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

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Abstract: Multi-substituted 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 challenging carbon quaternary 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. Here we disclose a one-step organic catalytic strategy for enantioselective access to this class of molecules. Our reaction involves an N-heterocyclic carbene-catalyzed process for direct benzene construction, indane formation, remote-carbon desymmetrization, and excellent chirality control. We expect this approach to benefit the concise synthesis of arene-containing molecules, including those with complex structures and challenging chiral centres.

Arenes and their derivatives are crucial structural motifs in natural products, synthetic molecules, and functional materials (Figure 1a). These aromatic molecules are typically prepared via two types of methods: one is based on functionalization of pre-existing benzene rings to introduce proper substituents; another is via 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 pre-functionalized 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're 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 attached with an all-carbon quaternary chiral

center (Figure 1a) are particularly difficult to make in optically enriched forms.^[5] For example, nature products coprinastatin epimer^[6] and preclinical drug^[7] MK-3207 are available only in a racemic form via current synthetic methods (Figure 1a). The use of chiral chromatography is required in order to get the enantiomerically enriched isomer.^[8] Bowl-shaped molecules tribenzotriquinacenes,^[9] building blocks used in host/guest supramolecular materials, needs chiral resolutions to get the optically enriched enantiomers after the racemic forms are synthesized.^[10] Another example is nature product fredericamycin A (Figure 1a). The first asymmetric total synthesis of this molecule was reported by 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 requires very long steps^[11, 12] or with poor (or even no) controls over the enantioselectivities.^[13]

(b) Typical methods for the installation of chirality to substituted arenes/indanes (literature)

(c) Catalytic simultaneous benzene construction and desymmetrization with chirality installation (this work)

Figure 1. Arenes bearing challenging chiral centers

Here we report a new and very efficient catalytic strategy to construct indane derivatives bearing challenging all-carbon quaternary chiral center (Figure 1c). Our design involves readily available diene (precursors) and electro-deficient cyclopentenones

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as the substrates (Figure 1c-1). The cyclopentene substrate bears a pre-installed all-carbon quaternary pro-chiral center. Our designed reaction involves two key simultaneous processes: one is a direct benzene construction^[14] via 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 (abbreviated as NHC, or carbene in this article) in the presence of an oxidant, reaction of an enal (**1a**) and a cyclopentenone with a pro-chiral center (**2a**) affords indane derivative **3a** with 85% yield and 94:6 er (Figure 1c-2). To the best of our knowledge, this is the first success of organocatalyzed^[15] intermolecular reaction that allows for simultaneous arene formation and desymmetrization with remote-chirality controls.^[16] It shall significantly simplify the synthesis of aryl-containing molecules with challenging chiral centers.

Table 1. Condition Optimization^[a]

Entry	condition	3a (yield %)	3a (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
condition variations 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 ₂ CO 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 isolated yields and the er was determined by chiral phase HPLC analysis.

We started by using enal **1a** and cyclopentenone^[17] **2a** to search for suitable conditions for the formation of proposed product **3a** (Table 1). Key results of condition optimizations are summarized in Table 1. The reaction was carried out with THF as the solvent, Cs₂CO₃ as the base, and quinone **4** as the oxidant.^[18] No product (**3a**) was formed in the absence of an

NHC pre-catalyst (entry 1). Imidazolium pre-catalyst **A**,^[19] a 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). Triazolium pre-catalyst **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**), product **3a** was obtained in 45% yield (entry 3). Additional survey on the catalyst effects revealed that triazolium **D**^[23] with morpholine fused with 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 aminoindanol-derived triazolium pre-catalyst **G**^[24] gave the best results, affording **3a** with 85% yield and 94:6 er (entry 7). The catalyst loading could be decreased to 1 mol% without affecting the enantioselectivity, although in this case a longer reaction time is necessary in order to achieve an acceptable yield (entry 8). This relatively low catalyst loading (1 mol%) allows for scalable preparations using our method. Both bases (entries 9-11) and solvents (see 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 an acceptable reaction condition 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 electro-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 Supporting Information for details). *ortho*-Substitution in 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 to note that the enals were synthesized via Vilsmeier formylation of commercially available styrene in nearly quantitative yields (see 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 aldehyde **1a** as model nucleophile, the scope of diketones was also examined. As shown in Scheme 1, product **3n-x**. Substituents with different electro-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 enantioselectivity, which may cause by undesired steric effect (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 benzyl group with more steric hindered benzhydryl group increased the enantioselectivity to 96:4 er (product **3x**).

Scheme 1. Scope of Substrates^[a]

[a] All yields are isolated yields and the er was determined by chiral phase HPLC analysis.

Cyclopentenedione with spirocyclic structures were also tested with the standard condition (Table 1, entry 7). The reactions all underwent smoothly and gave the desired spirocyclic indanes in good yields (products **3y–y2**). The enantioselectivity highly depends on the steric property of the spirocycles. Product **3y** and **3y1** were obtained with low enantioselectivities. When introducing proper substituents, product **3y2** could be obtained with excellent 95:5 er. It is worth

to note the asymmetric catalytic synthesis of product **3y2** represents a shortcut towards the BCDEF ring analogue structure of natural antibiotic fredericamycin A (Figure 1a) that are otherwise tedious to build enantioselectively.^[11]

We next demonstrated effective transformation of our optical active products to interesting multicyclic or spirocyclic compounds. Direct reduction of phenol **3u** with iron powder gave benzoindenoquinolinone **5**, while the reduction of methyl protected **3u** furnished tetracyclic compound **6** via a complete reverse regioselective cyclization (Scheme 2a). The divergent regioselective reductive cyclization were probably due to the ketone activation effect of intramolecular H-bonding in **3u**, and the steric hindrance of OMe group in the protected **3u**. Both transformations were in good yields with only slightly decline in enantioselectivities. These molecules were previously synthesized by methylation of pre-exist multicyclic compounds,^[25] and the asymmetric synthesis is unprecedented. Phenol **3x** was transformed to chiral tribenzotriquinacenes **7** with 62% total yields and 94:6 er via a 3 steps process including phenol protection, ketone hydrogenation and intramolecular Friedel–Crafts alkylation (Scheme 2b). Tribenzotriquinacene with unique bowl-shape framework is an interesting building block for macromolecular construction.^[9] The chirality of these building blocks may have a crucial effect to decide the shape of macromolecule.^[9d] However, the asymmetric synthesis of chiral tribenzotriquinacene is challenging. Recent methods mostly involve kinetic resolution pathway and with low yield.^[9b] Comparatively, our methods were much more efficient.

Scheme 2. Product Transformation

A plausible pathway of our NHC-catalyzed [4+2] cycloaddition involving formal γ - and carbonyl carbon activations of enal is illustrated in Scheme 3. Briefly, addition of the NHC catalyst to the aldehyde followed by deprotonation forms Breslow intermediate. This process is followed by oxidative transformation and then enal γ -C–H deprotonation leads to vinyl enolate intermediate **II**.^[26] Since diketone **2a** were proved to be good electrophile (or dipolarophile) and poor dienophile in previous studies,^[27] we proposed a stepwise Michael addition & intramolecular adol reaction pathway rather than a concerted [4+2] Diels–Alder reaction process (intermediate **II** to **III**). During

the cycloaddition process, the more steric mesityl moiety (2,4,6-trimethylphenyl group, Mes) would place apart and chiral indane moiety control the direction of diketone **2a** to set the more steric Bn group apart (Scheme 3, intermediate **II** and **III**). Finally, release of carbene catalyst and oxidative aromatization effectively affords phenol product **3a** with four substituents in predictable substitution patterns and a remote all-carbon quaternary chiral center. It is also worth to note, probably due to the slightly difference of α -H acidity in intermediate **III**, no proton transfer occurred and no [4+1] cyclization product was observed, which was quite different from our earlier work.^[17a]

Scheme 3. Postulated Pathway

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

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- [1] a) S. J. Hein, D. Lehnher, H. Arslan, J. U.-R. F. W. R. Dichtel, *Acc. Chem. Res.* **2017**, *50*, 2776; b) G. Dominguez, J. Perez-Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430; c) D. Mal, P. Pahari, *Chem. Rev.* **2007**, *107*, 1892.
- [2] a) G. Zhang, Y. Lin, X. Luo, X. Hu, C. Chen, A. Lei, *Nat. Commun.* **2018**, *9*, 1225; b) T. Wang, R. R. Naredla, S. K. Thompson, T. R. Hoye, *Nature* **2016**, *532*, 484; c) A. V. Iosub, S. S. Stahl, *J. Am. Chem. Soc.* **2015**, *137*, 3454; d) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209; e) J. Feierfeil, A. Grossmann, T. Magauer, *Angew. Chem. Int. Ed.* **2015**, *54*, 11835; *Angew. Chem.* **2015**, *127*, 12001; f) F. Ling, Z. Li, C. Zheng, X. Liu, C. Ma, *J. Am. Chem. Soc.* **2014**, *136*, 10914; g) T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby, B. P. Woods, *Nature* **2012**, *490*, 208; h) L. M. Geary, T. Y. Chen, T. P. Montgomery, M. J. Krische, *J. Am. Chem. Soc.* **2014**, *136*, 5920.
- [3] a) P. Finkbeiner, K. Murai, M. Ropke, R. Sarpong, *J. Am. Chem. Soc.* **2017**, *139*, 11349; b) M. Yang, X. Yang, H. Sun, A. Li, *Angew. Chem. Int. Ed.* **2016**, *55*, 2851; *Angew. Chem.* **2016**, *128*, 2901; c) Z. Lu, Y. Li, J. Deng, A. Li, *Nat. Chem.* **2013**, *5*, 679; d) K. C. Nicolaou, J. Wang, Y. Tang, L. Botta, *J. Am. Chem. Soc.* **2010**, *132*, 11350.
- [4] A. Link, C. Sparr, *Chem. Soc. Rev.* **2018**, *47*, 3804.
- [5] C. Borie, L. Ackermann, M. Nechab, *Chem. Soc. Rev.* **2016**, *45*, 1368.
- [6] G. R. Pettit, Y. Meng, R. K. Pettit, D. L. Herald, Z. A. Cichacz, D. L. Doubek, L. Richert, *J. Nat. Prod.* **2010**, *73*, 388.
- [7] I. M. Bell, S. N. Gallicchio, M. R. Wood, A. G. Quigley, C. A. Stump, C. B. Zartman, J. F. Fay, C. C. Li, J. J. Lynch, E. L. Moore, S. D. Mosser, T. Prueksaritanont, C. P. Regan, S. Roller, C. A. Salvatore, S. A. Kane, J. P. Vacca, H. G. Selnick, *ACS Med. Chem. Lett.* **2010**, *1*, 24.
- [8] C. A. Stump, I. M. Bell, R. A. Bednar, J. G. Bruno, J. F. Fay, S. N. Gallicchio, V. K. Johnston, E. L. Moore, S. D. Mosser, A. G. Quigley, C. A. Salvatore, C. R. Theberge, C. Blair Zartman, X. F. Zhang, S. A. Kane, S. L. Graham, J. P. Vacca, T. M. Williams, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 214.
- [9] a) L. He, C. F. Ng, Y. Li, Z. Liu, D. Kuck, H. F. Chow, *Angew. Chem. Int. Ed.* **2018**, *57*, 13635; *Angew. Chem.* **2018**, *130*, 13823; b) P. Wagner, F. Rominger, M. Mastalerz, *Angew. Chem. Int. Ed.* **2018**, *57*, 11321; *Angew. Chem.* **2018**, *130*, 11491; c) H. W. Ip, C. F. Ng, H. F. Chow, D. Kuck, *J. Am. Chem. Soc.* **2016**, *138*, 13778; d) D. Beaudoin, F. Rominger, M. Mastalerz, *Angew. Chem. Int. Ed.* **2016**, *55*, 15599; *Angew. Chem.* **2016**, *128*, 15828; e) S. Klotzbach, F. Beuerle, *Angew. Chem. Int. Ed.* **2015**, *54*, 10356; *Angew. Chem.* **2015**, *127*, 10497.
- [10] a) J. P. Campbell, S. C. Rajappan, T. J. Jaynes, M. Sharafi, Y. T. Ma, J. Li, S. T. Schneebeli, *Angew. Chem. Int. Ed.* **2019**, *58*, 1035; *Angew. Chem.* **2019**, *131*, 1047; b) W. Greschner, B. Neumann, H. G. Stammer, H. Groger, D. Kuck, *Angew. Chem. Int. Ed.* **2015**, *54*, 13764; *Angew. Chem.* **2015**, *127*, 13968; c) W. R. Xu, H. F. Chow, X. P. Cao, D. Kuck, *J. Org. Chem.* **2014**, *79*, 9335; d) P. Rommelmann, W. Greschner, S. Ihrig, B. Neumann, H.-G. Stammer, H. Gröger, D. Kuck, *Eur. J. Org. Chem.* **2018**, *2018*, 3891.
- [11] a) S. Akai, T. Tsujino, N. Fukuda, K. Iio, Y. Takeda, K. Kawaguchi, T. Naka, K. Higuchi, E. Akiyama, H. Fujioka, Y. Kita, *Chem. Eur. J.* **2005**, *11*, 6286; b) Y. Kita, K. Higuchi, Y. Yoshida, K. Iio, S. Kitagaki, K. Ueda, S. Akai, H. Fujioka, *J. Am. Chem. Soc.* **2001**, *123*, 3214.
- [12] S. Akai, T. Tsujino, N. Fukuda, K. Iio, Y. Takeda, K. Kawaguchi, K. I. T. Naka, K. Higuchi, Y. Kita, *Org. Lett.* **2001**, *3*, 4015.
- [13] a) D. L. Boger, O. Hueter, K. Mbiya, M. Zhang, *J. Am. Chem. Soc.* **1995**, *117*, 11839; b) D. L. J. Clive, Y. Tao, A. Khodabocus, Y.-J. Wu, A. G.

- Angoh, S. M. Bennett, C. N. Boddy, L. Bordeleau, D. Kellner, *J. Am. Chem. Soc.* **1994**, *116*, 11275.
- [14] a) K. Q. Chen, Z. Luo, Z. H. Gao, S. Ye, *Chemistry* **2019**, *25*, 3253; b) Q. Jia, J. Wang, *Org. Lett.* **2016**, *18*, 2212; c) Y. Nakano, D. W. Lupton, *Angew. Chem. Int. Ed.* **2016**, *55*, 3135; *Angew. Chem.* **2016**, *128*, 3187
- [15] Selected organometallic examples: a) R. Shintani, C. Takagi, T. Ito, M. Naito, K. Nozaki, *Angew. Chem. Int. Ed.* **2015**, *54*, 1616; *Angew. Chem.* **2015**, *127*, 1636; b) Y. Sato, T. Nishimata, M. Mori, *The Journal of Organic Chemistry* **1994**, *59*, 6133.
- [16] Selected atroposelective examples: a) D. Lotter, A. Castrogiovanni, M. Neuburger, C. Sparr, *ACS Cent. Sci.* **2018**, *4*, 656; b) A. Link, C. Sparr, *Angew. Chem. Int. Ed.* **2014**, *53*, 5458; *Angew. Chem.* **2014**, *126*, 5562.
- [17] Selective examples of desymmetrization of cyclopentenedione: a) S. Zhuo, T. Zhu, L. Zhou, C. Mou, H. Chai, Y. Lu, L. Pan, Z. Jin, Y. R. Chi, *Angew. Chem. Int. Ed.* **2019**, *58*, 1784; *Angew. Chem.* **2019**, *131*, 1798; b) M. S. Manna, S. Mukherjee, *J. Am. Chem. Soc.* **2015**, *137*, 130; c) X. Dou, Y. Lu, T. Hayashi, *Angew. Chem. Int. Ed.* **2016**, *55*, 6739; *Angew. Chem.* **2016**, *128*, 6851; d) K. Aikawa, T. Okamoto, K. Mikami, *J. Am. Chem. Soc.* **2012**, *134*, 10329; e) L. Yao, Q. Zhu, L. Wei, Z. F. Wang, C. J. Wang, *Angew. Chem. Int. Ed.* **2016**, *55*, 5829; *Angew. Chem.* **2016**, *128*, 5923.
- [18] a) S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190; b) S. De Sarkar, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9266; *Angew. Chem.* **2010**, *122*, 9452.
- [19] C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; *Angew. Chem.* **2004**, *116*, 6331.
- [20] a) T. Zhu, C. Mou, B. Li, M. Smetankova, B. A. Song, Y. R. Chi, *J. Am. Chem. Soc.* **2015**, *137*, 5658; b) T. Zhu, P. Zheng, C. Mou, S. Yang, B. A. Song, Y. R. Chi, *Nat. Commun.* **2014**, *5*, 5027.
- [21] N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518.
- [22] J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798.
- [23] P.-C. Chiang, M. Rommel, J. W. Bode, *J. Am. Chem. Soc.* **2009**, *131*, 8714.
- [24] M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418.
- [25] D. Tanaev, V. Lusi, D. Muceniece, *Chem. Heterocycl. Compd.* **2009**, *45*, 336.
- [26] L.-T. Shen, P.-L. Shao, S. Ye, *Adv. Synth. Catal.* **2011**, *353*, 1943.
- [27] W. C. Agosta, A. B. Smith, *J. Chem. Soc. D* **1970**, 685b.
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Layout 2:

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Indane formation: a one-step organic catalytic strategy for enantioselective access to indanes with attached all-carbon quaternary centers is disclosed. The reaction involves an N-heterocyclic carbene-catalyzed process for direct arene construction, indane formation, remote-carbon desymmetrization, and excellent chirality control. We expect this approach to benefit the concise synthesis of arene-containing molecules, including those with complex structures and challenging chiral centers.

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