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COMMUNICATION

A Unique Copper-Catalyzed Cross-Hydrogen (H_2) Removal Coupling to Stereoselective Synthesis of 3-Phosphoindoles

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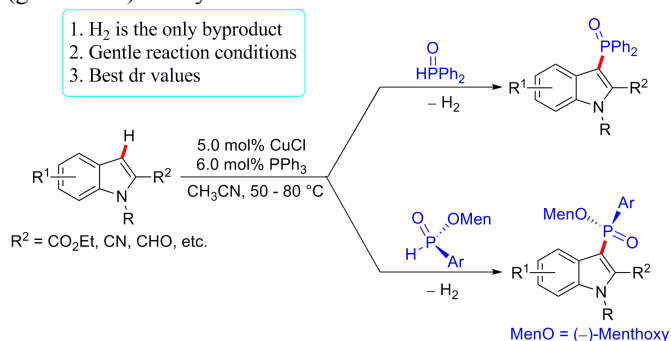
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The first Cu(I)-catalyzed cross-hydrogen (H_2) removal coupling reaction for stereoselective synthesis of 3-phosphoindoles is reported. Beyond the oxidative dehydrogenative coupling reactions reported recently, this reaction completely omits the oxidant and base, producing hydrogen (H_2) as the only byproduct.

Transition-metal-catalyzed direct C-H activation and functionalization has become a powerful tool in organic synthesis.¹ Over the past decades, various high efficiency and versatile protocols for C-H activation have been demonstrated,² in particular the building of C-C and C-heteroatom bonds directly from two simple carbon-hydrogen (C-H) bonds or C-H and H-Nu (Nu = B, O, N, S) bonds provides an unusually attractive pathway by virtue of its step economy, its lower cost, and its decrease in waste production.³ Overall, these novel strategies mainly include oxidative Heck-type dehydrogenative coupling, Li's cross-dehydrogenative coupling, and catalytic tandem direct arylation. Although these transformations have been described in terms of catalytic dehydrogenative cross-coupling, the hydrogen gas in these transformations is usually not released as the byproduct; thermodynamically, this is due to the unfavorable loss of H_2 when a C-C or a C-heteroatom bond is produced. Therefore, present metal-catalyzed dehydrogenative couplings usually require stoichiometric oxidants as an external driving force. Moreover, the base has also been added to the oxidative Heck-type dehydrogenative couplings. At present, the development of transition metal-catalyzed oxidative cross-coupling by direct removal of H_2 represents an enormous challenge and a hefty goal.⁴ Herein, we wish to report a unique copper-catalyzed cross-hydrogen (H_2) removal coupling reaction for the stereoselective synthesis of 3-phosphoindoles and Anti-HIV inhibitor of IDX899 precursor (Scheme 1). Beyond the oxidative dehydrogenative coupling reactions reported recently, this reaction completely omits the oxidant and base, producing hydrogen (H_2) as the only

byproduct and exhibiting a unique dehydrogenative pattern. What is more, setup is simple, conditions are mild, and scale-up (gram scale) ability is both attractive and efficient.

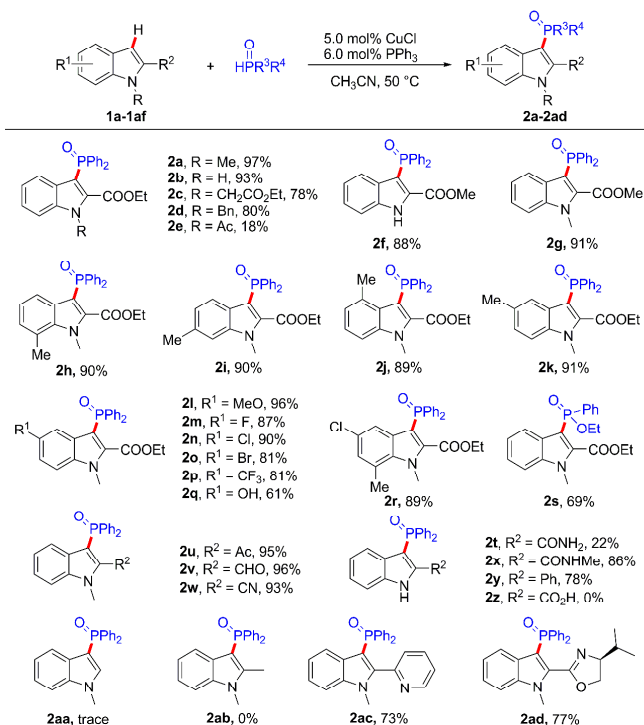


Scheme 1. CuCl-catalyzed Cross Hydrogen Removal Coupling.

Indole is an important structural motif commonly found in pharmaceutical drugs and natural products.^{5, 7} Therefore, the functionalization of indole derivatives by C-H bond activation has attracted much attentions.⁶ During the past several years, we have trained our focus on the development of new and efficient protocols for the transition metal-catalyzed C-P bond formation.⁷ In particular, the application of the C-H bond activation to the phosphorylation of indole interests us greatly. 3-phosphoindoles represent a novel second-generation NNRTIs (non-nucleoside reverse transcriptase inhibitors) that demonstrate excellent potency against wild-type and NNRTI-resistant HIV-1 *in vitro*.⁸ In an initial study, we chose the *N*-methylindole-2-ethyl formate (**1a**) and $Ph_2P(O)H$ (**5a**) as model substrates. We extensively screened catalysts, solvents, and temperatures in an argon atmosphere; Table S1 summarizes the results. Our endeavors obtained optimal reaction conditions through the use of CuCl (5 mol %) as a catalyst, PPh_3 (6 mol %) as the ligand in 3.0 mL of CH_3CN for 0.3 mmol **1b**, and 2 equiv **1a** at 50 °C under an argon atmosphere (details please see the Table S1 in Supporting Information).

With optimized reaction conditions in hand (Table S1, entry 18), we turned our attention to the examination of functional group compatibility and the scope of substrates. As illustrated in Table 1, an investigation into different *N*-protection groups showed that methyl, ethyl acetate and benzyl perform much better than Ac (**2a–2e**). We were delighted to discover that *N*-free indole-2-ethyl formate also works very well in the reactions and that corresponding products were obtained in high yields (**2b** and **2f**). The steric hindrance effect was inconspicuous and good yields were observed even if methyl lay on the 5-, 6-, or 7- position (**2h–2k**). A study of the electronic effect demonstrated that electron-donating groups are more reactive than electron-withdrawing groups; indeed, we report here excellent yields of the majority of products (**2l–2r**). Other phosphates such as HP(O)OEtPh were also compatible with the reaction and afforded the desired products in moderate yields (**2s**). This reaction displayed very good functional group tolerance. When the substituent groups (such as CONH₂, Ac, CHO, CN, CONHMe, and Phenyl) are situated to the 2-position of the *N*-methylindole, the reaction proceeds smoothly, affording good yields of corresponding products (**2t–2y**). Only carboxyl or methyl-substituted substrates and *N*-methylindole failed (**2z–2ab**). The reaction also works well when heterocycles (such as pyridine and oxazole) act as substituent groups. In this case the reaction produces good yields of the potential *P*, *N*-ligand (**2ac–2ad**). It is worthy of note that the reaction can be effectively scaled up with the highest yield (see

Table 1. CuCl-catalyzed Phosphorylation of Indoles^{a,b}



^a The reaction was carried out with CuCl (5 mol %), PPh₃ (6 mol %), **1a–1af** (0.60 mmol), H(O)PR³R⁴ (0.30 mmol) in CH₃CN (3.0 mL) at 50 °C for 24 h under argon. ^b Isolated yield.

Supporting Information).

Inspired by these results, we concentrated our attention on the stereoselective synthesis of chiral 3-phosphoindoles. The development of this stereoselective synthetic template is not only crucial to the study of asymmetric C–H bond functionalization, but also represents important research efforts toward HIV-1 therapy and drug treatments. We first examined various chiral phosphine and nitrogen ligands with *N*-methylindole-2-ethyl formate and HP(O)OMePh as substrates under previous optimized reaction conditions. Regrettably, we detected no good ee value, a result that urged us to focus instead on intramolecular chiral induction. Using the (*1R*, *2S*, *5R*)-(-)-Menthol as starting material, we prepared the chiral (*1S*, *2S*, *5R*)-(-)-Menthoxyl-phenylphosphinate and applied it to chiral 3-phosphoindoles construction (Table 2). To our delight, we found a wide range of indole substrates that are compatible with this protocol. Although the substituent group in the aromatic ring can be either electron-donating or electron-withdrawing, the corresponding chiral 3-phosphoindoles could be obtained with good yield and higher dr value. Moreover, different 2-position substituted *N*-free indoles also worked very well and displayed excellent functional group tolerance.

Table 2. Stereoselective Synthesis of Chiral 3-methoxyl-arylphosphoindoles.^{a,b,c}

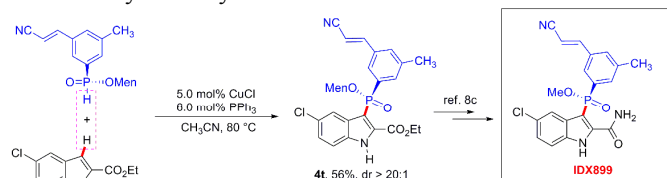
Reaction scheme for Table 2: Indole 3a-3a reacts with MentO-P(=O)(Ph) in the presence of 5.0 mol% CuCl and 6.0 mol% PPh₃ in CH₃CN at 80 °C to form chiral 3-phosphoindoles 4a-4s. The chiral auxiliary is (-)-Menthoxyl.

Entry	Product	Yield [%]	dr	Entry	Product	Yield [%]	dr
4a	R = Me, R ² = CO ₂ Et	88%	> 20/1	4l	R ² = CN	79%	> 20/1
4b	R = H, R ² = CO ₂ Et	65%	> 20/1	4m	R ² = CONHMe	52%	10/1
4c	R = Me, R ² = CO ₂ Me	86%	> 20/1	4n	R ² = CONHOMe	73%	12/1
4d	R = H, R ² = CO ₂ Me	67%	> 20/1	4o	R ² = CHO	82%	18/1
4e	R = Me, R ² = CO ₂ Et	80%	> 20/1	4p	R ² = Ac	82%	> 20/1
4f	R ¹ = Me	85%	> 20/1	4q	R ² = CONHOMe	68%	11/1
4g	R ¹ = MeO	84%	> 20/1	4r	R ² = CONHOMe	trace	–
4h	R ¹ = F	73%	> 20/1	4s	R ² = CHO	76%	17/1
4i	R ¹ = Cl	78%	> 20/1				
4j	R ¹ = Br	83%	> 20/1				
4k	R ¹ = CF ₃	79%	> 20/1				

^a All reactions were carried out in the presence of CuCl (5 mol %), PPh₃ (6 mol %), HP(O)(OMe)Ph (0.30 mmol), **3a–3s** (0.60 mmol) in 3.0 mL CH₃CN at 80 °C. ^b Isolated yield. ^c dr value determined by crude ³¹P NMR.

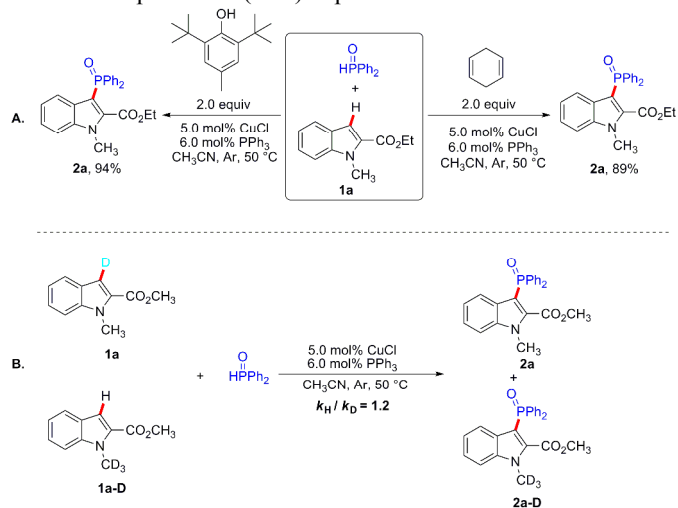
IDX899 as a novel second-generation NNRTIs exhibits a significantly greater barrier to resistance and substantially less toxicity, good patient adherence, and better pharmacokinetic

properties (Scheme 2). IDX899 has also been approved by the U.S. Food and Drug Administration (U.S. FDA) and is currently undergoing its second round of clinical trials.^{8b} In order to address the synthetic utility of our protocol, we were able to transform commercially available 5-chloro-1H-indole-2-carboxylate into a IDX899 precursor (**4t**) in 56% yield by cross-hydrogen (H_2) removal coupling with methoxyl-(3-methyl-5-acrylonitrilephenyl)-phosphinate. According to a previous report,^{8c} a straightforward sequence of deprotection and aminolysis will yield IDX899.



Scheme 2. Stereoselective Synthesis of IDX899.

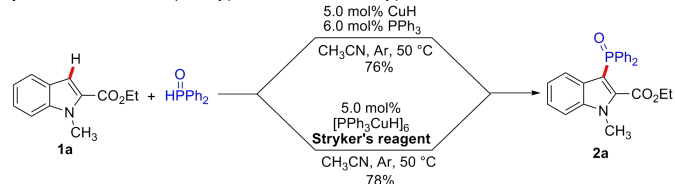
Although cross dehydrogenative coupling reactions involved in phosphorylation have been reported,⁹ our transformation did not require any oxidants or bases, which signifies that this carbon-phosphorylation pathway may be different from the former existed. We know from previous studies that some metal-catalyzed carbon-phosphorylation reactions with diphenylphosphine oxide $Ph_2P(O)H$ proceed via a radical process.^{7a,10} Therefore, we hypothesized that our dehydrogenative coupling reaction would involve a radical pathway. Preliminary mechanistic studies began with this assumption. We employed separate attempts to chemically trap radicals using cyclohexa-1, 4-diene and BHT (Scheme 3, A). While the 2.0 equivalent of cyclohexa-1, 4-diene or BHT was added under the normal reaction conditions, the product of **2a** was still obtained in high yields of 89% and 94%. These results demonstrate that in fact this transformation might not involve a radical process. TEMPO and ethene-1,1-diylidibenzene were also used, but without success: these compounds lead to the decomposition of the substrates. In addition, intermolecular kinetic isotope effects (KIE) experiments were also carried out



Scheme 3. Trapping of Radicals and KIE Experiments.

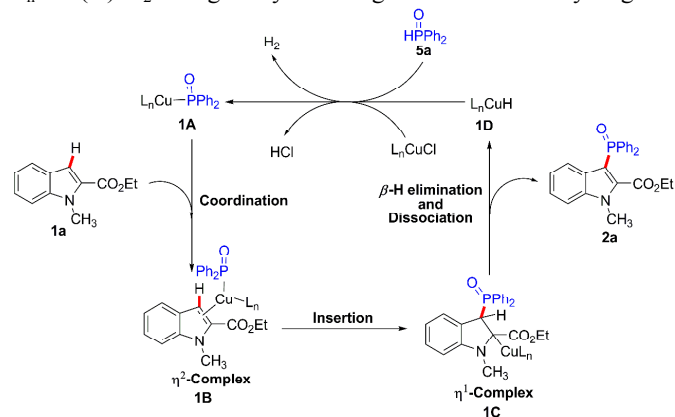
with equivalent deuterium-labeled substrates **1a-D** and **1a** (Scheme 3, B). The kinetic isotope effects were observed and $k_H/k_D = 1.2$. This result suggests that the C–H bond breaks after the turnover-limiting step. That certain possibilities were thus excluded prompted us to surmise that 1) our transformation likely involves a brand-new dehydrogenative pattern and 2) the hydrogen may be released in the procedure. To ensure straightforward data, we detected the production of hydrogen in our reactions; we would like to point to our use of hydrogen surveymeter to capture and detect the hydrogen at 233ppm in this experiment (see Supporting Information).

On the basis of this mechanistic understanding, we surmised that the formation of activated species of L_nCuH (**1D**) is a key step in this transformation. In order to collect proof of this assumption, we straight selected the CuH and Stryker's reagent $[PPh_3CuH]_6$ to catalyze the reaction under the model reaction conditions, respectively (Scheme 4). The phosphorylated product **2a** was obtained in 76% and 78% yields along with the H_2 evolution. These results confirmed the truth of our supposition as well as provided proof that the production of hydrogen is the driving force of reactions.



Scheme 4. CuH and Stryker's Reagent-Catalyzed 3-Phosphorylation.

Based on the above experiments and literature research,¹¹ we propose a tentative pathway of this transformation, illustrated in Scheme 5. First, diphenylphosphine oxide reacts with L_nCuCl ($L = PPh_3$) complex to form the intermediate $L_nCuP(O)Ph_2$ **1A** in reaction conditions. Then, this copper-phosphine complex coordinates with the *N*-methylindole-2-ethyl formate (**1a**) to form the η^2 -complex **1B**, which is then transformed into η^1 -complex **1C** by insertion. Finally, the product **2a** is afforded by anti- β -hydrogen elimination¹² and dissociation, upon which the active copper catalyst of L_nCuH (**1D**) is produced and reacted with diphenylphosphine oxide in order to form the intermediate $L_nCuP(O)Ph_2$ **1A** again by releasing monomolecular hydrogen



Scheme 5. The Proposed Mechanism of CuCl-Catalyzed cross-hydrogen (H_2) removal coupling.

and its entrance into the catalytic cycles.

In summary, we have developed a highly efficient protocol for the preparation of various 3-phosphoindoles via a copper-catalyzed cross-hydrogen (H_2) removal coupling reaction. We expect that this simple and atom-economical template can be structurally modified and applied to the construction of other C–X (X = C, N) bonds.

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- Current efforts are directed towards studying this unusual step.