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A unique copper-catalyzed cross-coupling reaction by hydrogen (H_2) removal for the stereoselective synthesis of 3-phosphoindoles†

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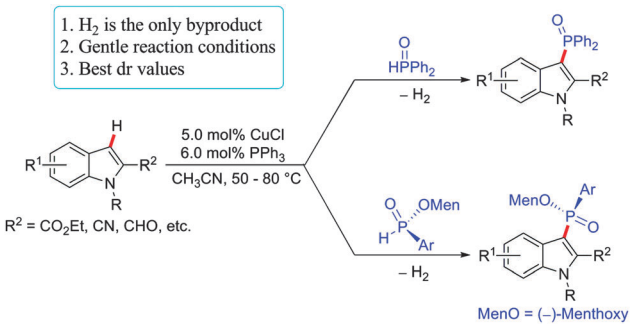
The first Cu(I)-catalyzed cross-coupling reaction by hydrogen (H_2) removal for the stereoselective synthesis of 3-phosphoindoles is reported. Going beyond the oxidative dehydrogenative coupling reactions reported recently, this reaction completely omits the oxidant and base, producing hydrogen (H_2)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

Transition-metal-catalyzed direct C–H activation and functionalization have become powerful tools in organic synthesis.[1] Over the past decades, various high efficiency and versatile protocols for C–H activation have been demonstrated;[2] in particular, building 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 the step economy, lower cost, and decreased 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, hydrogen gas is usually not released as the byproduct in these transformations; thermodynamically, this is due to the unfavorable loss of H_2 when a C–C or a C–heteroatom bond is formed. Therefore, metal-catalyzed dehydrogenative coupling usually requires a stoichiometric oxidant as an external driving force. Moreover, a base is also added in oxidative Heck-type dehydrogenative coupling reactions. At present, the development of transition metal-catalyzed oxidative cross-coupling by direct removal of H_2 represents an enormous challenge and a sizable goal.[4] Herein, we wish to report a unique copper-catalyzed cross-coupling reaction by hydrogen (H_2) removal for the stereoselective synthesis of 3-phosphoindoles and anti-HIV inhibitor of the IDX899 precursor (Scheme 1). Going 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 an unique dehydrogenative pattern. What is more, the setup is simple, the conditions are mild, and the ability to scale-up (gram scale) is both attractive and efficient.



Scheme 1 CuCl-catalyzed cross coupling by hydrogen removal.

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 attention.[6] During the past several years, we have focused on the development of new and efficient protocols for transition metal-catalyzed C–P bond formation.[7] In particular, the application of C–H bond activation in the phosphorylation of indole interests us greatly. 3-Phosphoindoles represent 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 *N*-methylindole-2-ethyl formate (**1a**) and $Ph_2P(O)H$ (**5a**) as model substrates. We extensively screened catalysts and solvents, and used different temperatures under an argon atmosphere; Table S1 (ESI†) summarizes the results. Our endeavors enabled us to determine the optimal reaction conditions using CuCl (5 mol%) as the catalyst and PPh_3 (6 mol%) as the ligand in 3.0 mL CH_3CN for 0.3 mmol **1b** and 2 equiv. **1a** at 50 °C under an argon atmosphere (for details please see Table S1 in the ESI†).

With the optimized reaction conditions in hand (Table S1 entry 18, ESI,†), we turned our attention to the examination of functional group compatibility and the scope of the substrates.

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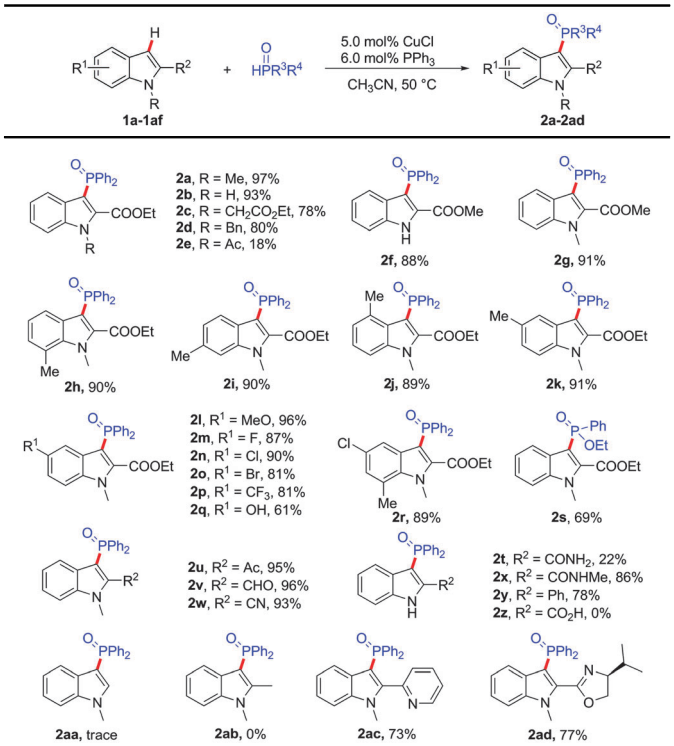
Table 1 CuCl-catalyzed phosphorylation of indoles[a,b]



[a] The reaction was carried out with CuCl (5 mol%), PPh_3 (6 mol%), **1a–1af** (0.60 mmol) and H(O)PR^3R^4 (0.30 mmol) in CH_3CN (3.0 mL) at 50 °C for 24 h under argon. [b] Isolated yield.

As illustrated in Table 1, an investigation into different *N*-protecting 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 reaction and that the corresponding products were obtained in high yields (**2b** and **2f**). The steric hindrance effect was inconspicuous and good yields were observed even with a methyl group present 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 for the majority of the products (**2l–2r**). Other phosphates, such as HP(O)OEtPh, were also compatible with the reaction and afforded the desired product in moderate yields (**2s**). This reaction displayed very good functional group tolerance. When a substituent group (such as $CONH_2$, Ac, CHO, CN, CONHMe, and phenyl) was situated at the 2-position of *N*-methylindole, the reaction proceeded smoothly, affording good yields of the corresponding products (**2t–2y**). Only the carboxyl or methyl-substituted substrates on *N*-methylindole failed (**2z–2ab**). The reaction also worked well when heterocycles (such as pyridine and oxazole) act as the substituent groups. In this case the reaction produced good yields of the potential *P*,*N*-ligand (**2ac** and **2ad**). It is worth noting that the reaction with the highest yield can be effectively scaled up (see ESI†).

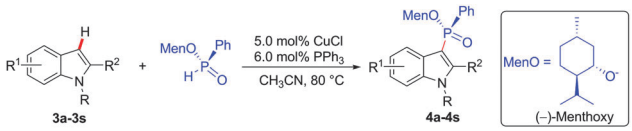
Inspired by these results, we concentrated our attention on the stereoselective synthesis of chiral 3-phosphoindoles. The development of this stereoselective synthetic template is not only crucial to the study of asymmetric C–H bond functionalization, but also represents important research efforts toward 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 the substrates under the previously optimized reaction conditions. Regrettably, we did not detect any high ee values, a result that urged us to focus instead on intramolecular chiral induction. Using (1*R*,2*S*,5*R*)-(−)-menthol as a starting material, we prepared chiral (1*S*,2*S*,5*R*)-(−)-menthoxyl-phenylphosphinate and applied it to the construction of chiral 3-phosphoindoles (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 can be obtained in good yields with high diastereomeric ratio (dr). Moreover, *N*-free indoles with different 2-position substitution also worked very well and displayed excellent functional group tolerance.

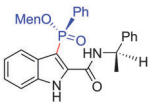
IDX899 as a novel second-generation NNRTI exhibits a significantly greater barrier to resistance and a substantially lower toxicity, good patient adherence, and better pharmacokinetic properties than other second generation NNRTIs (Scheme 2). IDX899 has also been approved by the U.S. Food and Drug Administration (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-1*H*-indole-2-carboxylate into a IDX899 precursor (**4t**) with a 56% yield by cross-coupling by hydrogen (H_2) removal with methoxyl-(3-methyl-5-acrylonitrilephenyl)-phosphinate. According to a previous report,[8c] a straightforward sequence of deprotection and aminolysis yields 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 former pathways. 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 3A). When 2.0 equivalent of cyclohexa-1,4-diene or BHT was added under the normal reaction conditions, product **2a** was still obtained in high yields of 89% and 94%. These results demonstrate that this transformation might not in fact involve a radical process. TEMPO and ethene-1,1-diyldibenzene were also used, but without success: these compounds led to the decomposition of the substrates. In addition, intermolecular kinetic isotope effect (KIE) experiments were carried out with equivalent deuterium-labeled substrates **1a-D** and **1a** (Scheme 3B). A kinetic isotope effect was observed and $k_H/k_D = 1.2$. This result suggests that the C–H bond breaks after the turnover-limiting step. Certain other possibilities could thus be excluded, prompting us to surmise that (1) our transformation likely involves a brand-new dehydrogenative pattern and (2) hydrogen may be released in the procedure. To provide some straightforward data to show this, we used a hydrogen survey meter to capture and detect hydrogen at 233 ppm in this experiment (see ESI†).

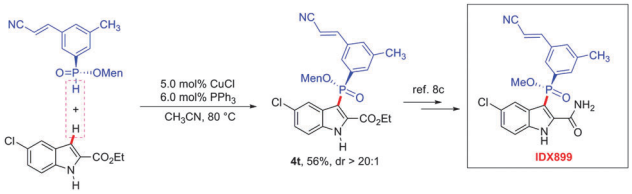
On the basis of this mechanistic understanding, we surmised that the formation of the activated species of L_nCuH (**1D**) is a key

Table 2 Stereoselective synthesis of chiral 3-methoxyl-arylphosphoindoles[a]

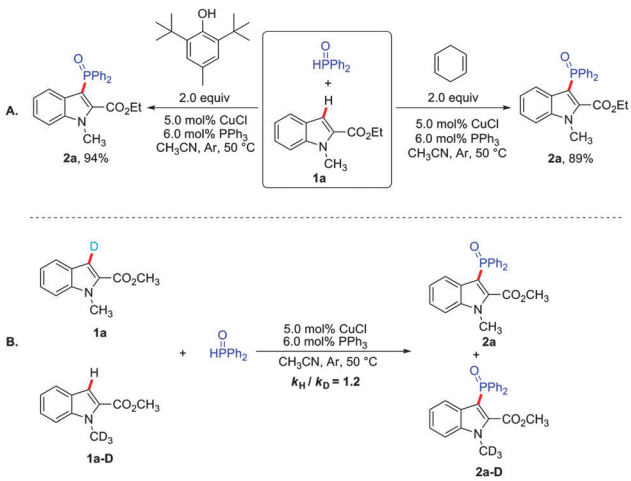


Entry	Product	Yield [%][b]	dr[c]	Entry	Product	Yield [%][b]	dr[c]
4a	R = Me, R^2 = CO_2Et	88	>20/1	**4l**	R^2 = CN	79	>20/1
4b	R = H, R^2 = CO_2Et	65	>20/1	**4m**	R^2 = CONHMe	52	=10/1
4c	R = Me, R^2 = CO_2Me	86	>20/1	**4n**	R^2 = CONHOMe	73	=12/1
4d	R = H, R^2 = CO_2Me	67	>20/1	**4o**	R^2 = CHO	82	=18/1
4e		80	>20/1	**4p**	R^2 = Ac	82	>20/1
4f	R^1 = Me	85	>20/1	**4q**		68	=11/1
4g	R^1 = MeO	84	>20/1				
4h	R^1 = F	73	>20/1	**4r**		Trace	—
4i	R^1 = Cl	78	>20/1				
4j	R^1 = Br	83	>20/1				
4k	R^1 = CF_3	79	>20/1	**4s**		76	=17/1

[a] All reactions were carried out in the presence of CuCl (5 mol%), PPh_3 (6 mol%), HP(O)(OMen)Ph (0.30 mmol) and **3a–3s** (0.60 mmol) in 3.0 mL CH_3CN at 80 °C. [b] Isolated yield. [c] dr value determined by crude ^{31}P NMR.



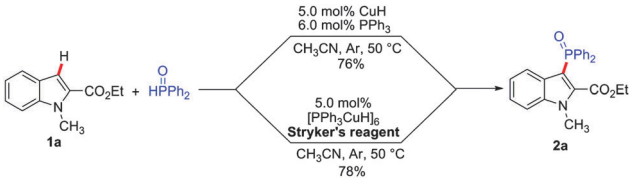
Scheme 2 Stereoselective synthesis of IDX899.



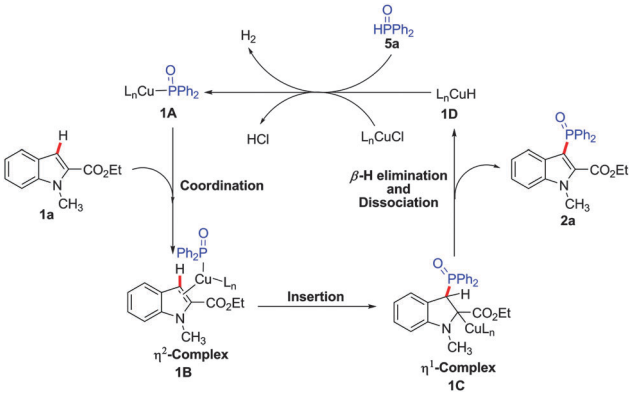
Scheme 3 Trapping of radicals and KIE experiments.

step in this transformation. In order to collect proof of this assumption, we selected CuH and Stryker's reagent, $[PPh_3CuH]_6$, to catalyze the reaction under the model reaction conditions (Scheme 4). The phosphorylated product **2a** was obtained in 76% and 78% yields, respectively, along with 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 the reaction.

Based on the above experiments and literature research,[11] we propose a tentative pathway for this transformation, illustrated in Scheme 5. First, diphenylphosphine oxide reacts with the L_nCuCl (L = PPh_3) complex to form intermediate $L_nCuP(O)Ph_2$ **1A** under the reaction conditions. Then, this copper–phosphine complex coordinates with *N*-methylindole-2-ethyl formate (**1a**) to form η^2-complex **1B**, which is then transformed into η^1-complex **1C** by insertion. Finally, product **2a** is afforded by anti-β-hydrogen elimination[12] and dissociation, upon which the active copper catalyst of



Scheme 4 CuH and Stryker's reagent-catalyzed 3-phosphorylation.



Scheme 5 The proposed mechanism for CuCl-catalyzed cross-coupling by hydrogen (H_2) removal.

L_nCuH (**1D**) is produced and reacts with diphenylphosphine oxide in order to form intermediate L_nCuP(O)Ph_2 **1A** again by releasing monomolecular hydrogen and HCl into the catalytic cycle.

In summary, we have developed a highly efficient protocol for the preparation of various 3-phosphoindoles *via* a copper-catalyzed cross-coupling reaction by hydrogen (H_2) removal. 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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12 Current efforts are directed towards studying this unusual step.

