

# N-Directing Group Assisted Rhodium-Catalyzed Aryl C–H Addition to Aryl Aldehydes

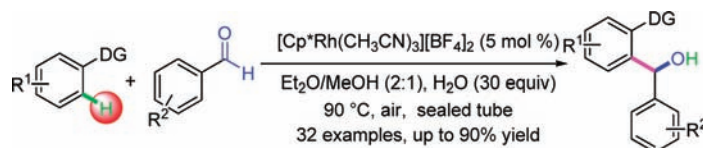
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## ABSTRACT



Direct aryl C–H addition to aryl aldehydes to produce biaryl methanols was reported *via* Rh catalysis with an N-containing directing group. The method is highly atom-, step-, and redox-economic. The procedure is robust, reliable, and compatible with water and air.

The addition of highly reactive organometallic reagents, such as Grignard reagents, to aldehydes and ketones is a fundamental reaction and has been well investigated and broadly applied in organic synthesis since the past

century.<sup>1</sup> The tedious procedure from environmentally unfriendly organic halide, metal reagents, and the manipulation of air and moisture sensitive organometallic reagents makes such a transformation undesirable. Transition metal catalyzed direct nucleophilic addition of C–H bonds in hydrocarbons and their derivatives to the carbonyl group to produce alcohols is a dream goal in organic synthesis. Obviously, this process would be the most step-, atom-, and redox-economical by avoiding the preactivation of starting materials and manipulating air and moisture sensitive organometallic reagents.

Significant progress has already been made to promote the synthetic efficiency by direct C–H transformation in the past several decades.<sup>2–4</sup> However, the successful examples of carrying out the direct addition of aryl C–H to polar multiple bonds are rarely reported.<sup>5–8</sup> Murai, Takai, and their co-workers made significant contributions to carry out the addition of aryl C–H to aldehydes with the directing strategy by quenching the resulting alcohols with silanes.<sup>5,6b,6d</sup> Recently, this method was successfully extended to the addition of 3-pyridinyl C–H bonds to aldehydes by our group.<sup>9</sup> With a brilliant design, another beautiful example was reported by Takai of carrying out the C–H addition, followed by the intramolecular nucleophilic addition to form the isobenzofuran derivatives with

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an *N*-phenyliminyl group as a directing group in the absence of silanes.<sup>6a</sup> More recently, Ellman and our group independently reported the Rh-catalyzed addition reaction of aryl C–H bonds to aldimine derivatives in the absence of any additives.<sup>10</sup> Based on this observation, Ellman and his co-workers subsequently reported the addition of aryl C–H to the isocyanates to produce the benzamides.<sup>11</sup> In this communication we demonstrated the successful direct C–H bond addition to aryl aldehydes with a wide substrate scope in the presence of water and air. Notably, when we were performing these studies, Li and his co-workers reported the beautiful example of the direct addition of aryl C–H bonds to ethyl 2-oxoacetate.<sup>12</sup> In their studies, they also first demonstrated the C–H addition to aryl aldehydes.

Before we performed the addition reaction of C–H bonds to aldimine derivatives, we had tested the Rh-catalyzed addition of C–H bonds of 2-phenylpyridine

(**1a**) to various aldehydes. At that moment, we observed the desired addition product 4-(trifluoromethyl)benzaldehyde (**2a**) albeit in 17% yield with [Cp\*Rh(CH<sub>3</sub>CN)<sub>3</sub>][BF<sub>4</sub>]<sub>2</sub> (**4**) as a catalyst (eq 1, Scheme 1). Unfortunately, after many tries, we failed in promoting such an addition with **2a**. To our delight, after screening many substrates with our full efforts, we found that the reaction of 2-phenylquinoline (**1b**) with highly electron-deficient 2-chloro-4-nitrobenzaldehyde (**2b**) gave an excellent yield. Noteworthy, by using the quinolinyl unit as a directing group, the C–H at the 8-position was kept untouched although it was found active in some transformations.<sup>13</sup> The regioselectivity of this transformation was further confirmed by obtaining the single-crystal X-ray crystal structure of **3b**.<sup>14</sup> The intramolecular hydrogen bond shown in the structure makes the designed product stable under the reaction conditions.

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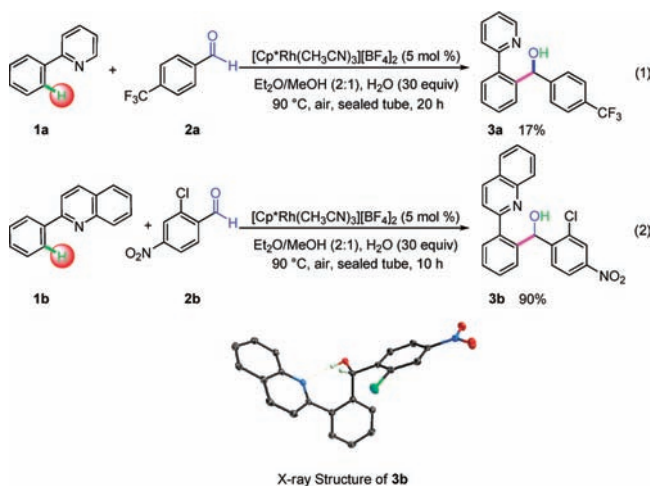
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Scheme 1<sup>a</sup>



<sup>a</sup> Thermal ellipsoids are drawn at 30% probability, and hydrogen atoms are omitted for clarity.

To accumulate experience to explore the reactivity of other C–H bonds and normal aldehydes, we systematically investigated such an addition reaction with commercially available 2-chloro-5-nitrobenzaldehyde (**2c**) as a model substrate (Scheme 2). The selection of **2c** is based on the easy transformation of final products into different functional groups from the nitro group through the well-known Sandmeyer procedure<sup>15</sup> and the potential orthogonal coupling reaction of a C–Cl bond.<sup>16</sup> To our satisfaction, by using **2c** as a substrate, the reaction also exhibited good efficiency (**3c**).

Under the optimized conditions, the reactivity of different 2-phenylquinoline derivatives was investigated (Scheme 2).

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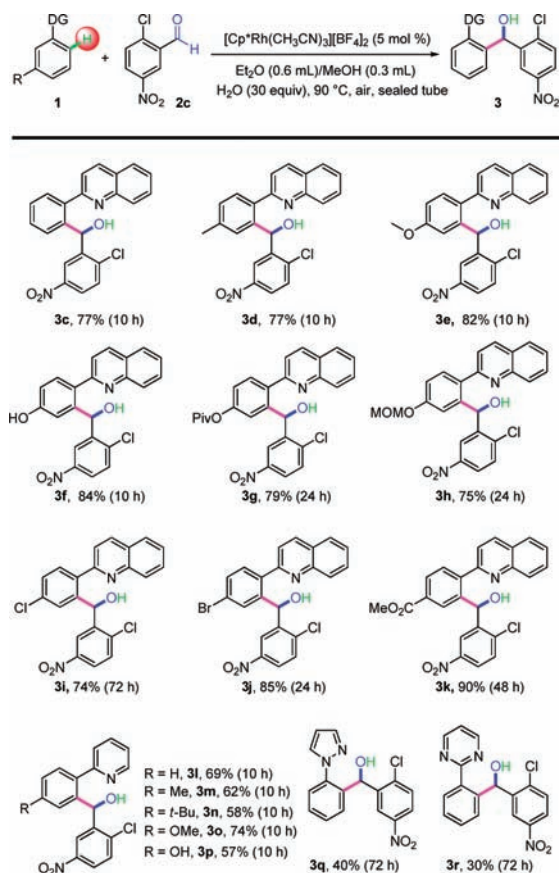
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First, electron-donating groups are introduced to the phenyl group. For examples, with a methyl group (**3d**) and a methoxyl group (**3e**), the reactions showed good reactivity. Importantly, the unprotected hydroxyl group (**3f**) was also compatible. Various electron-donating and -withdrawing groups on the phenyl unit were further tested. It was found that the electronic nature of the substituents on the phenyl ring did not play key roles (**3c** to **3k**). This transformation showed good compatibility with different functional groups, such as MOM (**3h**) and ester groups (**3k**). Pivalate protected hydroxyl groups exhibited good reactivity, which provided the potential chance for further functionalization.<sup>17</sup> Moreover, the tolerance of the halides (**3i** and **3j**) also offers the opportunity for further transformation.<sup>16</sup> This transformation was also investigated using other directing groups. Compared with quinolinyl directing groups, this C–H addition showed slightly lower yields using pyridinyl directing groups (**3l–3p**). Other *N*-based directing groups, such as pyrazolyl groups (**3q**) and pyrimidinyl groups (**3r**), were further tested, but the reactions gave relatively lower yields.

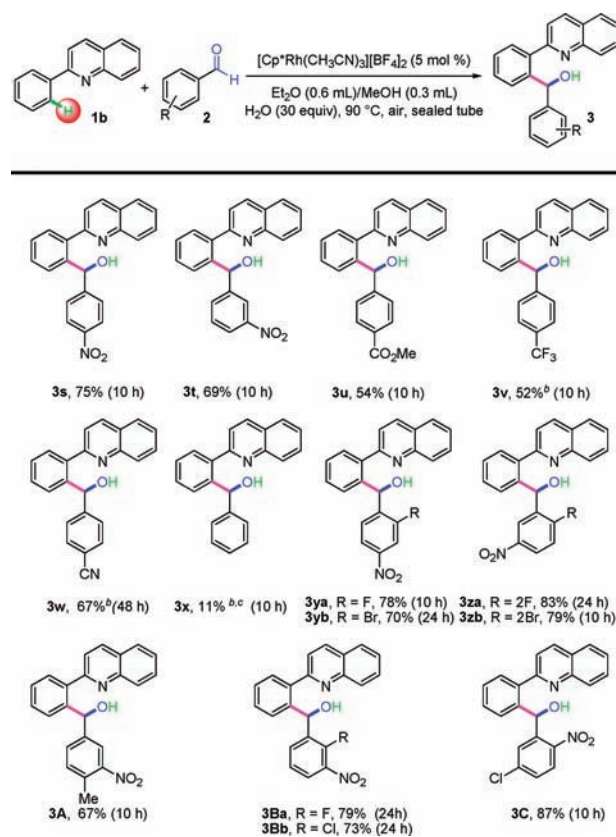
**Scheme 2.** Different 2-Phenylquinoline Derivative C–H Bond Additions to Aldehydes<sup>a</sup>



<sup>a</sup> All the reactions were performed on 0.25 mmol of 2-phenylpyridine derivatives and 0.75 mmol of aldehyde in a sealed reaction tube.

With 2-phenylquinoline as a substrate, different aryl aldehydes were further explored (Scheme 3). First, 4-nitrobenzaldehyde was tested, and the reaction gave a good yield (**3s**). It was found that the *meta*-nitro group (**3t**) also gave a comparable yield. Meanwhile, other different electron-withdrawing groups on the phenyl part of the aldehyde were explored. Ester groups (**3u**), trifluoromethyl groups (**3v**), and nitrile groups (**3w**) on substituted benzaldehydes were suitable, although the reactions exhibited moderate efficacy. When benzaldehyde was submitted (**3x**), the reaction gave a low yield (11%), accompanied by a large amount of recovered starting material **1b** (86% recovery of **1b**). Notably, to date, it is the first example that the C–H addition to simple benzaldehyde resulted in benzyl alcohol in the absence of any additives. Moreover, this observation exhibited great potential in extending such an addition into normal aryl aldehydes other than the electron-deficient aldehydes. Further efforts to approach such a goal are being studied in our laboratory.

**Scheme 3.** C–H Addition of 2-Phenylquinoline to Different Aryl Aldehydes<sup>a</sup>

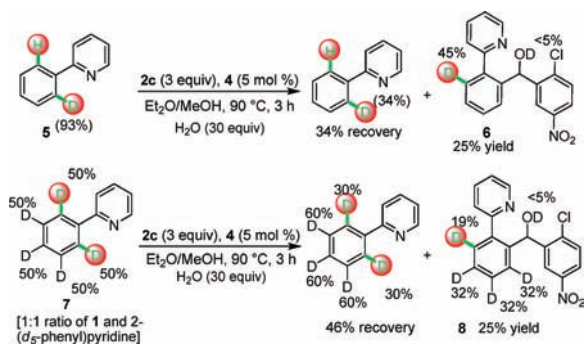


<sup>a</sup> If no special conditions are indicated, all the reactions were performed on 0.25 mmol of 2-phenylquinoline and 0.75 mmol of aldehyde in a sealed reaction tube. <sup>b</sup>The reactions were performed on 1.0 mmol of 2-phenylquinoline and 3.0 mmol of aldehyde. <sup>c</sup>86% recovery of **1b**

Since chloronitrobenzaldehyde showed great reactivity, other halides were further introduced to nitrobenzaldehyde at different positions for the same reason we used **2c**. When a nitro group was present at the *para*- or *meta*-position and

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#### Scheme 4. Preliminary Mechanism Research



different halide groups were introduced at the *ortho*-position (3ya, 3yb, 3za, 3zb, 3Ba, and 3Bb) or *para*-position (3A) of the formyl group, the addition ran smoothly and the desired products were isolated in good to excellent yields. At the same time, with the combination of *meta*-chloro and *ortho*-nitrobenzaldehyde (3C), the reaction also showed excellent efficiency. Obviously, these studies enhanced the potential applicability of the products in this transformation. Moreover, in the presence of an electron-donating methyl group with the nitro group, the desired product was isolated in good yield (3A).

To investigate the preliminary mechanism further, intra- and intermolecular isotopic studies were performed under the exact reaction conditions (Scheme 4). During the intramolecular reaction, the content of deuterium in the

recovered 2-([D1]-phenyl)pyridine (5) was decreased from 93% to 34%. Intermolecularly, the content of deuterium at the 2- and 6-positions of the phenyl group in 2-([D5]-phenyl)pyridine (7) was also decreased from 50% to 30%. As we predicted, all of these data showed that the first step of C–H cleavage is reversible in this transformation. Further studies to understand this transformation are underway.

In conclusion, we developed a highly atom-, step-, redox-economic method to carry out the Rh(III)-catalyzed aryl C–H bond addition to aldehydes to produce diarylmethanols. An *N*-containing directing group was found essential for this transformation. In this transformation the electron-deficient aldehydes are highly effective. The C–H bonds of inert arene substrates were used instead of Grignard reagents without the addition of any additive including any reductants and oxidants. The reaction is robust and not sensitive to water and air. Studies to apply this method to a wider range of substrates and realize the asymmetric synthesis are in progress.

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**Supporting Information Available.** Brief experimental details and other spectral data for products. This material is available free of charge via the Internet at <http://pubs.acs.org>.