



# C2-取代手性降冰片烯衍生物的高效合成

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**摘要** C2-取代手性降冰片烯衍生物已经在不对称钯/降冰片烯协同催化中得到了广泛应用. 目前报道的合成C2-取代手性降冰片烯的方法步骤冗长, 合成效率较低, 且不适合宏量制备. 本文发展了一条高效合成C2-取代手性降冰片烯衍生物的新路线, 采用廉价易得的环戊二烯与手性丙烯酸泛酸酯为起始原料, 通过Diels-Alder反应、酯水解、双键氢化、消除反应实现了高光学纯C2-取代手性降冰片烯衍生物的合成. 该路线具有原料廉价易得, 操作简单, 易于大量制备等优点.

**关键词** C2-取代手性降冰片烯衍生物, Diels-Alder反应, 消除反应, 协同催化

钯/降冰片烯(Pd/NBE)协同催化(又称Catellani反应)将交叉偶联反应和C(sp<sup>3</sup>)-H键活化有效结合在一起, 通过组合不同的亲电试剂和终止试剂, 可以实现芳基卤代物邻位和原位的依次双官能团化, 一步构筑多根化学键, 是一类高效合成多取代芳烃的重要策略<sup>[1-3]</sup>(图1(a)). 近年来, 钯/手性降冰片烯(Pd/NBE\*)不对称协同催化在合成手性多取代芳烃方面也取得了突破, 成功用于构筑含中心手性、轴手性以及面手性元素的取代芳烃<sup>[4-10]</sup>(图1(b)). 手性降冰片烯在Pd/NBE\*不对称协同催化中至关重要, 扮演了共催化剂和手性源双重角色. 目前, C2-取代的手性降冰片烯衍生物在Pd/NBE\*不对称协同催化中得到了广泛使用.

由于降冰片烯骨架具有高张力[2.2.1]双环骨架, 存在大位阻桥头碳中

心手性. 同时降冰片烯类化合物分子量小、易挥发, 合成要求较高, 因此对于该类手性降冰片烯的合成具有较大的挑战. 目前报道的合成C2-取代的手性降冰片烯方法主要有如下两种: (1) 手性碱诱导的不对称合成法; (2) 动力学拆分法.

第一种合成路线由余金权团队<sup>[4]</sup>于2018年首次报道(图2(a)). 该方法采用降冰片烯二酸酐**1**为原料, 以当量的生物碱奎尼丁(quinidine)作为手性试剂, 实现二酸酐的去对称醇解. 随后, 经过酸化以及Pd/C催化氢化, 能以当量的产率得到化合物**3**. 化合物**3**通过汉斯狄克反应, 得到脱羧溴代产物**5**. 该合成步骤需要使用高毒性的氧化汞和氧化性的Br<sub>2</sub>试剂. 溴代产物**4**最后在DBU的作用下发生消除反应得到产物**5**. 总结上述整个路线, 经过4步合成, 总产率可达63%, 然而需要使用大量高毒性的氧化汞试剂, 不利于

大量合成.

第二种合成路线是董广彬团队报道的拆分路线<sup>[6]</sup>(图2(b)). 该拆分路线可以同时获得两种不同构型的产品, 然而需要前期多步合成消旋体C2-取代降冰片烯酸, 然后原位制备成相应的酰氯. 同时需要制备当量的拆分试剂樟脑内磺酰胺, 该过程需要大量的氢氧化钠作为碱, 随后将预先制备的消旋的降冰片烯酰氯与樟脑内磺胺反应生成一对非对映异构体, 最后采用色谱柱分离得到非对映异构体**10a**和**10b**. 非对映异构体**10**进一步转化才能得到C2-取代手性降冰片烯. 总结上述整个路线, 需要8, 9步操作, 总产率低于10%, 且需要使用大量的氢氧化钠试剂.

总结上述两种合成方法, 其合成路线较长, 且部分反应需要使用有毒试剂, 不宜大量制备. 鉴于C2-取代手性降冰片

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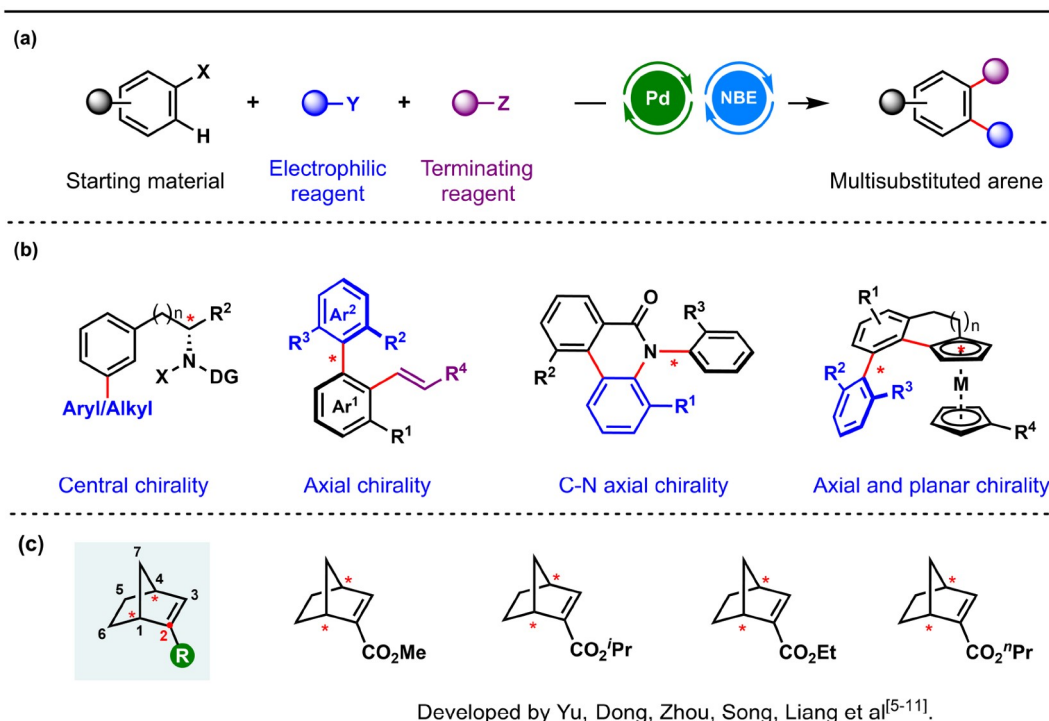


图1 (网络版彩色)手性降冰片烯衍生物在Pd/NBE\*不对称协同催化中的应用。(a) 钯/降冰片烯协同催化。(b) 手性多取代芳烃的构建。(c) C2-取代手性降冰片烯

Figure 1 (Color online) Application of chiral norbornene derivatives in Pd/NBE\* cooperative catalysis. (a) Palladium/norbornene (Pd/NBE) cooperative catalysis. (b) Construction of chiral polysubstituted arenes. (c) C2-Substituted NBs

烯衍生物在不对称协同催化中得到了日益广泛的应用,亟须开发它的高效实用制备新路线。

(1) 路线设计. 通过文献<sup>[12-16]</sup>调研,我们提出合成该类手性降冰片烯衍生物的新思路(图3(a)):首先,通过不对称Diels-Alder反应快速获取C5-酯基取代的手性降冰片烯中间体。接着,在C5-酯基取代降冰片烯骨架 $\alpha$ 位引入一个离去基团,再进行分子内消除反应,就可获取C2-取代降冰片烯(图3(b))。本文设计的新路线有望显著提高其合成效率。

(2) 关键反应设计与尝试. 基于上述合成思路,我们首先对其中的关键步骤:消除反应进行可行性研究。利用消旋的C5-取代降冰片烯( $\pm$ )-**13**为模板底物进行尝试。我们最初尝试在 $\alpha$ 位引入溴原子,然而经过多种尝试,没有得到目标产物<sup>[11,12]</sup>(图4(a))。随后,尝试了烯丙基钯催化促进的( $\pm$ )-**13**脱氢反应,该反应可以发生,但转化率较低,且产物( $\pm$ )-**5**与

原料( $\pm$ )-**13**的极性相近,分离纯化困难<sup>[13]</sup>(图4(b))。随后,我们尝试在( $\pm$ )-**13**的酯基 $\alpha$ 位引入含硫基团制备硫醚中间体,接着氧化成亚砷基进行消除引入双键得到目标产物( $\pm$ )-**5**。确实,该方法可以顺利得到( $\pm$ )-**5**,但是总体效率很低<sup>[14]</sup>(图4(c))。受该策略启发,我们接着尝试在酯基 $\alpha$ 位引入硒基团制备活性更高的硒醚中间体,后续经氧化成亚硒基再发生分子内消除反应,以90%的高收率得到目标产物( $\pm$ )-**5**<sup>[15]</sup>(图4(d))。

(3) C2-取代手性降冰片烯新合成路线. 基于以上成功的消旋C2-取代降冰片烯合成路线,我们发展了C2-取代手性降冰片烯新合成路线,成功实现了高对映纯C2-取代手性降冰片烯的高效、克级规模合成。具体合成路线如图5所示:选用廉价易得的丙烯酸酯与光学纯的D-(-)-泛酸内酯为初始原料,经过缩合得到光学纯的丙烯酸酯**19**。化合物**9**与环戊二烯发生Diels-Alder反应,高效制备C5-取

代的手性降冰片烯中间体**20**。该化合物易于结晶,可在乙酸乙酯与正己烷混合溶剂中经过2次重结晶操作,得到>20:1 *d.r.*单一构型的手性产物**20**,收率为78%。化合物**20**经过水解、氢化与酯化3步后,以90%收率得到手性降冰片烷中间体(+)-**13**。值得一提的是,以上3步简易操作均不需纯化即可直接进行后续反应。接下来在化合物(+)-**13**中引入双键是整个路线的关键步骤。我们预先通过二苯基二硒醚与液溴反应原位制备苯基溴化硒试剂,然后加入(+)-**13**,再加入碱完成酯基 $\alpha$ 位硒基化制备苯硒醚中间体。最后,加入过氧化氢水溶液对硒醚进行氧化,促进分子内消除反应得到目标产物(+)-**5**。该关键反应的副产物为大极性苯基硒化合物,且水溶性较好,经萃取干燥后通过简单的色谱柱分离,即可以获得高对映选择性的手性产物(+)-**5**。我们发展的手性C2-取代的降冰片烯新合成路线,无需额外的高毒性试剂,只需5

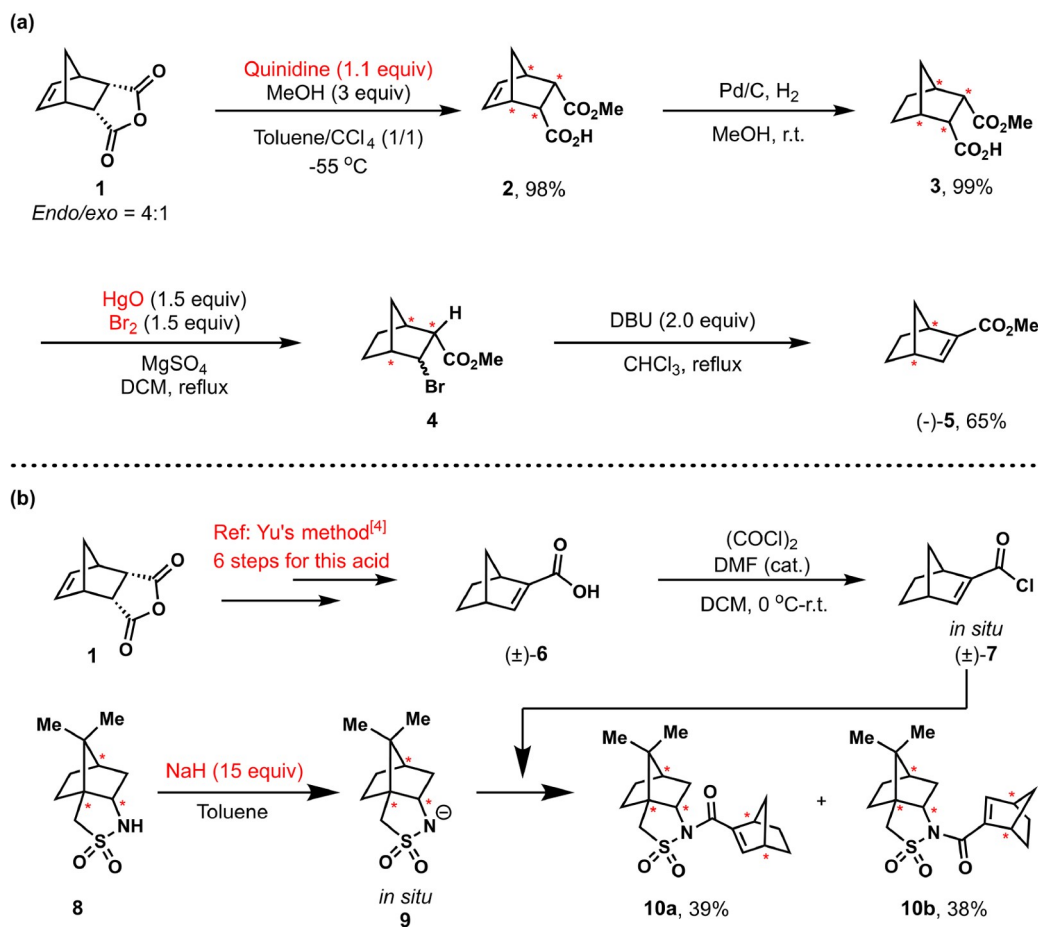


图 2 (网络版彩色) C2-取代手性降冰片烯衍生物的制备方法. (a) 余团队<sup>[4]</sup>报道的合成方法; (b) 董团队<sup>[6]</sup>报道的合成方法  
Figure 2 (Color online) Synthetic methods for C2-substituted chiral norbornene derivatives. (a) Yu's method<sup>[4]</sup>; (b) Dong's method<sup>[6]</sup>

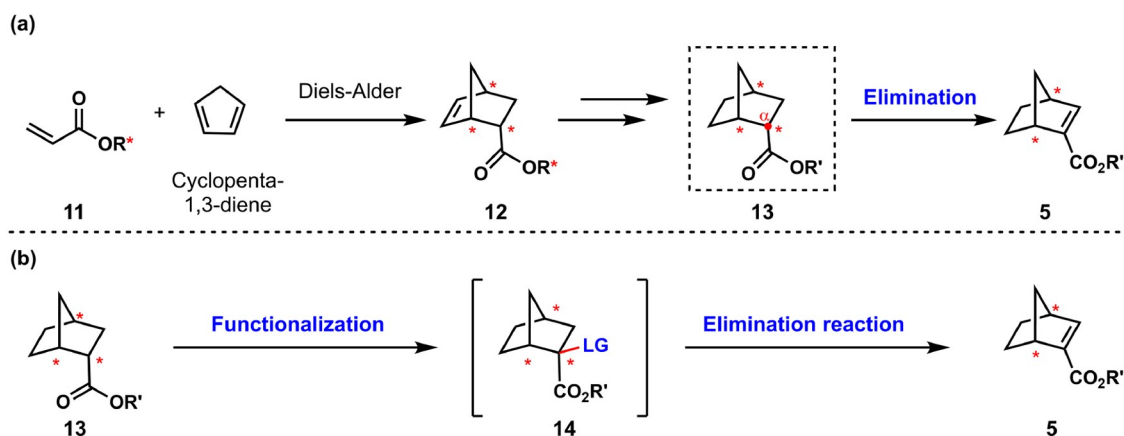


图 3 (网络版彩色) C2-取代手性降冰片烯衍生物合成新路线. (a) C2-取代手性降冰片烯合成新路线的设计. (b) 关键的消除反应  
Figure 3 (Color online) A new synthetic route for C2-substituted chiral norbornenes. (a) Design of a new synthetic route for C2-substituted chiral norbornenes. (b) The key step of elimination

步合成与2次柱层析就可以高效获取 (+)-5, 总产率高达54%. 值得一提的是, (+)-5还可以水解得到手性的酸(+)-6, 再进行后续一系列转化, 合成各种酰胺、酯等多样化的C2-取代手性降冰片烯产物<sup>[6,7,17~19]</sup>.

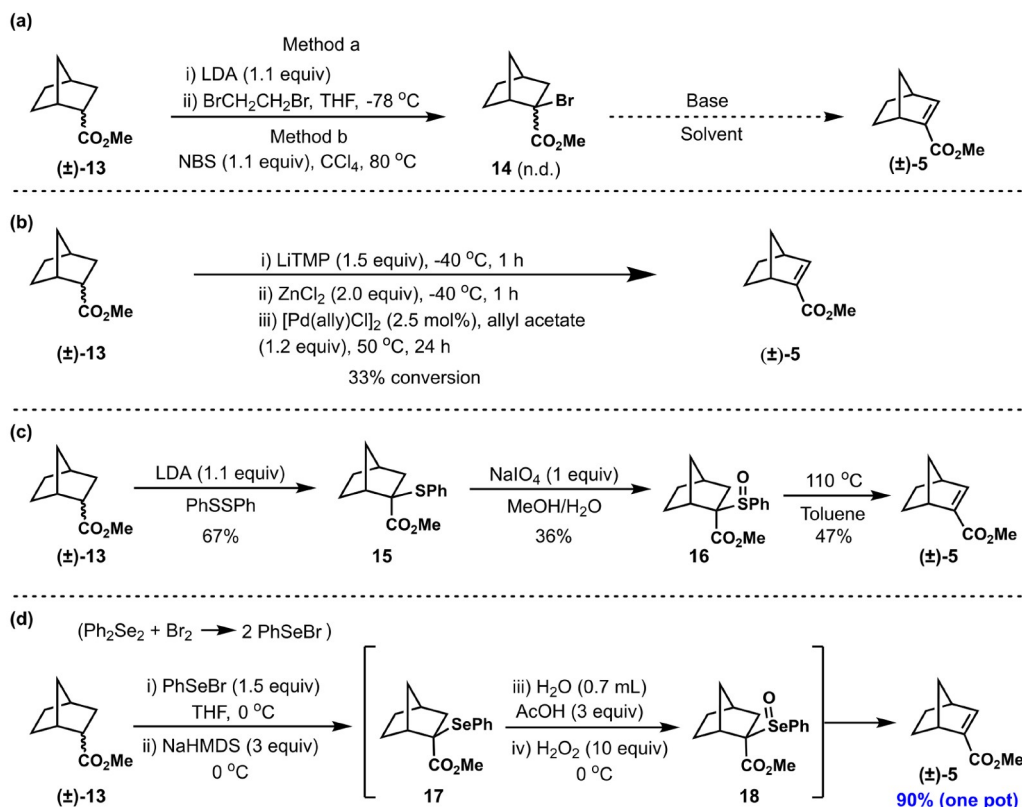


图4 (网络版彩色) C2-取代降冰片烯合成新路线的关键步骤可行性研究. (a) 溴代/消除路线. (b) 钯催化的脱氢路线. (c) 亚砷化/消除路线. (d) 亚硒化/消除路线

Figure 4 (Color online) The study of the key steps in a new synthetic route for C2-substituted norbornenes. (a) Bromination/elimination route. (b) Pd-catalyzed dehydrogenation route. (c) Sulfoxidation/elimination route. (d) Selenoxidation/elimination route

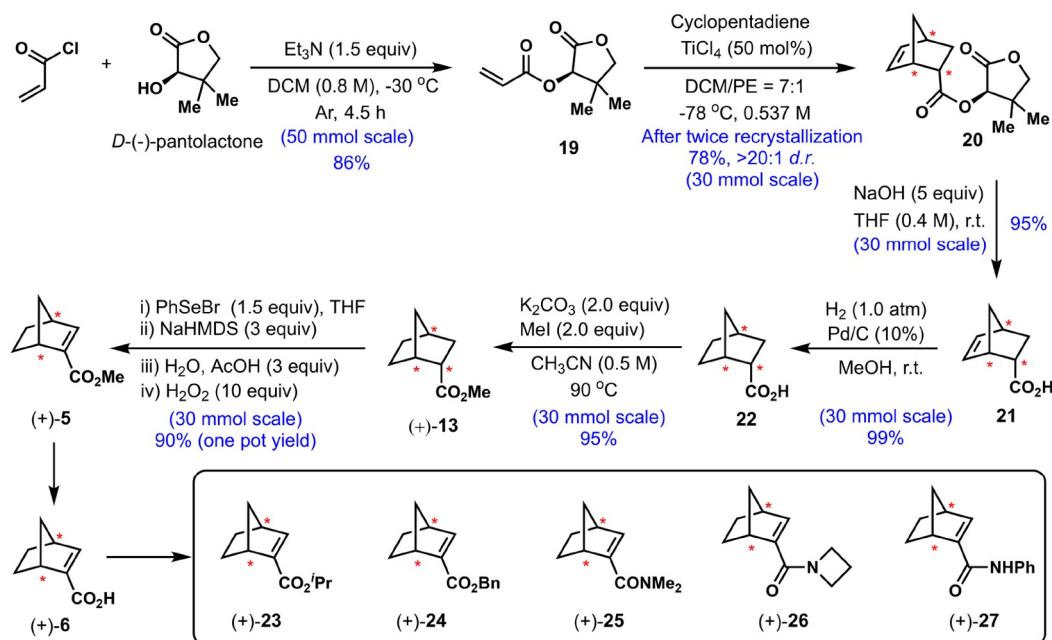


图5 (网络版彩色) C2-取代手性降冰片烯的新合成路线

Figure 5 (Color online) A new synthetic route for C2-substituted chiral norbornenes

C2-取代的手性降冰片烯衍生物在不对称钯/手性降冰片烯协同催化中扮演了至关重要的角色。然而, 现有制备C2-取代的手性降冰片烯衍生物的方法存在较多局限, 制约其广泛应用。我们经过长期的探索, 开发了一种高效合成C2-取代手性降冰片烯衍生物的新路线。该路线具有如下优点: 合成步骤操作简单, 易于放大, 原料廉价易得, 无需高毒性试剂, 无苛刻反应条件。我们发展的新路线实现了该类手性化合物的实用化制备, 将有力地促进相关研究的推进与应用。

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Summary for “C2-取代手性降冰片烯衍生物的高效合成”

## Efficient synthesis of chiral C2-substituted norbornene derivatives

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Palladium/norbornene (Pd/NBE) cooperative catalysis has emerged as a highly efficient strategy for synthesizing polysubstituted arenes. By combining different electrophiles and nucleophiles, this approach facilitates sequential bifunctional functionalization of aryl halides at the *ortho* and *ipso* positions, enabling the construction of complex polysubstituted arenes that are otherwise challenging to access. Recently, palladium/chiral norbornene (Pd/NBE<sup>\*</sup>) cooperative catalysis has demonstrated notable advancements in the synthesis of chiral polysubstituted arenes, which has been successfully applied to the construction of diverse chiral elements, including central, axial, and planar chirality. In this process, the chiral norbornene derivative is very crucial, acting both as a co-catalyst and the chiral source. Particularly, the C2-substituted chiral norbornene derivatives have been widely employed in Pd/NBE<sup>\*</sup> cooperative catalysis. However, current methods for synthesizing C2-substituted chiral norbornenes often require harsh conditions and the use of highly toxic, high-energy reagents. Therefore, there is an urgent need to develop a more general and efficient method for the efficient synthesis of C2-substituted chiral norbornene derivatives.

Due to the norbornene skeleton being a strained and rigid [2.2.1] bicyclic scaffold, which introduces significant steric hindrance at the bridgehead carbon center, substantial challenges arise in its synthesis. Additionally, most of its derivatives have small molecular weights, high volatility, and stringent synthesis requirements, making the synthesis more challenging. Currently, there are two primary methods for synthesizing C2-substituted chiral norbornenes. The first approach utilizes quinidine-induced asymmetric synthesis, while the second relies on kinetic resolution to separate enantiomers based on differences in reaction rates. However, both methods have inherent limitations. They usually require harsh reaction conditions, high-energy and toxic reagents, and often involve multistep processes, which limit their practicality for large-scale synthesis and broader application. Therefore, a more general, efficient, and scalable synthetic approach is urgently needed to expand access to C2-substituted chiral norbornene derivatives. Such a method would not only facilitate their use in Pd/NBE<sup>\*</sup> cooperative catalysis but also open new avenues in stereoselective synthesis and chiral molecule development.

Here, we report an efficient synthesis of C2-substituted chiral norbornene derivatives. High-purity C2-substituted chiral norbornene derivatives are synthesized through a series of reactions, including the Diels-Alder reaction, ester hydrolysis, hydrogenation, and elimination. This approach offers several advantages, such as simple synthesis steps, scalability, inexpensive and readily available starting materials, the use of non-toxic reagents, and mild conditions. The use of non-toxic reagents is another important benefit, minimizing both health and environmental risks, a key aspect of sustainable chemistry. Finally, the reaction conditions are mild, which not only promotes high yields but also obviates the need for specialized and costly laboratory equipment. The new synthesis method enables the practical preparation of these chiral compounds, which will significantly advance and broaden related research.

In conclusion, this novel synthetic pathway for C2-substituted chiral norbornene derivatives not only addresses the constraints of existing methods but also introduces a more sustainable and efficient approach to synthesis. This advancement holds the potential to significantly impact the field by enabling broader applications of Pd/NBE<sup>\*</sup> cooperative catalysis and advancing research in complex chiral molecules. The streamlined, practical preparation of chiral norbornene derivatives allows for the efficient production of high-purity C2-substituted compounds, greatly enhancing the scope and feasibility of Pd/NBE<sup>\*</sup> catalysis in synthesizing intricate chiral arenes. Furthermore, the increased accessibility of these chiral norbornene derivatives is likely to drive new research directions in polysubstituted arene synthesis, spanning diverse applications from stereochemically-defined drug development to the creation of advanced materials with tailored functional properties. This work represents a meaningful step forward in asymmetric catalysis, providing a scalable, environmentally friendly method that promises to elevate research capabilities and expand the practical utility of Pd/NBE<sup>\*</sup> cooperative catalysis in complex molecule construction.

**chiral C2-substituted norbornene derivatives, Diels-Alder reaction, elimination reaction, cooperative catalysis**

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