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A Direct C–C Cross-Coupling of Alcohols at the β-Position with Aldehydes under Co-Promotion of Tris(triphenylphosphine)-rhodium Chloride/Boron Trifuoride Etherate

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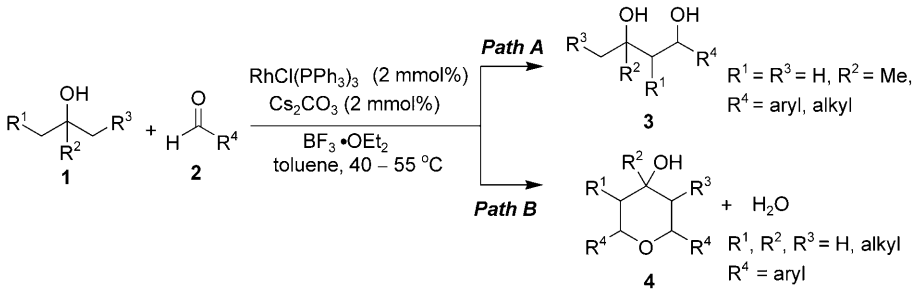
Abstract: The novel tris(triphenylphosphine)rhodium chloride/boron trifuoride etherate [$RhCl(PPh_3)_3/BF_3{\cdot}OEt_2$] co-promoted the C–C cross-coupling of tertiary alcohols at the β-position with aldehydes. This reaction provides an efficient synthesis of either structurally diverse 1,3-diols or polysubstituted tetrahydropyrans by controlling the substrate structures, and it could be developed to a practical synthetic method for numerous natural products and medicinally important compounds.

Keywords: C–C coupling; C–H functionalization; 1,3-diols; rhodium(I) catalyst; tetrahydropyrans

C–C bond formation *via* C–H bond functionalization is important and fundamental to organic chemistry, in which the direct C–C cross-coupling of alcohols[1] has recently become one of the most attractive reactions since it not only constructs new C–C bonds and directly introduces hydroxy functional groups, but also displays atom economy and an environmentally benign nature.[2] In connection with our group's interest in this subject, our previous efforts had led to a discovery that the combination of transition metal catalyst/Lewis acid system could accomplish the direct C–C cross-coupling of the *C=C bond of olefins with primary alcohols* at the α-position *via* sp^3 C–H activation.[3] This achievement encouraged us to make a more extensive study, and recently we found that a novel C–C cross-coupling of *alcohols at the* β*-position with the C=O bond of aldehydes* also could be realized through the co-promotion of the *$RhCl(PPh_3)_3$/$BF_3{\cdot}OEt_2$ system* (Scheme 1). It was noteworthy that this reaction could selectively achieve, by tuning the substrate structure, either the structurally diverse 1,3-diols (*Path A*) or polysubstituted tetrahydropyrans (THP) *(Path B*). To the best of our knowledge, this kind of Rh-catalyzed/Lewis acid mediated C–C cross-coupling reaction between alcohols and aldehydes has not been reported before.

1,3-Diols have long been used as important synthons, and several conventional methods are available to access them, such as aldol/reduction, conjugate addition/reduction, tandem semipinacol rearrangement/MPV reaction,[4] as well as the recently reported HLF



Scheme 1. Cross-coupling of tertiary alcohols with aldehydes.

reaction.[5] These methods generally involve multi-step synthetic manipulations or sometimes give by-products. The coupling protocol described here provides a new direct and simple way to the synthesis of a series of 1,3-diols. Also markedly, the polysubstituted THP skeleton is the key structural elements in many biologically active natural products, such as brevetoxin B, scytophycin C and (−)-apicularen A.[6] It alternatively provides a direct and concise approach towards polyfunctional THP units . In this paper, we present our preliminary experimental results.

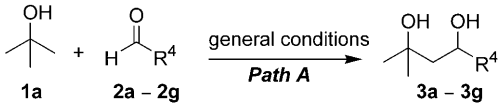
Our initial investigation was focused on a wide search for the coupling conditions of **1a** and **2a** as the model substrates. Among the conditions tested, the combination of $RhCl(PPh_3)_3$ (2 mmol%), additive Cs_2CO_3 (2 mmol%) and Lewis acid $BF_3{\cdot}OEt_2$ (1.5 mmol) in toluene was found to be the best. With these optimized conditions in hand, the substrate scope was examined. As list in Table 1, the coupling of the simple *t*-BuOH **1a** with both aromatic aldehydes bearing the electron-drawing groups (entries 1–5) or aliphatic aldehydes (entries 6 and 7) mainly tended to take the *Path A*, in which one molecule of **1a** only coupled with one molecule of the aldehyde to afford the 1,3-diol **3a**.

Remarkable is that the 1,3-diol products **3a–3e** are the important building blocks in the medicinal chemical synthesis. For example, as illustrated in Scheme 2, **3a** could be further effectively converted into a *chromanol-type* molecule **3a-1** bearing the key *2,2-dimethyl-benzopyran* core structure *via* palladium-catalyzed carbon-heteroatom coupling,[7] after which the known synthetic routes with the conventional conversions could be employed to accomplish the synthesis of some important medicaments or natural products, such as (−)-cromakalim, (−)-perrottetinene, (+)-machaeriol, and THC.[8]

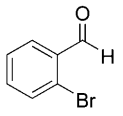
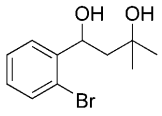
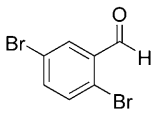
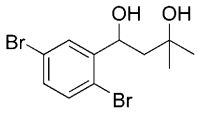
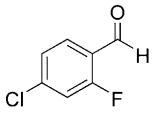
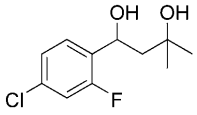
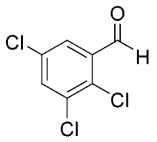
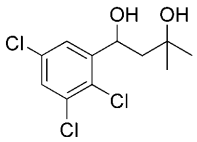
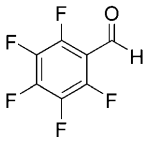
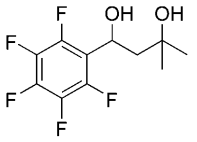
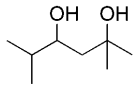
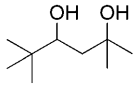
Our further investigation was expanded by using some aromatic aldehydes or other typical aliphatic tertiary alcohols **1b–1d.** The results obtained in Table 2 indicated that when **2h** or the electron-rich aromatic aldehyde **2i** was subjected to the coupling with **1a** under the same conditions as above, the coupling reaction tended to take *Path B*, which afforded the double coupling products, the tetrasubstituted THP **4a** and **4b** (entries 1 and 2). While employing branched tertiary alcohols **1b–1d** instead of **1a**, the coupling with **2h** and electron-deficient aromatic aldehydes **2a** and **2j** still took *Path B* to give the double coupling products, the polysubstituted THP **4c–4e**.

Although a detailed reaction mechanism remains unclear at this stage, one could be proposed formally on the basis of previous reports.[9] As shown in the sequences in Scheme 3, the tertiary hydroxy group in substrate **1** may undergo an elimination preferentially to furnish **5**. It should be noted that either $RhCl(PPh_3)_3$ or $BF_3{\cdot}OEt_2$ alone could not effectively promote this coupling reaction in parallel experiments. Based on this fact, the Lewis acid-promoted/Rh-catalyzed electrophilic addition of aldehyde to olefin **5** was proposed to give **6**, which was further hydrolyzed to give **3**, or underwent elimination to give the homoallylic alcohol **7**, depending on the substrate's properties. The latter could provide **4** *via* a Prins-type cyclization.

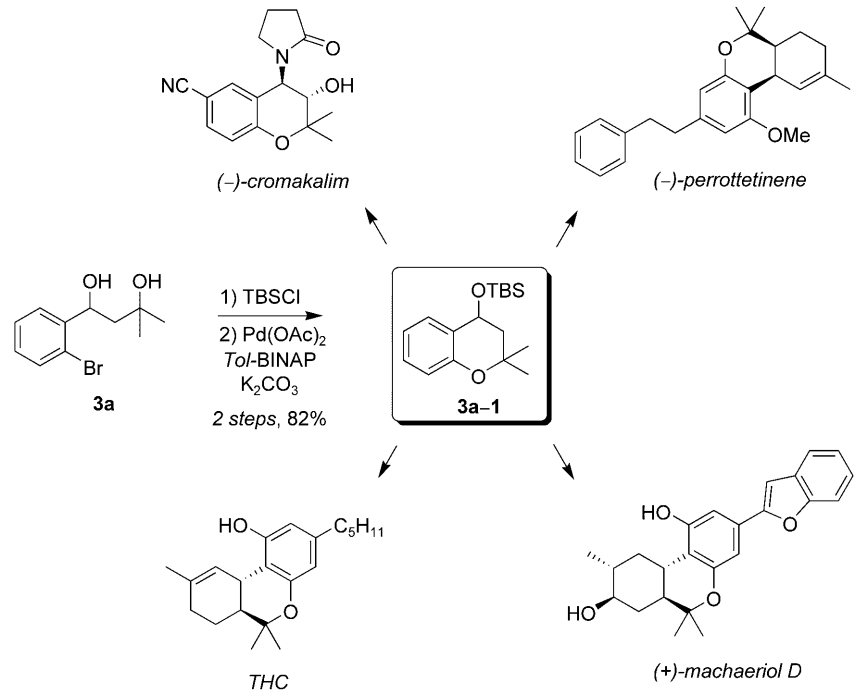
Table 1. The coupling reaction *via Path A* for synthesizing the 1,3-diol.[a]



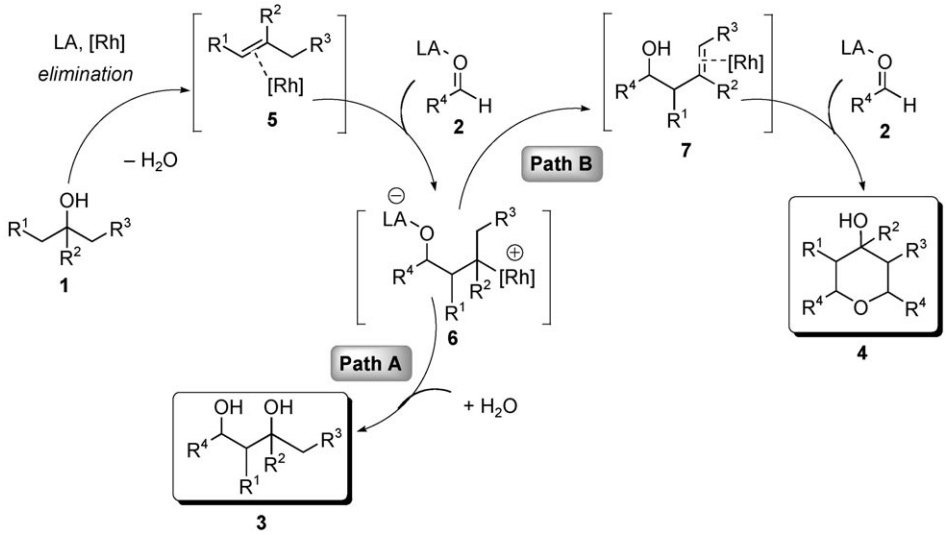
1a 2a – 2g 3a – 3g

Entry	Substrate	Product	Yield [%][b]
1	 2a	 3a	65
2	 2b	 3b	76
3	 2c	 3c	47
4	 2d	 3d	74
5	 2e	 3e	55 (91[c])
6	 2f	 3f	42
7	 2g	 3g	63

[a] *General conditions:* **2** (1.0 mmol), **1** (2.5 mmol.), $RhCl(PPh_3)_3$ (2 mmol%), $CsCO_3$ (2 mmol%), and $BF_3{\cdot}OEt_2$ (1.5 mmol) in toluene for 3-12 h.
[b] Isolated yield based on the aldehyde **2** used.
[c] Yield based on recovered starting material.



Scheme 2. Application model of **3a** in the synthesis of medicines and important molecules.



Scheme 3. Proposed pathways for the cross-coupling of tertiary alcohols with aldehydes.

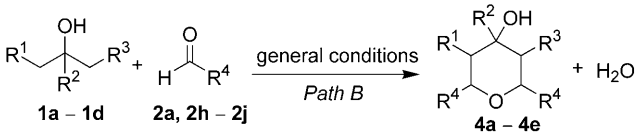
The observed reactivity could be understood through two reaction pathways (*Path A* and *Path B*) of intermediates **6** in Scheme 3, which could preferentially form the olefin intermediates **7** if the substitutes R^3 in **6** was an alkyl group, not hydrogen. In particular, reactions using the sterically hindered triethylmethanol **1d** gave only a low yield (37%) of the THP product (entry 6 in Table 2). Further studies on the mechanism, as well as the scope and application of this coupling reaction, are currently under investigation in our laboratory.

Experimental Section

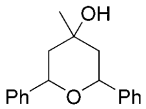
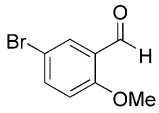
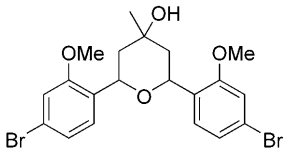
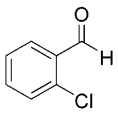
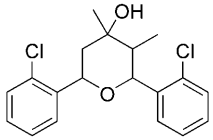
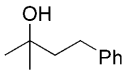
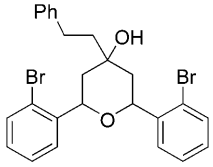
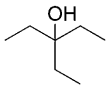
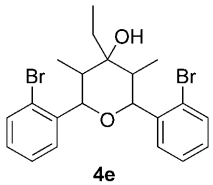
Typical Procedure

To a flame-dried, 25-mL flask were sequentially added toluene (4 mL), alcohol (2.5 mmol), and $RhCl(PPh_3)_3$ (20 mg, 0.02 mmol). The reaction system was stirred at 30 °C for 20 min. The aldehyde (1 mmol) and the additive Cs_2CO_3 (0.02 mmol) were added and stirred at 30 °C for 20 min under an argon atmosphere, and then the freshly distilled $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol) was introduced into the above reaction mixture. The reaction mixture was heated

Table 2. The coupling reaction *via Path B* for synthesizing the polysubstituted THP.[a]



1a – 1d **2a, 2h – 2j** **4a – 4e**

Entry	Substrates		Product[b]	Yield [%][c]
1	**1a**	 **2h**	 **4a**	72
2	**1a**	 **2i**	 **4b**	54
3	 **1b**	 **2j**	 **4c**	65
4	 **1c**	**2a**	 **4d**	63
5	 **1d**	**2a**	 **4e**	37

[a] *General conditions:* **2** (1.0 mmol), **1** (2.5 mmol.), $RhCl(PPh_3)_3$ (2 mmol%), $CsCO_3$ (2 mmol%), and $BF_3{\cdot}OEt_2$ (1.5 mmol) in toluene for 3–12 h.

[b] The *dr* of **4a** is 3:2, and for **4b–4e** only one diastereomeric form was isolated.

[c] Isolated yield based on the aldehyde **2** used.

using an oil bath to 50 °C, and further stirred at 50 °C for 3–12 h. After that, it was cooled to room temperature, and diluted with ethyl acetate (2 mL) followed by addition of saturated aqueous $NaHCO_3$ solution (3 mL). The organic layer was separated, and the aqueous phase was re-extracted with ethyl acetate (3×2 mL). The combined organic extracts were washed with brine (20 mL), and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by the flash chromatography to afford the desired separable products.

Acknowledgements

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