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Sequential C−H Functionalization Reactions for the Enantioselective Synthesis of Highly Functionalized 2,3-Dihydrobenzofurans

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Supporting Information

ABSTRACT: The enantioselective synthesis of 2,3-dihydrobenzofurans was achieved by using two sequential C−H functionalization reactions, a rhodium-catalyzed enantioselective intermolecular C−H insertion followed by a palladium-catalyzed C−H activation/C−O cyclization. Further diversification of the 2,3-dihydrobenzofuran structures was possible by a subsequent palladium-catalyzed intermolecular Heck-type sp^2 C−H functionalization.

C−H functionalization methodologies offer new strategies for the synthesis of complex natural products,[1] and in recent years, a number of elegant synthetic applications have been described.[2,3] Two distinct types of metal-catalyzed C−H functionalization processes are becoming broadly effective (Figure 1): one of these is C−H insertion by a metal-bound

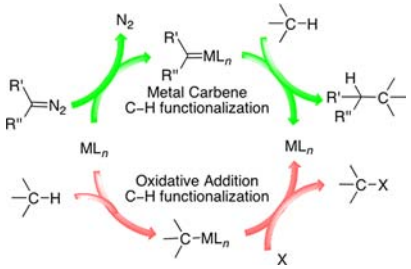
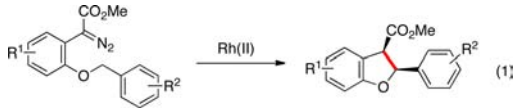


Figure 1. Complementary C−H functionalization methods.

carbene, nitrene, or oxo intermediate[4] and the other is "C−H activation" initiated by C−H insertion by a metal complex.[5] We have begun a program to explore opportunities to combine C−H functionalization methodologies to achieve the streamlined synthesis of advanced structural features present in natural products and pharmaceuticals. In this paper, we describe an enantioselective approach to dihydrobenzofurans that utilizes up to three C−H functionalization reactions in sequence.

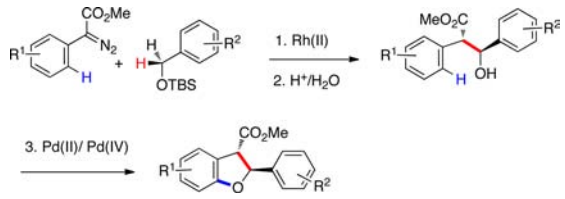
Dihydrobenzofurans are common subunits in a wide range of natural products and pharmaceuticals.[6] Therefore, the development of new methodologies for constructing this structural motif has been an important field in chemical research.[7] The Davies group developed an enantioselective intramolecular C−H insertion approach for the synthesis of 2-arylbenzofuran-3-carboxylates (eq 1).[8] Even though the approach has been used in the synthesis of complex natural products,[3] it suffers from the



necessity to synthesize the polysubstituted aromatic substrates for the intramolecular reactions. Furthermore, it often requires the use of both a chiral catalyst and an auxiliary to achieve acceptable levels of asymmetric induction.

In this paper, we describe an alternative approach to the synthesis of 2-arylbenzofuran-3-carboxylates that involves an intermolecular C−H insertion followed by an intramolecular C−H oxidation (Scheme 1). The major advantage of this new

Scheme 1. Sequential C−H Functionalization Approach to 2,3-Dihydrobenzofurans



approach is the range of 2,3-dihydrobenzofurans that can be generated with high levels of asymmetric induction (93−99% ee) using a single chiral catalyst without the need for a chiral auxiliary.

This program arose from independent studies by the Davies group on enantioselective intermolecular benzylic C−H insertion[9] and by the Yu group on C−H activation/C−O cyclization.[5b] For the benzylic C−H insertion to be useful in this context, it would be necessary to demonstrate that the enantioselective reaction is still feasible with electron-rich aryldiazoacetates and benzyl silyl ethers because these are the types of functionality that tend to be present in the biologically relevant dihydrobenzofurans.[6] The palladium-catalyzed C−H activation/C−O cyclization reaction has been conducted on relatively simple tertiary and secondary alcohols[5b] but has not been demonstrated to be feasible with secondary benzylic alcohols nor β-hydroxy esters. With the substrates required for this study, benzyl alcohol oxidation, dehydration, and retro-aldol reactions could potentially compete with the desired C−H activation/C−O cyclization reaction.

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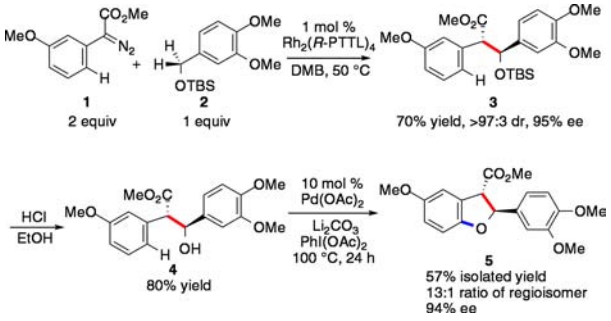
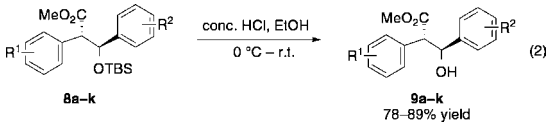
To test the feasibility of the proposed synthetic approach, the reaction of aryldiazoacetate **1** and *tert*-butyldimethylsilyl (TBS) ether **2** was evaluated (Scheme 2). As previously demonstrated,[9] the best chiral dirhodium complex for this reaction is Rh_2(PTTL)$_4$ (PTTL = *N*-phthaloyl-*tert*-leucinate). The C−H insertion product **3** was isolated in good yield with excellent levels of enantioselectivity (95% ee) and diastereoselectivity (>97:3 dr). Before the C−H activation/C−O cyclization could be conducted, the TBS group had to be removed. A variety of conditions were examined, but the best result for the formation of alcohol **4** was achieved using HCl in ethanol. With **4** in hand, dihydrobenzofuran **5** could be formed by employing the reaction conditions developed by the Yu group.[5b] The reaction gave good regiocontrol, favoring ring closure at the position para to the methoxy group, and did not result in any epimerization or racemization. Minor side reactions were the retro-aldol reaction (~10%) and aromatization of the product to give the benzofuran (trace amounts were observed).

Scheme 2. Exploratory Study of the Sequential C−H Functionalization Approach to Dihydrobenzofurans

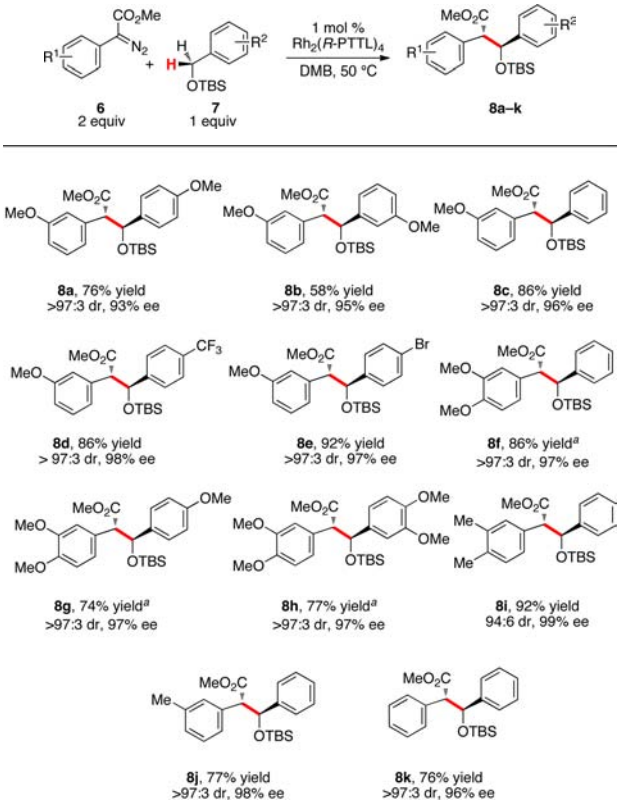


To test the substrate scope of this approach to 2,3-dihydrobenzofurans, a variety of aryldiazoacetates **6** and TBS-protected benzyl alcohols **7** were subjected to the Rh_2(*R*-PTTL)$_4$-catalyzed C−H insertion reaction conditions. The emphasis was placed on methoxy-substituted substrates in order to evaluate whether the C−H insertion with a highly electron-deficient carbenoid would be compatible with the electron-rich aromatic rings. As shown in Table 1, the products **8a−k** were obtained with high levels of diastereoselectivity (>97:3 dr) and enantioselectivity (93−99% ee). Under the same deprotection conditions as for compound **3**, alcohols **9a−k** required for the C−H activation/C−O cyclization were readily prepared from silyl ethers **8a−k** (eq 2).



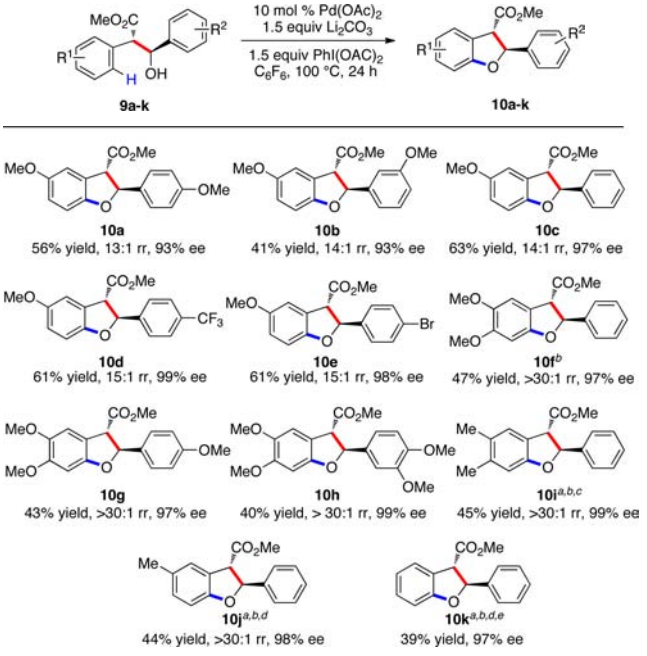
A variety of conditions for conducting the palladium-catalyzed C−H activation/C−O cyclization were explored (see the Supporting Information for details). The optimized conditions employed palladium acetate (10 mol %) as the catalyst, phenyliodonium diacetate as the terminal oxidant, and lithium carbonate or disodium phosphate as the base (Table 2). The typical reaction time and temperature were 24 h and 100 °C, respectively, but slightly more vigorous conditions were required for the less electronic-rich substrates. Under these conditions, alcohols **9a−k** cyclized to form the corresponding dihydrobenzofurans **10a−k**. In cases where a mixture of regioisomers could have been formed, the least sterically congested product (**10a−j**) was strongly favored. C−H

Table 1. Rhodium-Catalyzed C−H Insertion



[a]2,2-Dimethylbutane (DMB)/*α*,*α*,*α*-trifluorotoluene (3/1 v/v) was used as the solvent.

Table 2. Palladium-Catalyzed Cyclization



[a]20 mol % $Pd(OAc)_2$ was used. [b]Na_2HPO_4 was used as the base. [c]The reaction time was 48 h. [d]The reaction time was 72 h. [e]The reaction temperature was 120 °C.

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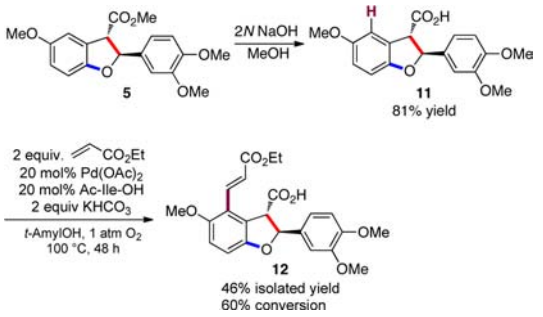
functionalization onto an electron-rich aromatic ring was favored. Cyclization to a position para to a methoxy group was favored, as illustrated for substrates **9a–h**, which gave dihydrobenzofurans **10a–h** within 24 h. However, in the case of **9f–h** containing two methoxy groups in the ring undergoing C–H oxidation, a significant amount of aromatized benzofuran side products were observed in the crude reaction mixtures. Substrates **9i–k** lacking a methoxy group in the ring undergoing C–H oxidations required more vigorous reaction conditions to form dihydrobenzofurans **10i–k**. The carboxylic acid derived from **10g** was crystalline, and its absolute configuration was unambiguously assigned by X-ray crystallography.[10] The absolute configurations of the other dihydrobenzofurans were assumed to be the same by analogy. Even though the yields of the dihydrobenzofurans were relatively modest (39–63%), these reactions illustrate the synthetic potential of C–H functionalization. The dihydrobenzofurans were produced with 93–99% ee without any observable epimerization.

As a further illustratration of the versatility of C–H functionalization strategies, a third C–H functionalization was attempted. Dihydrobenzofuran **5** was hydrolyzed to give acid **11**, which was then subjected to a Heck-type C–H functionalization (Scheme 3). This resulted in the formation

Scheme 3. Heck-Type C–H Functionalization



of benzofuranylacrylate **12** in 46% yield (77% based on recovered starting material), which contains key features that are present in the natural product lithospermic acid.[3d] The moderate conversion for the formation of **12** was presumably caused by the highly crowded nature of the flanked C–H bonds.

In conclusion, this work illustrates the potential of C–H functionalization for the streamlined synthesis of complex targets. Dihydrobenzofurans were synthesized in a highly regio-, diastereo-, and enantioselective manner by a synthetic sequence involving three distinct C–H functionalization steps. As selective C–H functionalization methodologies continue to develop, it is expected that they will have a great impact on the strategies used for the synthesis of complex targets, fine chemicals, natural products, and potential therapeutic agents. Controlling the site selectivity in multiple C–H functionalization steps will be critical in bringing this synthetic potential to fruition, and this study demonstrates that such levels of control are becoming achievable.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental data and X-ray crystallographic data (CIF). 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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(10) The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 921156 has been allocated.