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A Highly Chemoselective, Zr-Catalyzed C−O Bond Functionalization of Benzofuran

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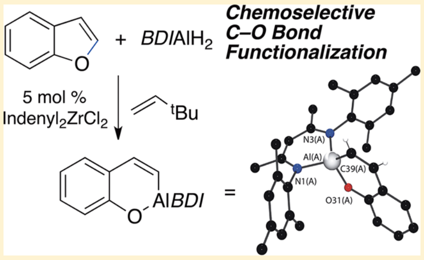
Supporting Information

ABSTRACT: The chemoselective C−O bond functionalization of benzofuran with an aluminum dihydride may be catalyzed by zirconocene dichlorides. The reaction proceeds with the formal addition of a C−O bond to, and elimination of dihydrogen from, aluminum. The product of C−O bond alumination reacts with benzaldehyde via insertion of the carbonyl into the newly formed Al−C bond.



In the face of the changing natural resource balance, the field of synthetic chemistry will need to adapt. In the coming years, dwindling petroleum resources will be replaced by alternative raw materials that will contain a higher amount of elemental oxygen by mass.[1] For example, saturated and unsaturated ethers are available from lignocellulosic biomass,[1,2] while benzofuran and dibenzofuran are minor byproducts of coal gasification.[3] Hence, methods for the activation and functionalization of chemically inert C−O bonds have the potential to underpin future chemical enterprise using renewable resources.

In the past few years, a number of catalysts have been reported for the hydrodeoxygenation and cross-coupling of C−O bonds.[4,5] Despite these advances, to our knowledge, a catalytic and selective C−O bond functionalization that generates an isolable product that is *more reactive* than the organic starting materials has yet to be reported. This observation is in direct contrast to studies in the related field of C−H functionalization.[6] For example, unreactive C−H bonds in alkanes or arenes may be catalytically transformed into reactive C−B bonds using boranes as stoichiometric reagents (Eqs 1 and 2; Bpin = pinacolborane). The reaction products of C−H borylation, boronic esters, provide an important point for synthetic diversification.[7]

$$\text{R−H} + \text{Bpin−Bpin} \xrightarrow{\textbf{catalyst}} \text{R−Bpin} + \text{HBpin} \qquad \text{(Eq. 1)}$$

$$\text{R−H} + \text{H−Bpin} \xrightarrow{\textbf{catalyst}} \text{R−Bpin} + H_2 \qquad \text{(Eq. 2)}$$

Inspired by this work, along with the precedent for stoichiometric C−O bond cleavage with early transition metals,[8,9] we envisioned the possibility of the C−O bond alumination of nonreactive ethers (Eq 3, *BDI* = κ^2-{MesNC(Me)}$_2$CH). We have recently reported *BDI*AlH$_2$ (**1**)[10] as a terminal reductant in the hydrodefluorination of sp^{2}C−F bonds[11] and speculated upon the use of this main-group hydride as a reagent for C−O bond cleavage.

$$\text{R−OR}^1 + \textit{BDI}\text{AlH}_2 \xrightarrow{\textbf{catalyst}} \textit{BDI}\text{Al}(\text{OR}^1)(\text{R}) + H_2 \qquad \text{(Eq. 3)}$$

The reaction in Eq 3 can be considered as a net elimination of H$_2$ from, and addition of the C−O bond to, aluminum. While the dearth of accurate data on Al−H and Al−C bond enthalpies currently precludes an assessment of the Gibbs free energy of this process, removal of the dihydrogen is expected to drive the equilibrium toward the products. Herein we report our initial findings upon the catalytic, chemoselective C−O bond functionalization of benzofuran.

Reaction of **1** with benzofuran in the presence of 5 mol % of Cp$_2$ZrCl$_2$ in C$_6$D$_6$ for 1h at 80 °C yielded 75% of a 1.1:1 mixture of the C−O bond functionalization products **2** and **2-H$_2$** (Table 1). There is precedent for this mode of reactivity. Activation of the carbon−oxygen bond in benzofuran by precoordination of the arene to manganese tricarbonyl followed by reaction with [(Ph$_3$P)$_3$Pt(η^2-C$_2$H$_4$)] has been reported previously.[12] Furthermore, excess lithium powder along with a catalytic quantity of 4,4′-di-*tert*-butyldiphenyl is known to effect the C−O bond cleavage of benzofuran.[13] The former reaction is stoichiometric in two transition metals, whereas the latter requires strongly reducing conditions and offers limited possibilities in terms of catalyst control over selectivity.

Following investigation of a series of catalysts and additives, conditions were discovered for the selective formation of **2** (Table 1; for full experimental details see the Supporting Information). Hence, employing 5 mol % of (indenyl)$_2$ZrCl$_2$ as a precatalyst in the presence of 7.5 equiv of the known H$_2$ trap 3,3-dimethylbut-1-ene after 15 h at 80 °C yielded 60% (47% isolated crystalline yield) of a >50:1 mixture of **2**:**2-H$_2$**.[14]

Attempts to bias the selectivity toward **2-H$_2$** were less successful, and performing the reaction with 5 mol % of

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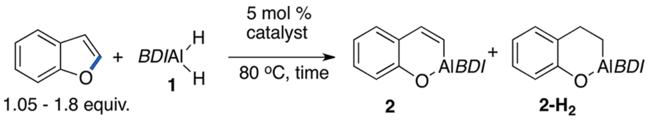
Table 1. Catalytic C−O Bond Functionalization of Benzofuran



time / h	Catalyst	Yield^a	2 : 2-H$_2$^{b}	Additive
168	–	0 %	–	–
1	Cp_2ZrCl_2	75 %^{c}	1.1 : 1	–
2	Cp_2ZrCl_2	76 %^{c}	1.8 : 1	H_2
3	Ind_2ZrCl_2	82 %^{c}	1.7 : 1	–
3	Ind_2ZrCl_2	82 %	7.9 : 1	^{t}Bu 3 equiv.
15	Ind_2ZrCl_2	**60 %**	**>50:1**	^{t}Bu 7.5 equiv.

^{a}Concentration of **1** 0.2 M in C_6D_6; yields calculated by ^{1}H NMR spectroscopy by comparison against ferrocene as an internal standard. ^{b}Ratio calculated by ^{1}H NMR spectroscopy. ^{c}An unidentified minor byproduct was present. Ind = indenyl, *BDI* = {MesNC(Me)C}$_2$H.

Cp_2ZrCl_2 under 1 atm of H_2 or varying the temperature of the reaction had little effect on the ratio of products (see the Supporting Information for details).

The organometallic products of C−O bond cleavage were fully characterized by multinuclear NMR spectroscopy and single-crystal X-ray diffraction (Figure 1). A comparison of the solid-state structures reveals a slight shortening of the Al−C bond in **2** in comparison to its saturated analogue **2-H$_2$**, while the Al−O bonds are comparable between the two. Exposing a crystalline sample of **2** in C_6D_6 to hydrogen in the presence of 5 mol % of (indenyl)$_2$ZrCl$_2$ and 5 mol % of **1** for 24 h at 80 °C did not yield **2-H$_2$**. Similarly heating an isolated sample of a 3:1 mixture of **2-H$_2$** and **2** in C_6D_6 either in the absence of a catalyst or in the presence of 5 mol % of (indenyl)$_2$ZrCl$_2$ and 7.5 equiv of 3,3-dimethylbut-2-ene for 40 h at 80 °C did not change the ratio. These data suggest that the reaction products cannot be interconverted by hydrogenation or dehydrogenation under the conditions we have examined.

To demonstrate the selectivity of C−O bond functionalization, an excess of benzofuran, 2,3-dihydro-2*H*-pyran, and tetrahydrofuran along with 3,3-dimethylbut-1-ene was reacted with **1** in the presence of (indenyl)$_2$ZrCl$_2$.[15] After 48 h, complex **2** was observed in 50% yield and excellent selectivity (Scheme 1). Despite five different types of carbon−oxygen bonds being present, **2** was formed in a yield comparable to that presented in Table 1. A similar competition experiment with a mixture of benzofuran and dibenzofuran, but run in only a slight excess of the substrates, was again selective for the formation of **2** (Scheme 2).

Despite the sterically crowded metal center in **2**, the aluminum vinyl moiety reacts selectively with an external electrophile. Hence, the reaction of **2** with 3 equiv of benzaldehyde in C_6D_6 solution after 5 days at 80 °C gave clean insertion of the carbonyl into the metal−carbon bond of **2**. While the corresponding aluminum alkoxide **3-Al** formed in 61% yield (by NMR spectroscopy, internal standard), it was not isolated from the crude mixture; following hydrolysis with citric acid, the known diol **3** was isolated in 33% unoptimized yield (Scheme 3).

In summary, we have reported the C−O bond cleavage of benzofuran by a *β*-diketiminate-supported aluminum dihydride

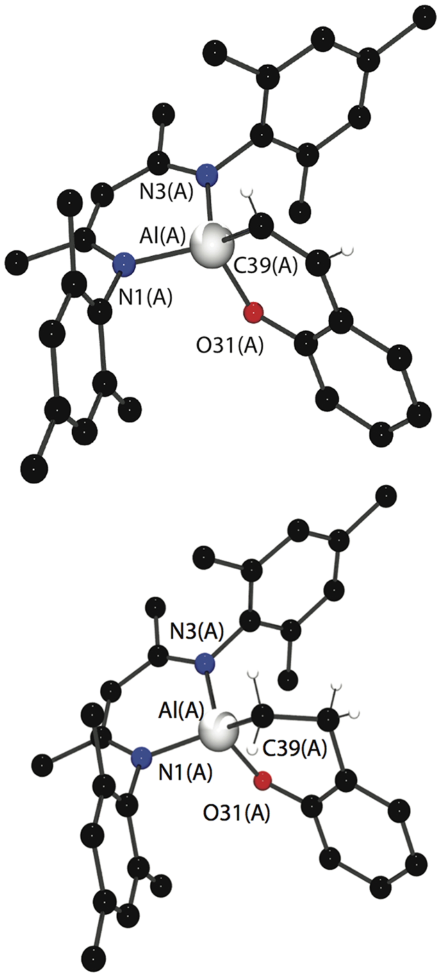
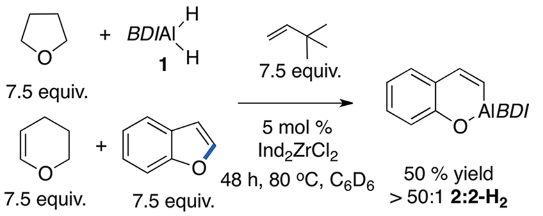
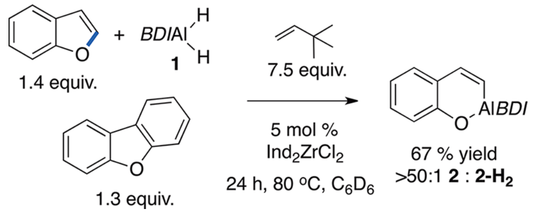


Figure 1. (top) Crystal structure of **2(A)**, one of the two independent molecules in the unit cell of **2**. Selected bond angles (deg) and bond lengths (Å): **2A**, Al−O = 1.7455(13), Al−C = 1.9260(19), C=C = 1.338(3), O−Al−C = 101.55(7); **2(B)**, Al−O = 1.7544(14), Al−C = 1.9328(18), C=C = 1.338(3), O−Al−C = 102.65(8). (bottom) Crystal structure of **2-H$_2$(A)**, one of the two independent molecules in the unit cell of a cocrystallized mixture of **2** and **2-H$_2$**. The second molecule in the unit cell of **2**/**2-H$_2$** is a disordered mixture of **2** and **2-H$_2$**; **2-H$_2$** is the dominant species. Selected bond angles (°) and bond lengths (Å): Al−O = 1.7507(13), Al−C = 1.9498(17), C−C = 1.519(3), O−Al−C = 102.46(7).

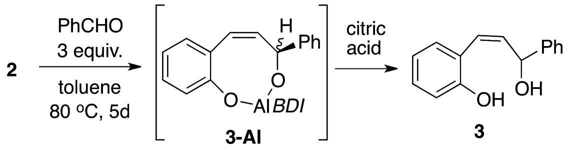
Scheme 1. Catalytic C−O Bond Functionalization of Benzofuran in the Presence of Saturated and Unsaturated Ethers



Scheme 2. Catalytic C−O Bond Functionalization of Benzofuran in the Presence of Dibenzofuran



Scheme 3. Ring Expansion of 2 with Benzaldehyde



catalyzed by group 4 metallocenes. The reaction represents a formal two-electron redox process at a main-group element (addition of C−O, elimination of H_2) catalyzed by a transition-metal catalyst. The reaction is highly chemoselective, and benzofuran reacts preferentially in the presence of dibenzofuran or saturated/unsaturated cyclic ethers. We are continuing to study the mechanism and scope of this new C−O bond transformation and expand the reactivity of the C−O bond cleavage products reported herein.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and CIF files giving full experimental details and crystallographic data for **2** and **2**/**2-H$_2$**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(14) Reaction of diphenyl ether, 2-methoxynaphthalene, or 4-methoxybiphenyl with 5 mol % of Cp_2ZrCl_2 and **1** in C_6D_6 failed to yield any new products after 1−2 days at 80 °C.

(15) Attempts to achieve a similar competition experiment with 2,5-dihydrofuran in the place of THF failed.