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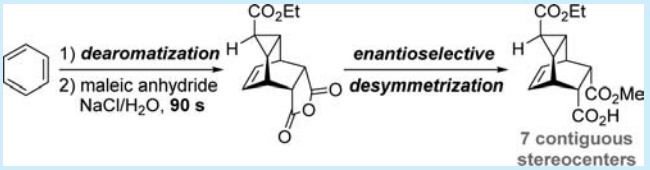
# Kinetic Separation and Asymmetric Reactions of Norcaradiene Cycloadducts: Facilitated Access via $H_2O$-Accelerated Cycloaddition

William D. Mackay and Jeffrey S. Johnson*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

Supporting Information

**ABSTRACT:** We exploit the Buchner reaction to access 1,2-disubstituted cyclohexadiene synthons (norcaradienes), which participate in $H_2O$-accelerated cycloaddition with dieneophiles to provide cyclopropyl-fused [2.2.2]-bicyclooctene derivatives in good yields. Regioisomeric mixtures can be kinetically separated by exploiting different reaction rates in Diels–Alder reactions. *Meso*-Diels–Alder products may be enantioselectively desymmetrized, providing highly substituted cyclohexanes with up to seven contiguous stereocenters.

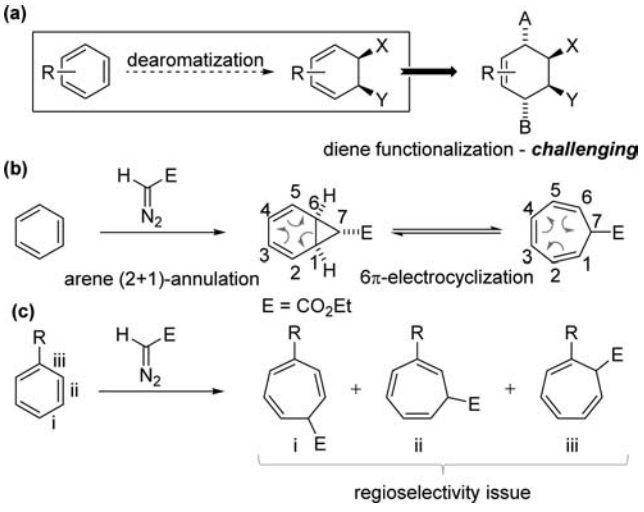



Highly substituted cyclohexanes comprise a large subset of valuable natural and laboratory-prepared molecules;[1] consequently, efficient assembly of these structural subunits remains a topic a great interest.[2] The impact of cycloaddition reactions on advances in this general area cannot be overstated;[3] however, traditional cycloaddition approaches to the preparation of these functionalities are often constrained to specific substitution patterns, and stereochemistry is dictated by the nature of the starting materials employed.[4] Despite their obvious potential in preparing substituted cyclohexanes, the direct manipulation of benzene derivatives in such endeavors remains an underutilized approach. As inexpensive commodity feedstock materials, benzene derivatives are frequently available in kilogram quantities and in a variety of substitution patterns.[5] Furthermore, the pre-existing six-membered ring and latent unsaturation in benzene derivatives (enabling downstream functionalization) could streamline the preparation of stereodefined cyclohexanes (Scheme 1a).

Extant methods for complexity-building dearomatizations of benzenes include oxidative[6] and reductive processes,[7] stoichiometric metal complexation,[8] and enzymatic reactions.[9] As part of our ongoing studies in complexity generation via manipulation of strained carbocycles,[10] we envisioned the union of benzene dearomatization and cyclopropane annulation would provide expedient access to substituted cyclohexanes. This could be accomplished via the Buchner reaction—the (2 + 1)-annulation of carbenes with arenes—to access substituted norcaradienes (NCD) (or their valence tautomeric cycloheptatrienes (CHT))[11] (Scheme 1b). These intermediates would then be poised to participate in a variety of useful diene functionalizations.

At least three barriers stand in the way of broader deployment of intermolecular Buchner adducts in synthesis: (1) The NCD products exist as a substrate-dependent equilibrating mixture of the NCD and the corresponding CHT adduct via electrocyclic ring opening and closure.[12] Reactions must be developed in which only the NCD (and not the CHT) reacts productively to give the desired product. (2)

**Scheme 1. Benefits and Challenges of Norcaradienes as Synthetic Intermediates**




The use of NCDs as Diels–Alder dienes is severely hindered by impractically slow reaction rates. (3) From a practical standpoint, mixtures of isopolar constitutional isomers are almost always present intractable separation/purification problems. For a monosubstituted benzene, three regioisomeric possibilities exist for the Buchner product identity via cyclopropanation at each site of unsaturation (Scheme 1c).[13] This problem is further complicated as the substitution pattern is increased. In prior work, this regiochemical preference has been biased by rendering the cyclopropanation intramolecular;[14] however, there currently exists no general regioselective method for the analogous *inter*molecular reaction.[15] We show in this communication that Diels–Alder reactions of norcar-

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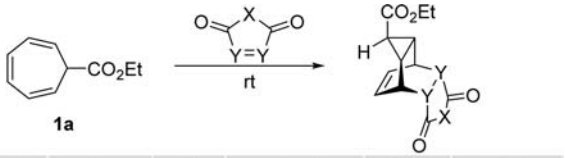
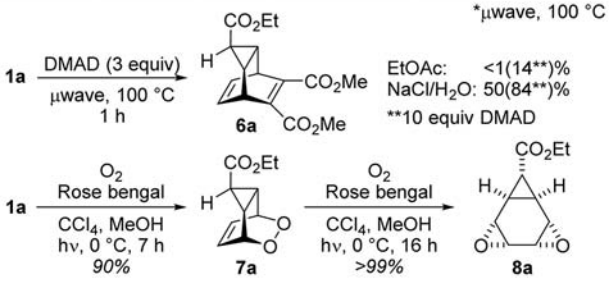
adienes are dramatically accelerated in an aqueous reaction medium and that significant rate differences between Buchner adduct regioisomers can facilitate kinetic separation of troublesome constitutional isomer mixtures. Also demonstrated herein is the enantioselective desymmetrization of *meso*-norcaradiene-[4 + 2] cycloadducts.

Central to confronting the Diels–Alder reaction rate problem was the recognition that conventional activation modes for accelerating Diels–Alder cycloaddition (e.g., Lewis acid catalysis) might be precluded by the tendency of the norcaradienes to rearomatize.[12,16] While we continue to pursue reaction conditions that would have a lower propensity toward cyclopropane opening (e.g., iminium ion catalysis), in a parallel investigation we have discovered a dramatic solvent effect that renders norcaradiene cycloadditions immediately more user-friendly. Specifically, by using saturated aqueous NaCl as the reaction solvent,[17] the reaction of cycloheptatriene **1a** with a variety of activated dienophiles (Scheme 2) led to exclusive

**Scheme 2. Scope of the Diels–Alder Reaction of 1a and the Rate Enhancement on Water**




| product | X | Y | solvent | time | yield |
|---|---|---|---|---|---|
| **2a** | O | CH | $Et_2O$ | 3 h | >99% |
| **2a** | O | CH | NaCl/$H_2O$ | 90 s | >99% |
| **3a** | NBn | CH | $Et_2O$ | 16 h | >99% |
| **3a** | NBn | CH | NaCl/$H_2O$ | 90 s | >99% |
| **4a** | o-$C_6H_4$ | CH | EtOAc | 1 h | <2%* |
| **4a** | o-$C_6H_4$ | CH | NaCl/$H_2O$ | 1 h | 93%* |
| **5a** | NPh | N | THF | 60 s | >99% |



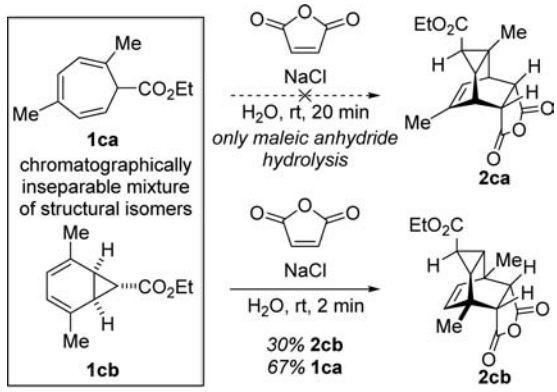

reaction via the norcaradiene isomer to providing *endo*-Diels–Alder products **2a**–**4a** as single diastereomers (via dieneophile facial approach *anti* to the cyclopropyl moiety);[18] the structure was confirmed by an X-ray diffraction study of **2a** (see the Supporting Information).

The rate increase for the aqueous Diels–Alder reaction was pronounced in the room temperature formation of **2a** or **3a** using maleic anhydride or *N*-benzylmaleimide, respectively, as the dienophiles (reaction times: **2a**, $Et_2O$, 3 h; brine, 90 s; **3a**, $Et_2O$, 16 h; brine, 90 s). The solvent effect was especially dramatic in the case of naphthoquinone: after stirring at room temperature in brine for 20 h, 22% conversion to **4a** was observed with naphthoquinone as the dieneophile. In diethyl ether under otherwise similar conditions, only trace product formation was observed. Under microwave irradiation (100 °C, 1 h) in brine, 95% conversion to the Diels–Alder product **4a** was observed, whereas the use of ethyl acetate under the same conditions provided less than 2% conversion of **1a**. Related reactions using naphthoquinone are reported to require prolonged heating (>120 °C, 7 d) to achieve suitable conversion.[19] Treating **1a** with dimethyl acetylenedicarboxylate (DMAD)[20] under analogous microwave conditions provided **6a** in 50% yield in brine, compared with trace product formation in EtOAc. The dramatic rate enhancements observed for these Diels–Alder reactions conducted in brine) are most likely a manifestation of the hydrophobic effect.[21]

Hetero-Diels–Alder reactions also proceeded with the norcaradiene isomer of **1a**. Treating **1a** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) in tetrahydrofuran provided complete conversion to the desired adduct **5a** in under 60 s.[22] Photochemically generated singlet oxygen[23] smoothly afforded the endoperoxide **6a** in 7 h; however, this product was challenging to isolate when the reaction was further scaled as prolonged irradiation of **7a** resulted in homolysis of the O–O bond and subsequent cyclization with the pendent alkene to provide the *syn*-bis-epoxide **8a**.[24] Productive reactivity with less reactive dienophiles (acrylates, acroleins, fumarates, etc.) in brine or organic solvents has been elusive to date; a screen of Lewis acid[25] or iminium[26] activators have been ineffective although efforts in this vein are continuing.

With proof-of-concept demonstrated for selective NCD (over CHT) reactivity Diels–Alder reactions, we turned our attention to expanding the scope of the reaction to encompass the regioisomerically impure substituted CHTs (Scheme 3).[27]

**Scheme 3. Kinetic Separation of Chromatographically Inseparable Regioisomers**[a]




[a]The $^1H$ NMR yield was determined using 1,4-dimethylterephthalate as internal standard.

In our initial screen with *p*-xylene-derived **1ca**/**1cb** and maleic anhydride using brine as the reaction medium, we observed complete conversion of the stable NCD **1cb** in under 2 min, while CHT **1ca** failed to react prior to hydrolysis of maleic anhydride (<20 min). However, when *N*-benzylmaleimide (which exhibits increased hydrolytic stability relative to maleic anhydride) was employed, full conversion to both regioisomeric products was realized upon prolonged stirring in brine (16 h). In light of these results and in order to resolve both product regioisomers, we envisioned a kinetic separation of the two isomers via successive treatment of the **1ca**/**1cb** with maleic anhydride followed by *N*-benzylmaleimide in a one-pot procedure. While this approach was effective in delivering the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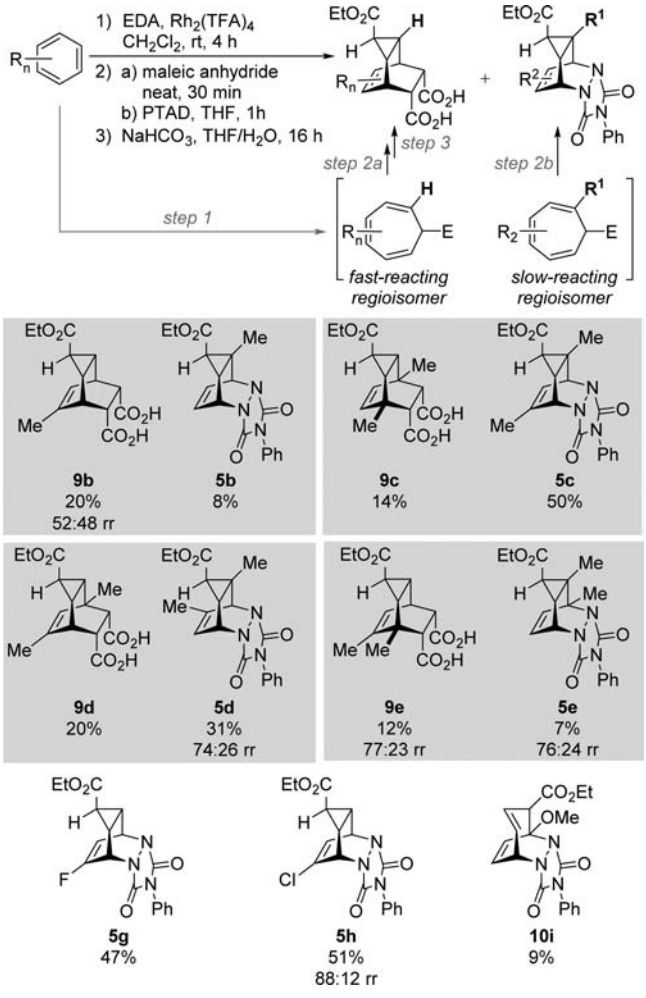
desired orthogonal reactivity pattern, isolation of the two products was complicated by challenges associated with their purification (see the Supporting Information for more detailed discussion).

To address these issues, we devised a two-step procedure to facilitate isolation and purification of both products. Two considerations were key to this endeavor: first, given that PTAD reacts with **1a**−**k** more rapidly than *N*-benzylmaleimide, we transitioned to using the former as the second dieneophile in the reaction sequence. Furthermore, the anhydride moieties of **2** could be selectively hydrolyzed in the presence of the urazoles **5** to generate diacids **9**, which allowed for facile separation of the two products by an aqueous extraction (Scheme 4). We were, however, unable to isolate the diacids from 3-methoxy substituted cycloheptatrienes under this manifold, although the initial Diels−Alder adducts with maleic anhydride were readily identified by $^1$H NMR prior to hydrolysis. The halo-substituted cycloheptatrienes **1g**,**h** were slow to react with maleic anhydride, and we were only able to convert the 3-halo-substituted isomers to product using PTAD, with the other regioisomers being inert to the reaction conditions, even upon stirring for multiple days.

**Scheme 4. Optimized Kinetic Separation via Buchner/Diels−Alder Reaction Sequence**[a]



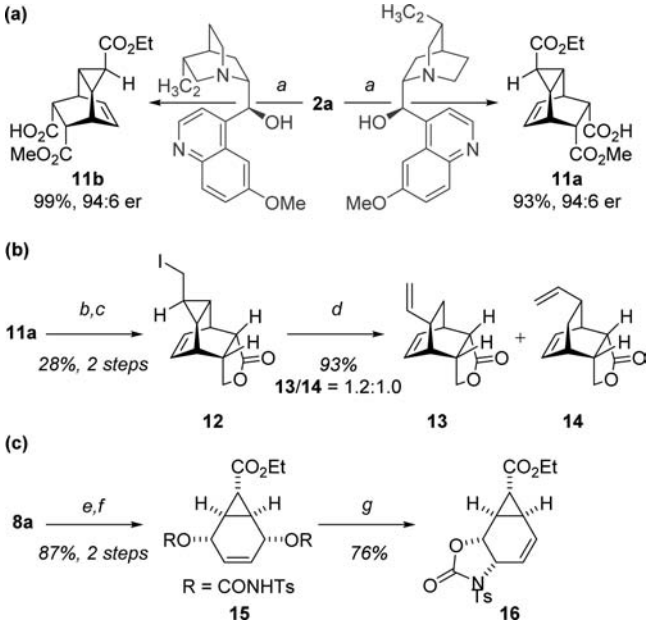

[a]Yields and regioisomeric ratios (rr) of the Diels−Alder products were determined by $^1$H NMR of the isolated products. In cases of regioisomeric mixtures, only the major regioisomer is shown (see the Supporting Information for a complete listing of the regioisomeric products).

In our screening, we observed that the rate of the reaction of the dienes corresponded well with the position of the CHT/NCD equilibrium. While there are many factors that influence the equilibrium,[12] in the context of **1a**−**k**, substitution at the 1- or 6-position shifted the equilibrium toward the CHT. Notably, electron-donating substituents at this position greatly favored the CHT, as evidenced by the isolation of **10i**, resulting from the (4 + 2)-cycloaddition of the 1-methoxy-substituted CHT isomer.

The benzene-derived norcaradiene Diels−Alder adducts are *meso* compounds containing six asymmetric centers. The viability of these products in stereoselective cyclohexane synthesis was explored in the context of a number of symmetry-breaking product manipulations. First, using cinchona alkaloids and alcoholic nucleophiles,[28] the anhydride **2a** underwent enantiotopic group-selective nucleophilic acyl substitution, providing hemiesters **11a** and **11b** in 94:6 er with excellent diastereoselectivity (>20:1). Either enantiomer was accessible with comparable selectivity via appropriate selection of cinchona alkaloid promotor. Monoacids **11a**/**b** contain seven contiguous stereocenters, accessed from an achiral, *meso*-Diels−Alder adduct **2a**, obtainable in three steps from benzene.

The hemiesters **11a**/**11b** were then further manipulated toward the goal of cyclopropane ring-opening (Scheme 5b). Accordingly, reduction of **11a** using $LiEt_3BH$ followed by acid-promoted lactonization provided the cyclopropyl methanol, which could then be converted to the alkyl iodide **12** via Appel reaction. Photolysis of the alkyl iodide in the presence of $Bu_3SnH$ revealed a primary cyclopropylmethyl radical that rearranged rapidly to form a secondary radical concomitant

**Scheme 5. Desymmetrization of *Meso*-Products and Cyclopropyl Ring-Opening**




[a]MeOH, PhMe/$CCl_4$ (1:1), −55 °C. [b]$LiEt_3BH$, THF, 0 °C to rt; 1 M HCl, rt. [c]$PPh_3$, imidazole, $I_2$, 0 °C to rt. [d]$Bu_3SnH$, *hν*, $CH_2Cl_2$, rt. [e]MeMgI, $Bu_3SnH$, THF, 0 °C. [f]TsNCO, THF, rt. [g]$Pd_2(dba)_3$·$CHCl_3$, $(2\text{-furyl})_3P$, THF, rt.



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with cyclopropane ring-opening,[29] providing a regioisomeric mixture of **13** and **14** in 93% yield.

Finally, *meso*-bis-epoxide **8a** (derived from prolonged photolysis of endoperoxide **7a**, vide supra) also may be converted to new chiral structures (Scheme 5c). Reduction of **8a** via treatment with MeMgI and $SnBu_3H$ to afford the resulting *syn*-1,4-diol. Desymmetrization of the *meso*-diol was then accomplished via condensation with *p*-toluenesulfonyl isocyanate to provide the bis-carbamate **15** in 87% yield from **8a**. Selective $\pi$-allyl displacement of the enantiotopic carbamates[30] under Pd catalysis afforded the protected 1,2-*syn*-amino alcohol **16**. Extension of this methodology to enantioselective methods is well-precedented.[31]

In conclusion, we have shown that inexpensive, commercially available aromatic compounds may be deployed in the synthesis of complex cyclohexane derivatives in an expedient manner. As a means to independently isolate both regioisomers in the Buchner reaction of *p*-xylene (**1ca**/**1cb**), the inseparable regioisomeric NCD/CHT mixture was kinetically resolved upon successive treatment with dieneophiles of variable rates of reaction. Furthermore, enantioselective desymmetrization of *meso*-Diels–Alder products **2a**, **8a** enables access to up to seven stereocenters in a single operation from achiral materials. The present method should provide a new conceptual blueprint for the expedient assembly of complex carbocyclic structures. Additional improvements to Buchner reaction regioselectivity and further extension of CHT product transformations are currently underway and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03577.

Experimental conditions and spectroscopic and analytical data for all new compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: jsj@unc.edu.


### Notes

The authors declare no competing financial interest.

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