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Carbene-Catalyzed Desymmetrization and Direct Construction of Arenes with All-Carbon Quaternary Chiral Center

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Abstract: *Multisubstituted arenes such as indanes with attached all-carbon quaternary centers are unique scaffolds in synthetic functional molecules and sophisticated natural products. A key challenge in preparing such molecules lies in the enantioselective installation of the quaternary carbon centers. Conventional methods in this direction include asymmetric substitution reactions and substrate-controlled cyclization reactions. These reactions lead to poor stereoselectivities and/or require long and tedious synthetic steps. Disclosed here is a one-step organic catalytic strategy for enantioselective access to this class of molecules. The reaction involves an N-heterocyclic carbene catalyzed process for direct benzene construction, indane formation, remote-carbon desymmetrization, and excellent chirality control. This approach will enable the concise synthesis of arene-containing molecules, including those with complex structures and challenging chiral centers.*

Arenes and their derivatives are crucial structural motifs in natural products, synthetic molecules, and functional materials (Figure 1a). These aromatic molecules are typically prepared by two types of methods: one is based on functionalization of pre-existing benzene rings to introduce proper substituents; another is by direct construction of the benzene cores using substrates with pre-installed functional groups.[1] In particular, the direct formation of benzene cores by using readily available prefunctionalized substrates can offer shortcuts to prepare both small molecules[2] and large sophisticated natural products.[3] However, when chiral centers (particularly all-carbon quaternary centers) are present in the neighboring regions of the arenes, the synthetic tasks become very challenging. There are few effective approaches available for construction of substituted benzenes with simultaneous installation of chiral centers.[4] Among the molecules containing arenes with chiral centers, indane derivatives having an all-carbon quaternary chiral center (Figure 1a) are particularly difficult to make in optically enriched forms.[5] For example, the natural product coprinastatin epimer[6] and preclinical drug[7] MK-3207 are available only in a racemic form by current synthetic methods (Figure 1a). The use of chiral chromatography is required to obtain the enantiomerically enriched isomer.[8] The bowl-shaped molecules tribenzotriquinacenes,[9] building blocks used in host/guest supramolecular materials, need chiral resolutions to get the optically enriched enantiomers after the racemic forms are synthesized.[10] Another example is the

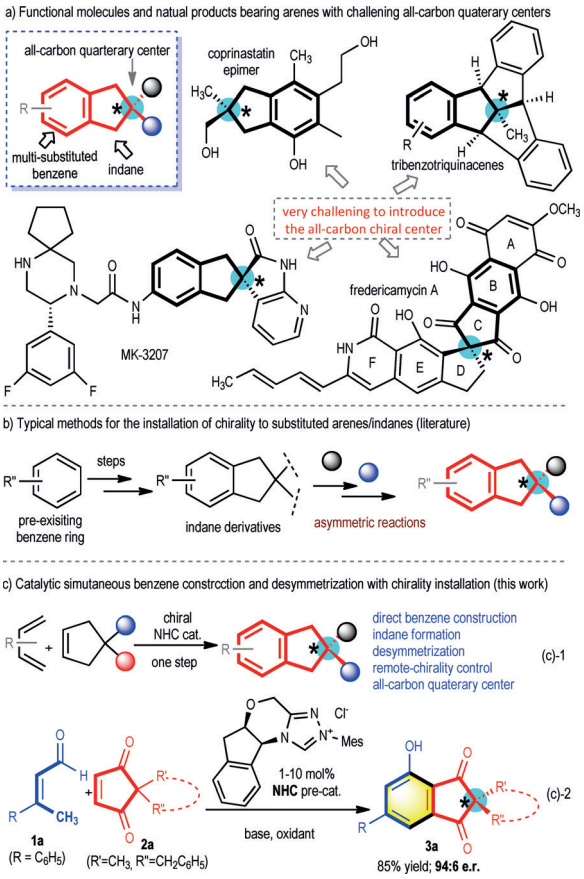

Figure 1. Arenes bearing challenging chiral centers.

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natural product fredericamycin A (Figure 1a). The first asymmetric total synthesis of this molecule was reported by the group of Kita.[11] Among the 25 steps involved in Kita's total synthesis, around 15 steps were used mostly for the introduction of the all-carbon quaternary chiral center. Current methods (Figure 1b) for the preparation of such molecules typically require multiple steps[11,12] or proceed with poor (or even no) control over the enantioselectivity.[13]

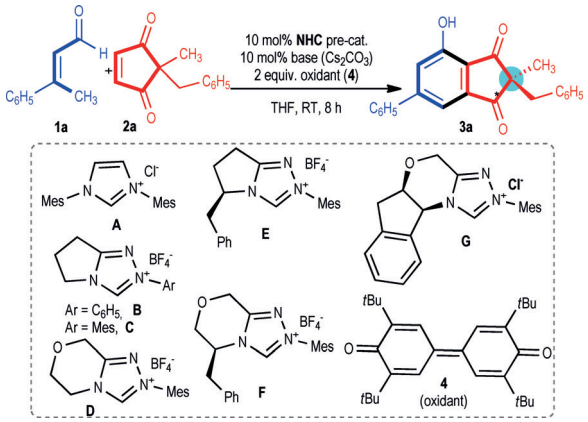
Here we report a new and very efficient catalytic strategy to construct indane derivatives bearing an all-carbon quaternary chiral center (Figure 1c). Our design involves readily available diene (precursors) and electron-deficient cyclopentenes as the substrates (Figure 1c-1). The cyclopentene substrate bears a pre-installed all-carbon quaternary prochiral center. Our designed reaction involves two key simultaneous processes: one is a direct benzene construction[14] by a cyclization/oxidation/isomerization cascade; another is a desymmetrization process that sets up the all-carbon quaternary chiral center (Figure 1c-1). Specifically, under the catalysis of an N-heterocyclic carbene (NHC, or carbene in this article) in the presence of an oxidant, reaction of an enal (**1a**) and a cyclopentenedione with a prochiral center (**2a**) affords the indane derivative **3a** with 85% yield and 94:6 e.r. (Figure 1c-2). To the best of our knowledge, this is the first success of an organocatalyzed[15] intermolecular reaction that allows simultaneous arene formation and desymmetrization with remote-chirality control.[16] It shall significantly simplify the synthesis of aryl-containing molecules with challenging chiral centers.

We started by using **1a** and **2a**[17] to search for suitable reaction conditions for the formation of proposed product **3a** (Table 1). Key results of the reaction condition optimizations are summarized in Table 1. The reaction was carried out with THF as the solvent, Cs_2CO_3 as the base, and quinone (**4**) as the oxidant.[18] No product (**3a**) was formed in the absence of an NHC precatalyst (entry 1). The imidazolium precatalyst **A**,[19] the most effective catalyst in our earlier achiral benzene formation reaction,[20] could not catalyze the reaction of **1a** and **2a** to form **3a** here (entry 2). The triazolium precatalyst **B**[21] was not effective either (entry 2). We then found that by replacing the N-phenyl substituent of **B** with a *N*-Mes substituent[21] (NHC pre-catalyst **C**), **3a** was obtained in 45% yield (entry 3). Additional survey on the catalyst effects revealed that the triazolium **D**,[23] with morpholine fused to the triazolium unit, performed better, giving **3a** with 65% yield (entry 4). We next studied chiral catalysts for enantioselective reactions (entries 5–7), and eventually found that the use of the aminoindanol-derived triazolium precatalyst **G**[24] gave the best results, affording **3a** with 85% yield and 94:6 e.r. (entry 7). The catalyst loading could be decreased to 1 mol% without affecting the enantioselectivity, although in this case a longer reaction time was necessary to achieve an acceptable yield (entry 8). This relatively low catalyst loading (1 mol%) allows scalable preparations using our method. Both bases (entries 9–11) and solvents (see the Supporting Information for details) show significant effects on the reaction outcomes. When necessary, the use of other solvents (such as 1,4-dioxane) and bases (such as DBU) is feasible.

With acceptable reaction conditions in hand (Table 1, entry 7), the scope of the reaction was evaluated. We firstly choose **2a** as a model diketone substrate to study the generality of the enal substrates (Scheme 1, products **3a–m**). Both electron-withdrawing (products **3c–e**) and electron-donating groups (products **3b–c**, **3g–i**) at the *para*-position (products **3b–f**) and *meta*-position (product **3g**) of the β-phenyl group were well tolerated. The absolute configuration of **3i** was unambiguously confirmed as *S* by single-crystal X-ray diffraction analysis (see the Supporting Information for details). *ortho*-Substitution of the β-phenyl group led to a slight decrease in enantioselectivity (product **3h**). Replacement of the β-phenyl substituent with a naphthyl (products **3j**,**k**) or heteroaryl unit (products **3l**,**m**) had little effect on the reaction outcome. It is worth noting that the enals were synthesized by Vilsmeier formylation of commercially available styrene in nearly quantitative yields (see the Supporting Information for details), and the *E*/Z mixture of enals can be directly used (the two isomers gave essentially the same yields and enantioselectivities).

With **1a** as a model nucleophile, the scope with respect to the diketones was also examined (Scheme 1, products **3n–x**). Substituents with different electronic properties at the *para*-position (products **3n–o**, **3r–t**) and *meta*-position (product **3p**) of the phenyl group were well tolerated. *ortho*-Substitution of the phenyl group led to some decrease in enantiose-

Table 1: Optimization of reaction conditions.[a]



Entry	Conditions	Yield [%]	e.r.
1	no NHC pre-cat.	0	–
2	**A** or **B**	trace	–
3	**C**	45	–
4	**D**	65	–
5	**E**	77	88:12
6	**F**	81	92:8
7	**G**	85	94:6
	variation in conditions from entry 7		
8	1 mol% **G**, 48 h	61	94:6
9	base = DBU	45	90:10
10	base = DIEA or NaOAc	trace	–
11	base = K_2CO_3	53	92:8

[a] Reactions were carried out with **1a** (0.20 mmol, 1.0 equiv), **2a** (0.22 equiv), **NHC** pre-cat. (10 mol%), base (10 mol%), and oxidant (2.0 equiv) in THF for 8 h. All yields are those of isolated products and the e.r. values were determined by chiral-phase HPLC analysis. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIEA = *N*,*N*-diisopropylethylamine, THF = tetrahydrofuran.

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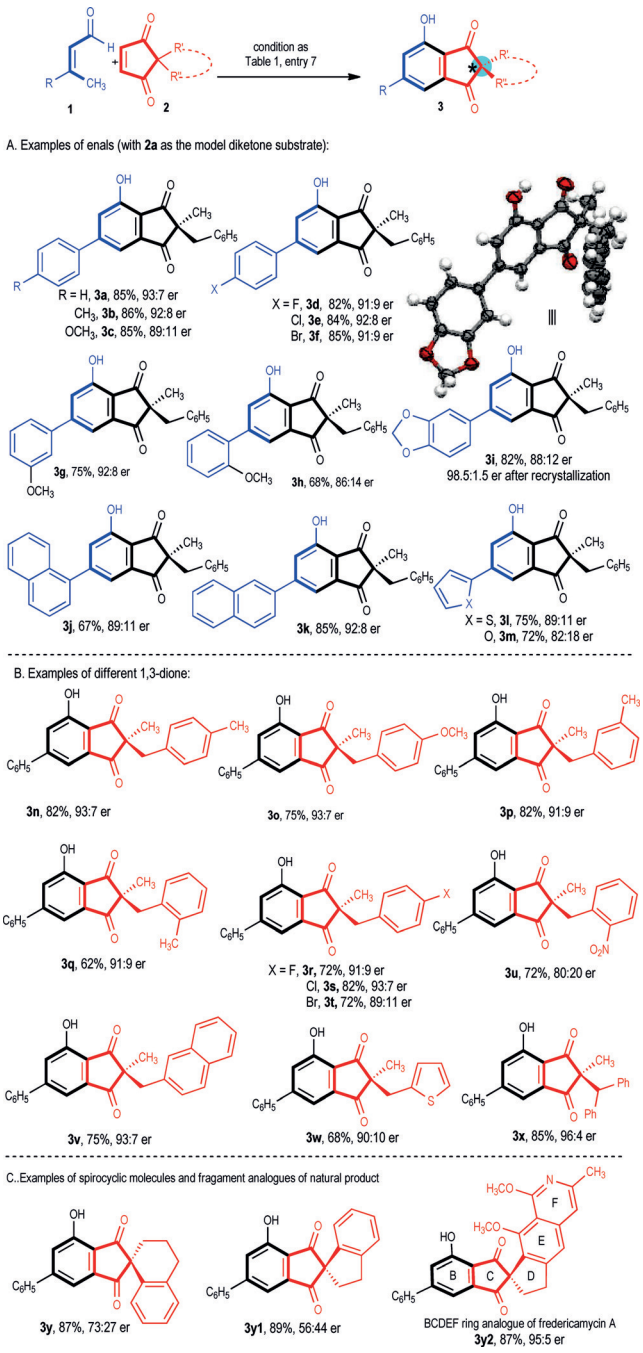
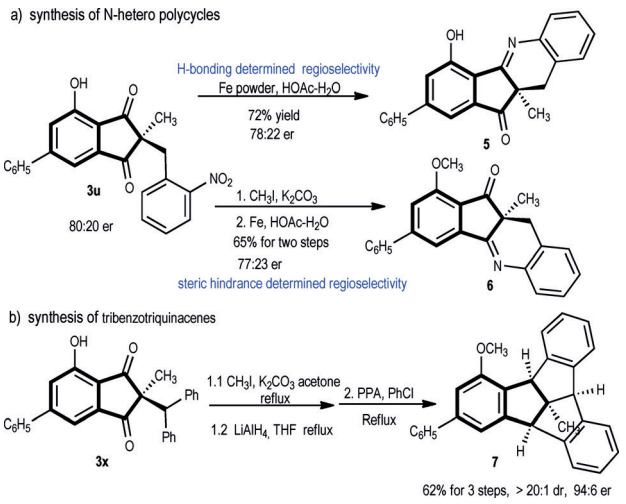


Scheme 1. Scope with respect to substrates. All yields are those of isolated products and the e.r. values were determined by chiral-phase HPLC analysis. The X-ray structure of **3i** is shown with thermal ellipsoids at 50% probability.[28]

lectivity, and may be caused by undesired steric effects (products **3q**, **3u**). Replacement of the phenyl substituent with a naphthyl (product **3v**) or heteroaryl unit (product **3w**) had little effect on the reaction outcomes. Although the reactivity of different ketones was shown to be general, the enantioselectivities of the reactions were influenced by the steric differences of two substituents on the quaternary carbon. Replacing the benzyl group with more steric hindered benzhydryl group increased the enantioselectivity to 96:4 e.r. (product **3x**).

Cyclopentenedione with spirocyclic structures were also tested under the standard reaction conditions (Table 1, entry 7). The reactions all proceeded smoothly and gave the desired spirocyclic indanes in good yields (Scheme 1, products **3y**–**y2**). The enantioselectivity highly depends on the sterics of the spirocycles. The products **3y** and **3y1** were obtained with low enantioselectivities. When introducing proper substituents, **3y2** could be obtained with an excellent 95:5 e.r. It is worth noting the asymmetric catalytic synthesis of **3y2** represents a shortcut towards the BCDEF ring analogue structure of the natural antibiotic fredericamycin A (Figure 1a), which is otherwise tedious to build enantioselectively.[11]

We next demonstrated effective transformation of our optically active products into interesting multicyclic or spriocyclic compounds. Direct reduction of the phenol **3u** with iron powder gave the benzoindenoquinolinone **5**, while the reduction of methyl-protected **3u** furnished the tetracylic compound **6** by a complete regioselective cyclization (Scheme 2a). The divergent regioselective reductive cyclization was probably a result of the ketone activation effect of intramolecular hydrogen bonding in **3u**, and the steric bulk of OMe group in the protected **3u**. Both transformations proceeded in good yields with only a slight decline in the enantioselectivities. These molecules were previously synthesized by methylation of pre-existing multicyclic compounds,[25] and the asymmetric synthesis is unprecedented. The phenol **3x** was transformed into the chiral tribenzotriquinacenes **7** with 62% total yield and 94:6 e.r. by a three-step process including phenol protection, ketone hydrogenation, and intramolecular Friedel–Crafts alkylation (Scheme 2b). Tribenzotriquinacene, with a unique bowl-shape framework, is an interesting building block for macromolecular construction.[9] The chirality of these building blocks may have a crucial effect on the determination of the shape of the macromolecule.[9d] However, the asymmetric synthesis of chiral tribenzotriquinacene is challenging. Recent methods mostly involve kinetic resolution pathway and with low



Scheme 2. Product transformation.

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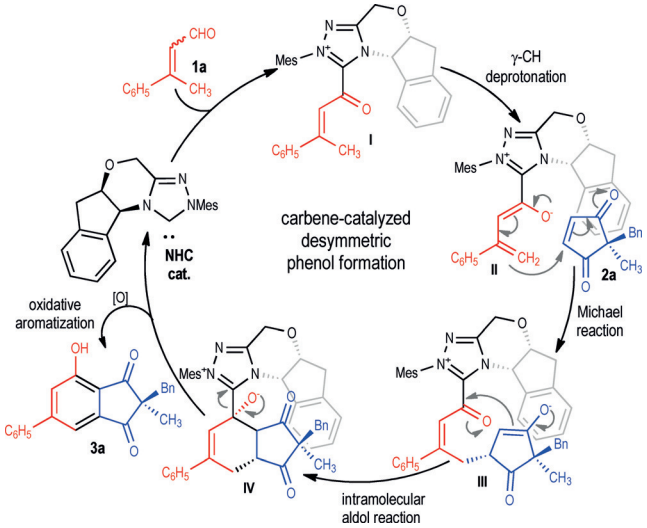
yield.[9b] Comparatively, our methods were much more efficient.

A plausible pathway of our NHC-catalyzed [4+2] cycloaddition involving formal γ- and carbonyl carbon atom activations of the enal is illustrated in Scheme 3. Briefly, addition of the NHC catalyst to the aldehyde followed by deprotonation forms the Breslow intermediate. This process is followed by oxidative transformation and then enal γ-C–H deprotonation leads to the vinyl enolate intermediate **II**.[26]



Scheme 3. Postulated pathway.

Since **2a** proved to be a good electrophile (or dipolarophile) and poor dienophile in previous studies,[27] we proposed a stepwise Michael addition and intramolecular adol reaction pathway rather than a concerted [4+2] Diels–Alder reaction process (**II**→**III**). During the cycloaddition process, the chiral indane moiety controls the approach of **2a**, placing the more bulky Bn group on the top face (Scheme 3, **II**→**III**). Finally, release of carbene catalyst and oxidative aromatization effectively affords **3a** with four substituents with a predictable substitution pattern and a remote all-carbon quaternary chiral center. It is also worth noting the because of the slightly different α-H acidity in **III**, no proton transfer occurred and no [4+1] cyclization product was observed, which was quite different from our earlier work.[17a]

In summary, we have developed an NHC organic catalytic strategy for the enantioselective formal [4+2] construction of multisubstituted phenols. Our method employs easily accessible enals and diketones to construct a phenol framework with the simultaneous highly enantioselective installation of a remote all-carbon quaternary chiral center by desymmetrization. This method offers new insights for the design of concise routes in complex molecule synthesis. Further studies regarding mechanistic details of remote chirality control and rapid asymmetric synthesis of complicated molecules by direct benzene construction are in progress in our laboratories.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chirality · cyclizations · desymmetrization · N-heterocyclic carbenes · synthetic methods

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[28] CCDC 1872147 (**3i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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