan, A., Jiménez-Osés, G., Liu, P., Negretti, S., Zhao, W.-X., Gilbert, M., Ramabhadrann, R., Yang, Y., Furan, L., Li, Z., Podust, L., Montgomery, J., Houk, K., and Sherman, D. (2015). Enzymatic hydroxylation of an unactivated methylene C–H bond guided by molecular dynamics simulations. Nature Chem. 7, 653-660.

Burkhart, B., Khlyabich, P., and Thompson, B. (2012). Solar cells based on semi-random P3HT analogues containing dithienopyrrole: influence of incorporating a strong donor. J. Photon. Energy 2, 021002.

Jin, Y., and Wang, C. Nickel-catalyzed asymmetric reductive areylalkylation of unactivated alkenes. (2019). Angew. Chem. Int. Ed. 58, 6722-6726.
