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Straightforward Access to the [3.2.2]Nonatriene Structural Framework via Intramolecular Cyclopropenation/Buchner Reaction/Cope Rearrangement Cascade

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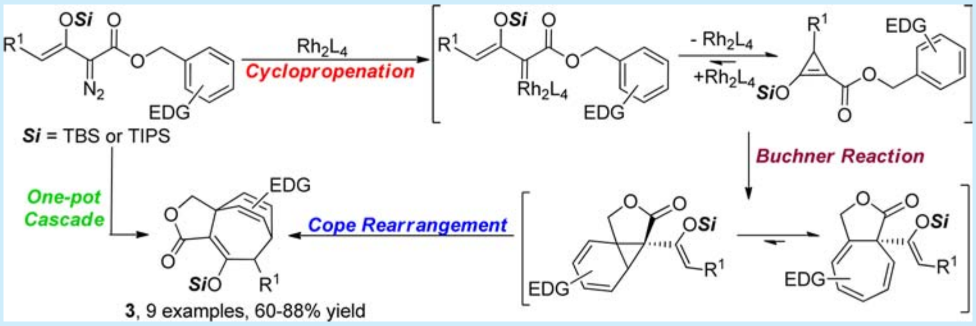
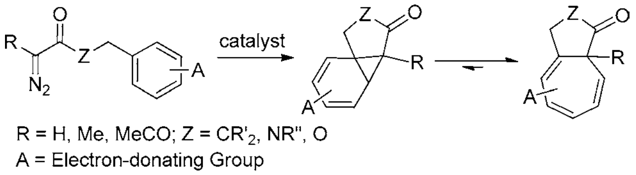
S *Supporting Information*



ABSTRACT: A one-pot cascade process of benzyl enoldiazoacatates, initiated by dirhodium(II)-catalyzed intramolecular cyclopropene formation, occurs via a subsequent Buchner reaction and Cope rearrangement to provide straightforward access to bicyclo[3.2.2]nonatriene derivatives in high yields and selectivities.

The Buchner reaction, a two-step C−C bond-forming reaction between aromatic hydrocarbons and carbene species[1] that is an important method for the preparation of seven-membered ring compounds, has been successfully applied to the total synthesis of natural products.[2] In this transformation, carbene addition to the aromatic ring forms a norcaradiene structure[3] that exists in equilibrium with its valence tautomeric cycloheptatriene structure, with the latter usually being the more stable (Scheme 1).[4b,5] Dirhodium catalysts have proven to be superior to those of copper for the Buchner reaction,[5] but recently introduced ruthenium catalysts also show potential.[6] Intramolecular reactions of diazo ketones and diazoacetamides have been examined to elucidate structural influences of the diazo compound on selectivity (e.g., aromatic cycloaddition vs substitution vs C−H insertion),[2,7] and dirhodium ligand influences on reactivity and selectivity have shown that electron-withdrawing ligands favor aromatic cycloaddition.[4]

Scheme 1. Intramolecular Buchner Reaction



Intramolecular Buchner reactions performed with diazoketones and diazoacetamides are common,[2−7] but we are aware of only three reports using diazoacetates and none with enol diazoacetates.[8] In an effort to determine if the Buchner reaction from reactions with diazoacetates could be developed for subsequent electrocyclic processes, we have chosen to examine catalytic reactions of benzyl enol diazoacetates.[9] The positioning of the vinyl groups in the norcaradiene structure from intramolecular aromatic cycloaddition with the vinyl group from the silylated enol substituent provides a structural framework that is suitable for a subsequent Cope rearrangement which could form either or both of two bicyclic products (Scheme 2). We now report a straightforward and highly selective access to one of these bicyclononatriene derivatives via a dirhodium-catalyzed intramolecular cascade process that was initiated from readily accessible enol diazoacetates.

Rapid and quantitative conversion of benzyl enol diazoacetate **1a** to the corresponding donor−acceptor cyclopropene was observed when **1a** was treated with a catalytic amount of rhodium acetate at room temperature. The intermediate formation of donor−acceptor cyclopropenes from enol diazoacetates in dirhodium(II) catalyzed reactions, and their possible role as reactive metal carbene precursors, has recently been established.[10] However, once formed, only relatively slow decom-

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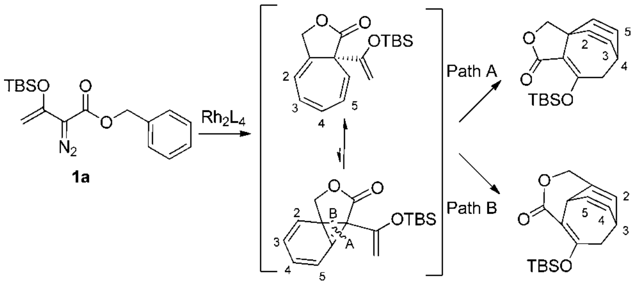
Scheme 2. Aromatic Cycloaddition/Cope Rearrangement Cascade to Bicyclononatrienes



position of this cyclopropene was observed in a broad survey that examined a range of temperatures (0−60 °C) with dirhodium catalysts, including $Rh_2(tfa)_4$ and $Rh_2(pfb)_4$, that favor aromatic cycloaddition over C−H insertion.[7] Figure 1 describes the ^{1}H NMR spectral monitored course of the reaction with **1b** catalyzed by $Rh_2(OAc)_4$, whose electron-rich *p*-methoxybenzyl group is conducive toward aromatic cycloaddition.

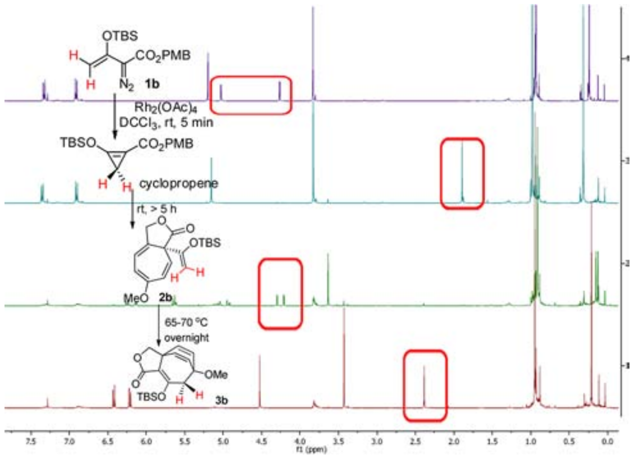


Figure 1. Sequential conversion of enol diazoacetate **1b** to donor−acceptor cyclopropene to aromatic cycloaddition product **2b** then to Cope rearrangement product **3b**.

At room temperature in $CDCl_3$, **1b** undergoes dinitrogen extrusion and rearrangement to the donor−acceptor cyclopropene rapidly with no evidence of further reaction during the first 5 min. At 40 °C within 1 h (or at room temperature in over 5 h), cyclopropene is converted to the aromatic cycloaddition product **2b** exclusively, and this product is stable at these low temperatures. However, heating the reaction solution in the sealed vessel overnight causes formation of the structurally symmetric bicyclo[3.2.2]nona-2,6,8-triene product **3b** by Cope rearrangement (Scheme 2, path A) as the only product in 80% isolated yield. Control reactions showed that the dirhodium catalyst is essential for the Buchner reaction from reaction with both the enol diazoacetate and the corresponding donor−acceptor cyclopropene.

The structures of bicyclo[5.3.0]nonatriene **2b** and bicyclo[3.2.2]nonatriene **3b** were confirmed by single-crystal X-ray diffraction analysis (Figure 2).[11] Bicyclo[3.2.2]nona-2,6,8-trienes have unique structural frameworks that have attracted synthetic and theoretical interest,[12] and they have recently been found to be a core unit in some polycyclic bioactive natural compounds.[13] However, synthetic methods used to access these structures are rare,[14] especially for those with diverse functional groups.

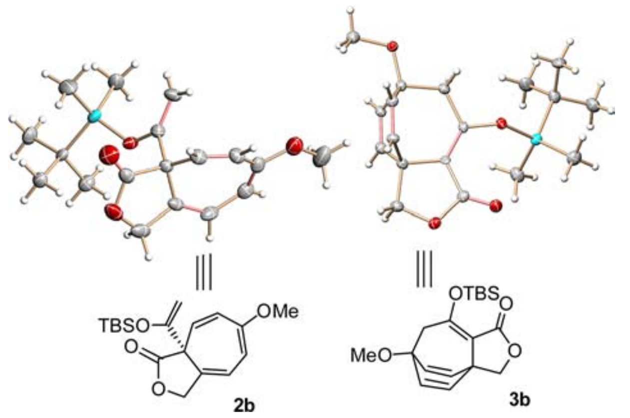
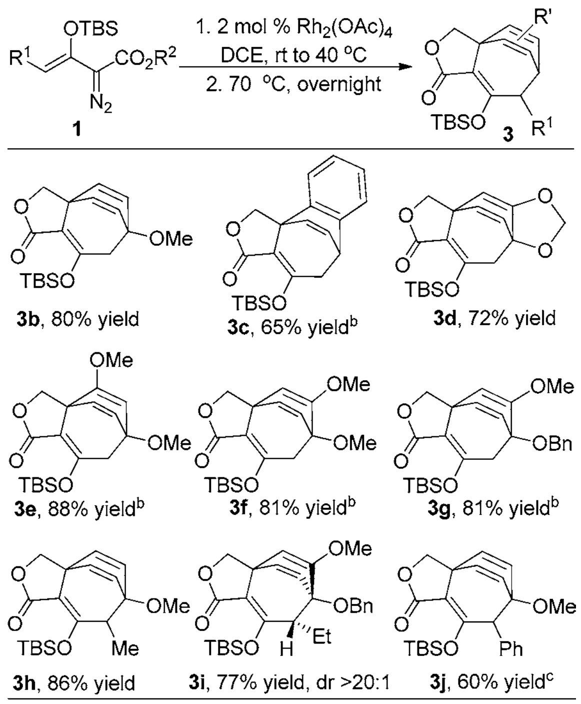


Figure 2. X-ray crystal structures of **2b** and **3b**.

The influence of substituents was investigated with various electron-rich benzyl enol diazoacetates (Scheme 3). Reactions were initiated with $Rh_2(OAc)_4$ in 1,2-dichloroethane at room temperature which caused a rapid loss of dinitrogen and generation of the corresponding donor−acceptor cyclopropene within 5 min. Warming to 40 °C caused aromatic cycloaddition in 1 h, and then continued heating at 70 °C overnight converted the Buchner reaction product **2** to **3** via the Cope rearrangement. All of the reactant diazo compounds with electron-donating benzyl ester substituents gave bicyclo[3.2.2]nona-2,6,8-triene products from aromatic cycloaddition/Cope rearrangement in

Scheme 3. Applications of Aromatic Cycloaddition/Cope Rearrangement

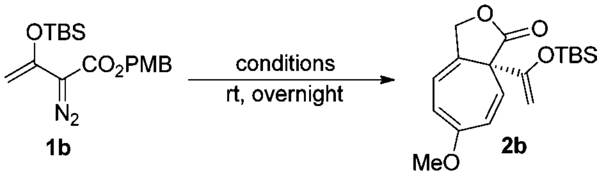


[a]Reactions were carried out on a 0.5 mmol scale in 2.0 mL of DCE with 2.0 mol % of $Rh_2(OAc)_4$. [b]The Cope rearrangement was carried out at 40 °C instead of 70 °C, and the reaction was complete in 5 h. [c]The Cope rearrangement was carried out at 80 °C instead of 70 °C, and the reaction was complete in 24 h.

high yield (60−88% yield). Those enol diazoacetates without electron-donating alkoxy substituents also formed their corresponding donor−acceptor cyclopropenes rapidly but on warming to higher temperatures underwent slow decomposition to product mixtures that were not further analyzed. 1-Naphthyl and 3,4-(methylenedioxy)benzyl esters generated the corresponding bicyclo[3.2.2]nonatrienes **3c** and **3d** in 65% and 72% yield, respectively. Substrates with two electronic donating groups were more reactive compared to those with one alkoxy substituent, and their reactions formed Cope rearrangement products **3e−g** in greater than 81% yield at 40 °C. Enol diazoacetates with substitutents at the vinylogous position (R^1 = Me, Et, and Ph) were also examined, and they smoothly generated the Cope rearrangement products in high yield **3h−j**, although higher temperatures and longer reaction times were necessary for the phenyl-substituted enol diazoacetate **1j**. It should be noted that high diastereoselectivity was observed for product **3i**, and its relative structure was confirmed by 1D NOE analysis, in which the ethyl group and the 3-methoxy group of the original aryl ring are on opposite sides.

Attempts to perform these reactions with enantiocontrol were made with initial attention given to the aromatic cycloaddition process. Previous reports of asymmetric induction in the Buchner reaction with diverse chiral catalysts have shown optimum enantiocontrol in the general range of 56−81% ee.[8c,15] Key results from our survey with **1b** are reported in Table 1. The more sterically encumbered catalysts provided higher selectivities, and Hashimoto's sterically bulky dirhodium carboxylate catalyst $Rh_2(S\text{-PTTL})_4$ (entry 13) was optimum for enantiocontrol among those that were investigated. Solvent influenced enantioselectivity with α,α,α-trifluorotoluene being the optimum solvent for this transformation. The chiral dirhodium catalysts were more reactive toward aromatic cycloaddition than was $Rh_2(OAc)_4$.

Table 1. Determination of Optimum Reaction Conditions for Asymmetric Catalysis in Aromatic Cycloaddition[a]

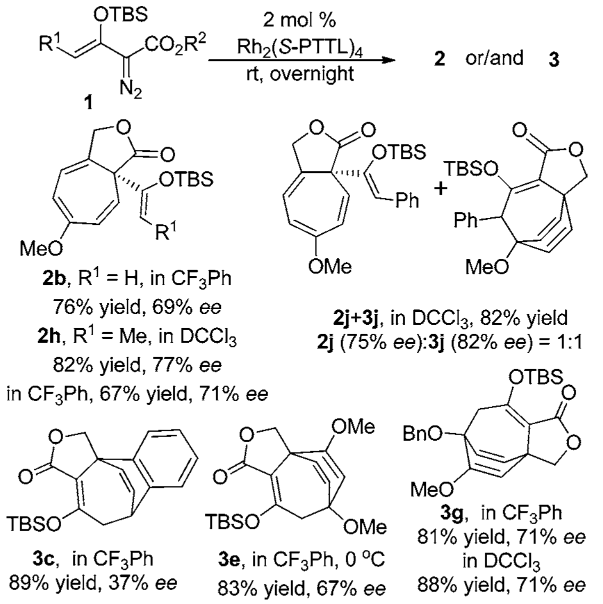


entry	Rh(II)	solvent	yield[b] (%)	ee[c] (%)
1	$Rh_2(S\text{-PTA})_4$	DCM	80	30
2	$Rh_2(S\text{-PTPA})_4$	DCM	75	29
3	$Rh_2(S\text{-PTL})_4$	DCM	72	48
4	$Rh_2(S\text{-PTTL})_4$	DCM	82	51
5	$Rh_2(S\text{-DOSP})_4$	DCM	75	6
6	$Rh_2(S\text{-PTTL})_4$	DCE	80	44
7	$Rh_2(S\text{-PTTL})_4$	*n*-heptane	75	60
8	$Rh_2(S\text{-PTTL})_4$	chloroform	65	45
9	$Rh_2(S\text{-PTTL})_4$	fluorobenzene	80	54
10	$Rh_2(S\text{-PTTL})_4$	chlorobenzene	81	53
11	$Rh_2(S\text{-PTTL})_4$	toluene	85	45
12	$Rh_2(S\text{-PTTL})_4$	α,α,α-trifluorotoluene	76	69
13	$Rh_2(S\text{-PTAD})_4$	α,α,α-trifluorotoluene	81	65

[a] Reactions were conducted by adding **1b** (0.2 mmol) in 1.0 mL of the solvent to the solution of catalyst in 0.5 mL of the solvent via syringe pump over 30 min. [b] Isolated yield. [c] The enantioselectivity was determined by chiral HPLC analysis: IB-3 column, 254 nm, 0.7 mL/min, hexanes:IPA = 95:5, t_R = 7.5, 8.4 min.

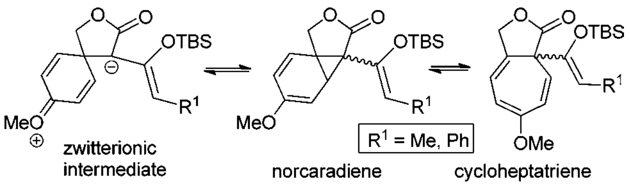
Examination of substrates from Scheme 3 under optimized conditions from Table 1 showed that several of the substrates (**1c**, **1e**, and **1g**) are directly converted to the final Cope rearrangement products **3** at room temperature with moderate enantioselectivity and high yield (Scheme 4).[16] Even at 0 °C, **1e** gave bicyclo[3.2.2]nona-2,6,8-triene **3e** in 83% yield with 67% ee. The Buchner reaction products **2b** and **2h** were isolated as only products from their corresponding enol diazoacetates at room temperature, both in high yield and with 69% ee and 77% ee, respectively. However, loss of the enantiomeric excess was observed during the process leading to the Cope rearrangement of **2h** to form **3h**, either with or without dirhodium catalyst at 60 °C ; enantiomeric excess decreased from 71% ee for **2h** to 41% (with catalyst) and 25% (without catalyst) for **3h**. This was the result of epimerization of the newly formed chiral center in the intermediate norcaradiene at the higher temperature used for the Cope rearrangement, and this equilibrium with a stabilized ylide was facilitated by the methoxy group in the *para* position of the original aryl ring (Scheme 5). Moody and co-workers reported a similar epimerization for loss of diastereoselection in a Buchner reaction of a *p*-methoxybenzyl diazomalonate ester.[4b] The same phenomenon was also observed during the formation of **2j** and **3j** under standard reaction conditions. Although **2j** and **3j** were obtained in 1:1 ratio with 75% ee and 82% ee, respectively, slow

Scheme 4. Catalytic Asymmetric Synthesis of 2 and 3[a]



[a] Reactions were carried out on a 0.2 mmol scale in 1.0 mL of solvent with 2.0 mol % of $Rh_2(S\text{-PTTL})_4$.

Scheme 5. Loss of Enantioselectivity Due to Zwitterionic Intermediate



racemization of **2j** occurred either with or without $Rh_2(S\text{-}PTTL)_4$ at room temperature, and total loss of optical purity for **2j** was observed after just 3 days at room temperature; on the other hand, no loss in enantioselectivity for **3j** was observed even after heating in DCE at 80 °C for a few hours.

In conclusion, we have developed a straightforward access to bicyclo[5.3.0]- and bicyclo[3.2.2]nonatriene derivatives in high yields and selectivities. This one-pot cascade intramolecular transformation was initiated by dirhodium-catalyzed donor—acceptor cyclopropene formation from corresponding enol diazoacetates, followed by the dirhodium-catalyzed Buchner reaction and subsequent Cope rearrangement by gradually increasing the reaction temperature and without the use of additional catalyst(s). Further studies exploring the scope and development new transformations by interception of active intermediates/products during metal carbene reactions, including asymmetric catalysis, are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1010091 contains the supplementary crystallographic data for **2b**, and CCDC 1010092 contains the supplementary crystallographic data for **3b**. These data can be obtained free of charge from the Cambridge crystallographic data centre via www.ccdc.cam.ac.uk/data_request/cif.

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