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Asymmetric Synthesis of a 5,7-Fused Ring System Enabled by an Intramolecular Buchner Reaction with Chiral Rhodium Catalyst

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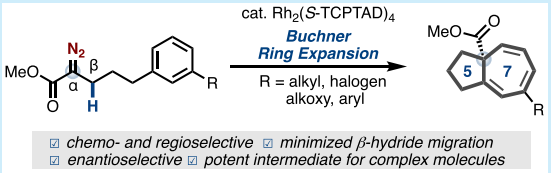
Supporting Information

ABSTRACT: A Rh-catalyzed asymmetric intramolecular Buchner ring expansion of α-alkyl-α-diazoesters has been developed. The present protocol generates a 5,7-fused ring system in an enantioselective manner while minimizing β-hydrogen migration, which has been a competing reaction when using α-alkyl-α-diazoesters. The ester functionality at the bridgehead position would be a useful synthetic handle for further derivatization to complex molecules including natural products.



A fused polycyclic architecture is one of the most characteristic motifs in bioactive molecules. Particularly, a 5,7-fused ring system is broadly recognized in terpenoidal frameworks with multiple stereocenters.[1] For example, anticancer agents ingenol[2a] and pseudolaric acids[2b,c] as well as rudmollin[2d] and other natural products[2e,f] have an all-carbon quaternary center at the bridgehead position (Figure 1A). Construction of this quaternary carbon at the bridgehead position frequently requires multiple synthetic sequences and cumbersome transformations, making facile access to this skeleton challenging. As a powerful approach for the preparation of such 5,7-fused ring systems, intramolecular Buchner ring expansion of α-diazocarbonyl has been utilized.[1c,3,4] An attractive feature of this reaction is the ability to form 5,7-fused rings with a quaternary carbon at the bridgehead position in a single step from readily prepared substituted benzenes (Figure 1B). However, the nature of the substituents on the diazo carbon significantly affects the reaction outcome, restricting the structural diversity of α-diazo carbonyls that can be used.

In the intramolecular Buchner reaction, a carbene species prepared from the diazo compounds attacks to the benzene ring to form a cyclopropane as an intermediate, and then subsequent divinylcyclopropane rearrangement provides the 5,7-fused ring. Rhodium and copper have been the most commonly employed catalysts for the generation of the carbene.[3] The vast majority of α-diazo carbonyl substrates have hydrogen or methyl group on the diazo carbon because a competing β-hydride migration frequently occurs when the α-diazocarbonyl has β-hydrogen atom.[5] The propensity of β-hydride migration is related to β-C−H bond strength, where the C−H bond in a methyl group is the least likely to migrate. On the other hand, β-keto-α-diazoester furnishes a 5,7-fused ring with an angular quaternary ester group as a versatile synthetic handle. Although this ring formation can proceed even in an enantioselective manner,[6] undesired 6,6-fused ring is often observed via rearomatization in a broad range of substrates due to the electrophilic nature of the carbonyl group at the β-position.[7] Meanwhile, Buchner reaction of α-alkyl-α-diazoesters predominantly results in β-hydrogen migration to give α,β-unsaturated esters.[5,8]

Despite extensive research on the intramolecular Buchner reaction, only one example demonstrated 5,7-fused ring formation with high chemoselectivity over β-hydride migration.[9,10] Moreover, its enantioselective variant has not been reported to our knowledge.[11] Thus, we sought to extend the capability of the intramolecular Buchner reaction to enable facile access to chiral 5,7-fused ring systems with an all-carbon quaternary center at the bridgehead position, which could be help facilitate the asymmetric synthesis of complex terpenoidal natural products.

To overcome the main issue of β-hydride migration, we set out to screen various rhodium catalysts with α-diazo benzenepentanoic acid methyl ester (**1A**) as a substrate (Table 1).[12] The reaction was performed using **1A** with 1 mol % rhodium catalyst in 1,2-dichloroethane (1,2-DCE) at 0 °C. With $Rh_2(OAc)_4$, 5-phenyl-2-pentenoic acid methyl ester (**3A**) was predominantly obtained, which is consistent with previous studies (Table 1, entry 1).[5,8] Use of $Rh_2(TFA)_4$ and $Rh_2(TPA)_4$ did not suppress the formation of **3A** although $Rh_2(OPiv)_4$ furnished 55% of **2A** with decreased amount of **3A** (Table 1, entries 2−4).[9] $Rh_2(esp)_2$[13a] further improved the yield along with a suppressed amount of **3A** (Table 1, entry 5). Thus, by a judicious choice of Rh catalyst, suppression of β-hydride migration was achieved. Next, we turned our attention to enantioselective Buchner ring expansion. When chiral Rh catalyst $Rh_2(S\text{-PTPA})_4$[13b] was used, **2A** was produced in 58%

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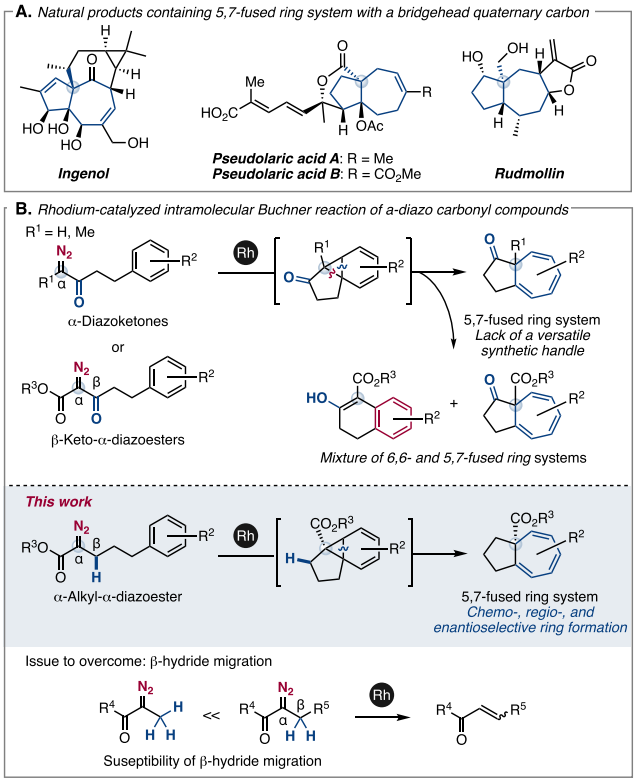
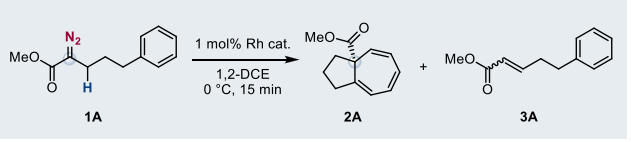
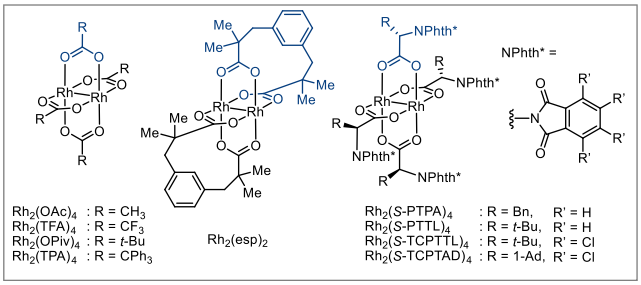


Figure 1. (A) Natural products with a 5,7-fused ring system and a bridgehead quaternary carbon. (B) Rhodium-catalyzed intramolecular Buchner reaction of α-diazo carbonyl compounds.

Table 1. Screening of Rhodium Catalysts*



entry	Rh catalyst	2A/%[a]	3A/%[a]	2A/*ee*
1	$Rh_2(OAc)_4$	9	53	-
2	$Rh_2(TFA)_4$	30	60	-
3	$Rh_2(TPA)_4$	10	57	-
4	$Rh_2(OPiv)_4$	55	20	-
5	$Rh_2(esp)_2$	62	14	-
6	Rh_2(*S*-PTPA)$_4$	58	18	48
7	Rh_2(*S*-PTTL)$_4$	66	13	75
8	Rh_2(*S*-TCPTTL)$_4$	66	16	91
9	Rh_2(*S*-TCPTAD)$_2$	72 (61)[b]	15	91

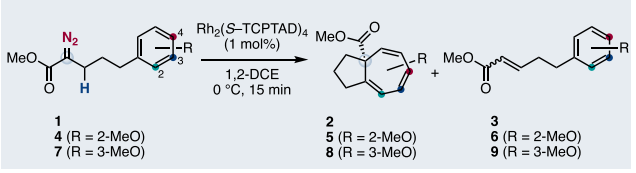


*Conditions: **1A** (0.20 mmol), rhodium catalyst (1 mol %), 1,2-DCE (4.0 mL), 0 °C, 15 min. [a]^{1}H NMR yield was determined by using CH_2Br_2 as an internal standard. [b]The number in parentheses is the isolated yield.

yield in an enantioselective manner while maintaining the low yield of **3A** (Table 1, entry 6). Rh_2(*S*-PTTL)$_4$[13c] and Rh_2(*S*-TCPTTL)$_4$[13d] were more effective and the latter exhibited excellent enantioselectivity (Table 1, entries 7 and 8). Finally, we found that Rh_2(*S*-TCPTAD)$_4$[13e] is the most effective catalyst affording **2A** in 72% yield with 91% ee (Table 1, entry 9).

With the optimal conditions (Table 1, entry 9) in hand, we investigated the substrate scope using substituted benzenes (Table 2). Buchner reaction of fluorobenzene **1B**, chlorobenzene **1C**, and bromobenzene **1D** all furnished **2** along with significant amounts of olefin **3** (Table 2, entries 1−3). Since electron-donating substituents would enhance nucleophilicity of the benzene ring and accelerate the Buchner reaction,[3] electron-donating groups were also examined. Although methyl group (**1E**) furnished bicyclic skeleton **5** in 60% yield with less formation of **3**, use of more electron-donating methoxy (**1F**) substituents did not improve the yield of **2** (Table 2, entry 5). These results indicated that a steric effect rather than an electronic effect of the substituents on the benzene ring influences the product distribution in this Buchner ring expansion. To compare the effect of the substituent position on the benzene ring, we further examined the reaction using substrates possessing a methoxy group on different positions (Table 2, entries 6 and 7). Whereas the 2-methoxy substituent **4** gave 24% yield of the desired product **5**, 3-methoxy **7** furnished the corresponding product **8** in excellent yield along with a suppressed amount of the migration product **9**.

Table 2. Substrate Scope of Buchner Reaction with Substituted Benzenes*



entry	R	2, 5, 8[a] (%)	3, 6, 9[a,b] (%)
1	4-F	38	48
2	4-Cl	22	58
3	4-Br	17	66
4	4-Me	60	30
5	4-OMe	41	54
6	2-OMe (**4**)	24[c]	55
7	3-OMe (**7**)	87[c]	<5

*Conditions: **1**, **4**, or **7** (0.20 mmol), Rh_2(*S*-TCPTAD)$_4$ (1 mol %), 1,2-DCE (4.0 mL), 0 °C, 15 min. [a]^{1}H NMR yield was determined by using CH_2Br_2 as an internal standard. [b]*E*/*Z* mixture. [c]single regioisomer.

Given that 3-substituted benzenes are suitable substrates for minimizing the formation of olefins, we next examined the applicability of this reaction for enantioselective ring formation (Scheme 1). A 3-methyl substituent on the parent benzene (**7B**) successfully resulted in enantioenriched 5,7-fused ring **8B**. Fluoro (**7C**), chloro (**7D**), and bromo (**7E**) groups were accommodated to form the corresponding products **8C**−**8E** with high levels of enantioselectivity. Methoxy (**7A**), phenoxy (**7F**), as well as trifluoromethoxy (**7G**), which is particularly attractive for the pharmaceutical industry, were tolerated. Additionally, a variety of aromatic rings including phenyl (**7H**),

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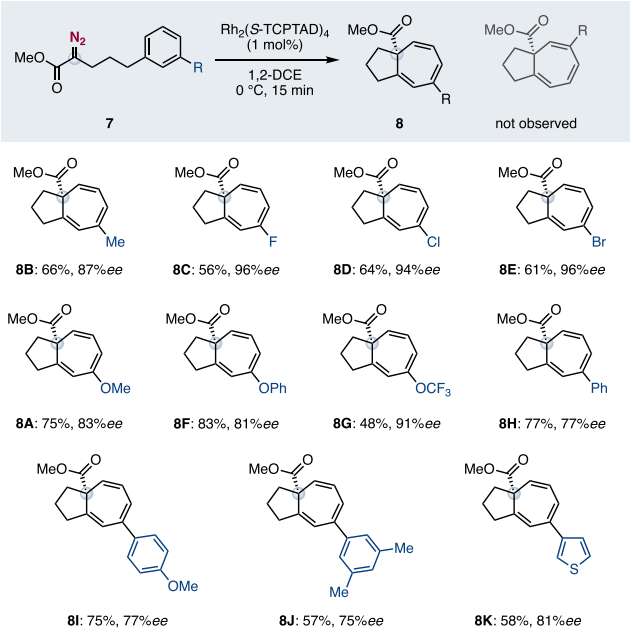
Scheme 1. Substrate Scope of Buchner Reactions with 3-Substituted Benzenes[a]



[a]Conditions: **7** (0.20 mmol), Rh_2(*S*-TCPTAD)$_4$ (1 mol %), 1,2-DCE (4.0 mL), 0 °C, 15 min. Yields signify isolated and purified materials. Enantiomeric excess was determined by HPLC analysis.

4-methoxyphenyl (**7I**), and even bulky 3,5-dimethylphenyl (**7J**) and thienyl (**7K**) were found to be suitable substrates. Remarkably, in all cases the reaction provided 5,7-fused rings as a single regioisomer.

At this moment, we can only speculate on structure of the rhodium carbenoid intermediate that rationalizes the chemo- and regioselectivity observed above. Davies and co-workers reported a rhodium-catalyzed asymmetric intermolecular C−H insertion in which the stable structure of Rh_2(*S*-TCPTAD)$_4$[(*p*-Br-C_6H_4)C(COOMe)] carbene intermediate was proposed by a combination of X-ray structural analysis and computational studies.[14] According to this study, $\pi-\pi$ interaction between the aromatic ring in the substrate and phthalimide in the rhodium catalyst, as well as CO−π interaction exists in the intermediate carbene. If a similar rhodium carbenoid is generated in our ring expansion, a plausible intermediate to provide the cyclopropane could be as depicted in Figure 2. Similar to Davies' proposal, the $\pi-\pi$ interaction in this intermediate was assumed between the aromatic ring in the substrate and the phthalimide ligand as well. The methylene chain linking the benzene and ester would adopt the least strained conformation to form a transition state involving the double bond on the benzene ring. In this assembly, steric repulsion between the substituent at the 4-position and the phthalimide ligand would interfere with cyclopropanation to decrease the yield of cyclized product **2**, providing poor chemoselectivity because of the competing β-hydrogen migration. On the other hand, the substituent at the 3-position is more distant from the ligand and reduces steric hindrance, leading to the preferential formation of desired product **2**.[15] To determine the absolute configuration of the product **2**, X-ray crystallographic analysis was performed. The crystal structure of **8E** possessing a bromide on the 7-membered ring revealed that the cyclized product has an (*R*)-configuration, which is expected as a result of the Buchner ring expansion via the proposed transition state.

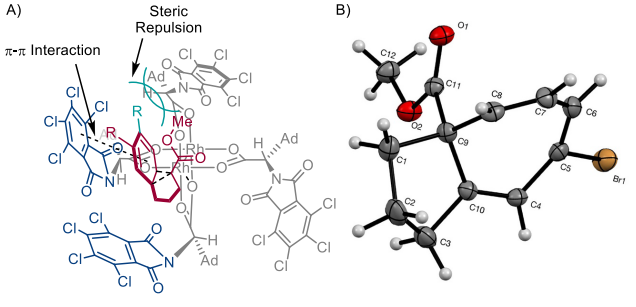


Figure 2. (A) Plausible transition state of the rhodium carbenoid derived from α-diazoester and Rh_2(*S*-TCPTAD)$_4$. (B) X-ray crystallographic analysis. ORTEP drawing of **8E** with 50% thermal ellipsoid.

In conclusion, we present a new catalytic method for the asymmetric synthesis of a 5,7-fused ring system that possesses a chiral center at the bridgehead carbon. The choice of Rh_2(*S*-TCPTAD)$_4$ minimized the competing olefination to enable access to a wide range of bicyclic products starting from an α-diazoester possessing a β-hydrogen. The development of more efficient catalysts and the expansion of the substrate scope, as well as application to natural product synthesis, are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04048.

Detailed experimental procedures, spectral data for all compounds, and ^{1}H, and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1962381−1962382 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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