C–H Functionalization

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Direct Annulations toward Phosphorylated Oxindoles: Silver-Catalyzed Carbon-Phosphorus Functionalization of Alkenes**

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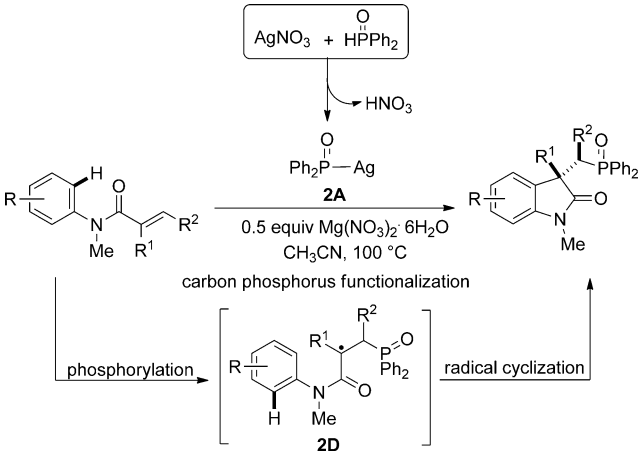
Aromatic organophosphorus compounds play very important roles and are ubiquitous. They can be found in a wide range of nucleotides, pharmaceuticals, and phosphine-containing ligands.[1] Therefore, the development of a more concise and efficient method for C–P bond formation is highly desirable and presents a considerable challenge.[2] Recent, transition metal catalyzed difunctionalization of alkenes provide a powerful strategy for the synthesis of various organic compounds,[3] including diamination,[4] aminooxygenation,[5] dioxygenation,[6] fluoroamination,[7] and aminohalogenation.[8] In particular, the palladium-catalyzed oxidative carbo- and heterofunctionalization of alkenes with different nucleophiles by direct C–H functionalization of arenes offers a new way to synthesize various functionalized oxindoles.[9] However, application of this method to the synthesis of phosphorylated oxindoles with phosphorus-based nucleophiles has not been achieved, and may be due to the strong coordinating abilities of both the substrate and the product. In addition, these related reactions generally used $PhI(OAc)_2$ as an oxidant, which causes the phosphorus nucleophiles to decompose under strong oxidative conditions. In the past several years, we have focused our efforts on the development of new and efficient protocols for transition metal catalyzed C–P bond formation.[10] It has been found that relatively mild copper and silver salts can work with $Ph_2P(O)H$ to form the corresponding active $[Ph_2P(O)Cu]$ or $[Ph_2P(O)Ag]$ complexes, which may be applied to the addition of alkenes.[11] In light of these factors, we hypothesized that silver or copper salts might catalyze carbon phosphorus functionalization of alkenes and conduct the direct cyclization to afford the corresponding phosphorylated oxindoles which have the potential to be novel insecticides or herbicides.[12] Moreover, it also could be used as a P,O-ligand for transition metal catalyzed reactions. Through our endeavors, a new method for the $AgNO_3$-catalyzed carbon phosphorus functionalization of alkenes has been developed and exhibits several unique features (Scheme 1): 1) unlike palladium, silver first reacts with $Ph_2P(O)H$ and forms the crucial active intermediate **2A**, which promotes the reactions; 2) a cheap, nontoxic silver salt is employed in catalyzing the hydrophosphorylation of alkenes for the first time; 3) the substrates for the transformation are simple and readily accessible, and no additional ligand or oxidant is needed.



Scheme 1. Silver-catalyzed difunctionalization of alkenes.

In an initial study, we chose the *N*-methyl-*N*-arylacrylamide **1a** and $Ph_2P(O)H$ as the model substrates, and various copper and silver catalysts were tested in different solvents at different temperatures. To our delight, this reaction occurred in the presence of 50 mol% of either copper or silver salts such as Cu_2O, CuCl, $Cu(OAc)_2$, Ag_2O, and $AgNO_3$ in CH_3CN at 100 °C, with $AgNO_3$ affording the desired product **2a** in the highest yield of 79% (Table 1, entries 1–5). Encouraged by this result, we further optimized the reaction conditions. Our focus was to decrease the loading of the silver catalyst, however, when the quantity of catalyst was reduced to 20 mol%, only $AgNO_3$ could promote the reaction to work smoothly and **2a** was obtained in 21% yield (Table 1, entry 6). Attempts using nitrogen-containing ligands were similarly unsuccessful. These results prompted us to consider that the anion may be critical in this reaction. A variety of nitrates having potential in this transformation were evaluated in the presence of 10 mol% $AgNO_3$ in CH_3CN at 100 °C. The results demonstrate that our hypothesis was reasonable. Using 0.5 equivalents of $Mg(NO_3)_2{\cdot}6H_2O$ as an additive gave the best result (Table 1, entries 7–9). Excitingly, when the loading

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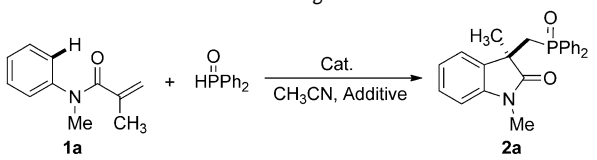
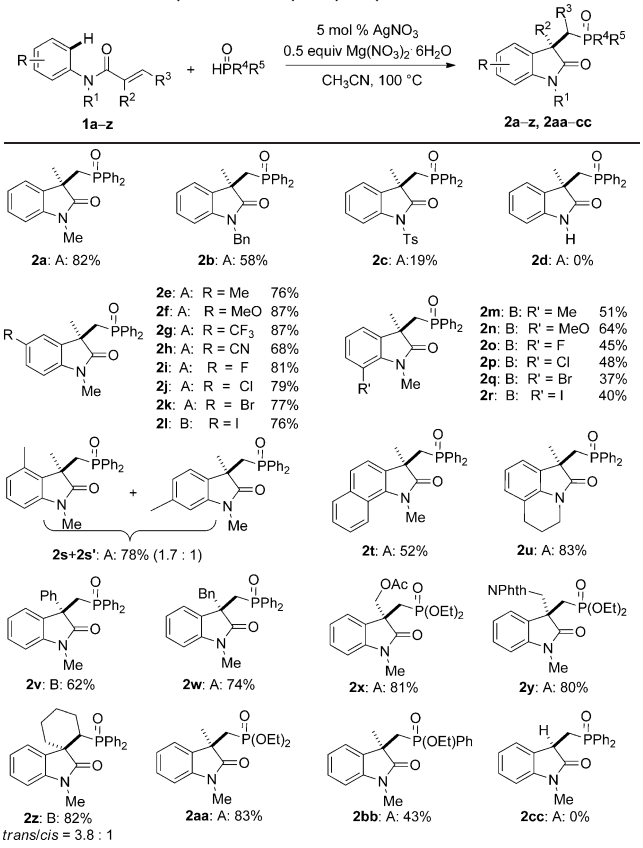
Table 1: Reaction conditions screening.[a]



Entry	Cat. (mol %)	Additive (equiv)	Yield [%][b]
1	Cu_2O (50)	–	43
2	CuCl (50)	–	51
3	$Cu(OAc)_2$ (50)	–	39
4	Ag_2O (50)	–	60
5	$AgNO_3$ (50)	–	79
6	$AgNO_3$ (20)	–	21
7	$AgNO_3$ (10)	$Mg(NO_3)_2{\cdot}6H_2O$ (1.0)	76
8	$AgNO_3$ (10)	$Mg(NO_3)_2{\cdot}6H_2O$ (0.5)	78
9	$AgNO_3$ (10)	$Mg(NO_3)_2{\cdot}6H_2O$ (0.3)	71
10	$AgNO_3$ (5)	$Mg(NO_3)_2{\cdot}6H_2O$ (0.5)	82
11	$AgNO_3$ (5)	$Cu(NO_3)_2{\cdot}3H_2O$ (0.5)	38
12	$AgNO_3$ (5)	$La(NO_3)_3{\cdot}6H_2O$ (0.5)	76
13	$AgNO_3$ (5)	$Yb(NO_3)_3{\cdot}6H_2O$ (0.5)	60
14	$AgNO_3$ (5)	$Co(NO_3)_2{\cdot}6H_2O$ (0.5)	56
15	$AgNO_3$ (5)	$Ce(NO_3)_2{\cdot}6H_2O$ (0.5)	75
16	$AgNO_3$ (5)	$NaNO_3 + H_2O$ (0.5)	0
17	Ag_2O (5)	$Mg(NO_3)_2{\cdot}6H_2O$ (0.5)	68
18	AgOTf (5)	$Mg(NO_3)_2{\cdot}6H_2O$ (0.5)	59
19	$AgSbF_6$ (5)	$Mg(NO_3)_2{\cdot}6H_2O$ (0.5)	65
20	$AgBF_4$ (5)	$Mg(NO_3)_2{\cdot}6H_2O$ (0.5)	61
21	AgOAc (5)	$Mg(NO_3)_2{\cdot}6H_2O$ (0.5)	59
22	$AgNO_3$ (5)	$MgCl_2$ (0.5)	< 5
23	$AgNO_3$ (5)	$MgSO_4$ (0.5)	< 5
24	$AgNO_3$ (5)	$Mg(OAc)_2{\cdot}4H_2O$ (0.5)	< 5
25	$AgNO_3$ (5)	$MgClO_4$ (0.5)	0
26	$AgNO_3$ (5)	$Mg(NO_3)_2{\cdot}6H_2O$ (0.5)	75
27	–	$Mg(NO_3)_2{\cdot}6H_2O$ (0.5)	0

[a] Reaction conditions: **1a** (0.3 mmol), $Ph_2P(O)H$ (0.6 mmol), catalyst, and additive in dry CH_3CN (3 mL) with stirring at 100 °C under argon for 12 h. [b] Yield of the isolated product. [c] Reaction temperature: 80 °C.

Table 2: Silver-catalyzed carbon phosphorylation of alkenes.[a,b]



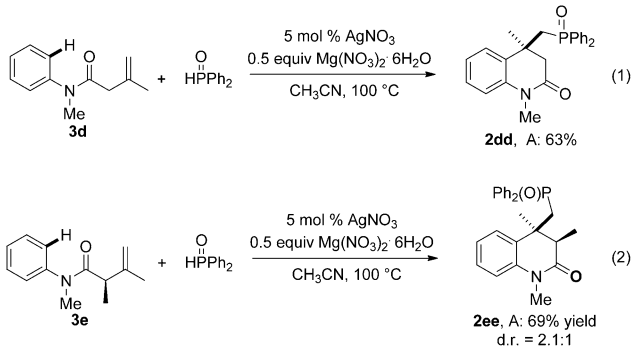
[a] All the reactions were carried out in the presence of 0.3 mmol of **1a**–**1z**, $Mg(NO_3)_2{\cdot}6H_2O$ (0.5 equiv) in 3 mL CH_3CN at 100 °C. Conditions A: 5 mol % $AgNO_3$, 2.0 equiv $HP(O)R^4R^5$; Conditions B: 20 mol % $AgNO_3$, 2.0 equiv $HP(O)R^4R^5$; [b] Yield of the isolated product.

of $AgNO_3$ was reduced to 5 mol %, the yield of **2a** improved to 82 % yield (Table 1, entry 7). Other nitrates such as $Cu(NO_3)_2{\cdot}3H_2O$, $La(NO_3)_3{\cdot}6H_2O$, $Y(NO_3)_3{\cdot}6H_2O$, $Co(NO_3)_2{\cdot}6H_2O$, and $Ce(NO_3)_3{\cdot}6H_2O$ also performed well in this reaction (Table 1, entries 10–15). If the additive was an aqueous solution of $NaNO_3$, the desired product **2a** was not produced (Table 1, entry 16). By using 0.5 equivalents of $Mg(NO_3)_2{\cdot}6H_2O$ as an additive, we revaluated different silver catalysts but lower yields were obtained (Table 1, entries 17–21). Different magnesium salts were also examined and the results show that $Mg(NO_3)_2{\cdot}6H_2O$ is still the best choice (Table 1, entries 22–25). In addition, decreasing the temperature caused the yield descend (Table 1, entry 26). A control experiment showed that $Mg(NO_3)_2{\cdot}6H_2O$ alone could not promote this reaction (Table 1, entry 27).

With the optimized reaction conditions in hand (Table 1, entry 7), we turned our attention to the scope with respect to the substrates. As shown in Table 2, an investigation into different *N*-protecting groups showed that methyl and benzyl are much better than tosyl (**2a**–**2c**) and that N-free arylacrylamide does not work at all (**2d**). Substrates with both electron-donating and electron-withdrawing groups on the *para*-position of the arylacrylamide reacted well and the majority of products were obtained with high yields (**2e**–**2l**). With substituent groups at the *ortho* position of the arylacrylamide, the effect of the steric bulk was very distinct and lower yields were observed as a result (**2m**–**2r**). For some substrates the loading of the catalyst had to be increased to 20 mol % to furnish the products (**2m**–**2r**). Substrates bearing *meta* substituents exhibited good reactivity but poor regioselectivity (**2s**). When the benzene ring of the substrates was changed to naphthalene, the reaction successfully provided the product **2t**. In addition, cyclization of the tetrahydroquinoline derivative furnished the tricyclic oxindole **2u** in 83 % yield. However, using heterocyclic substrates such as pyridine, quinolone, and pyrimidine led to no reaction as a result of lower reactivity. Next, variously substituted alkenes were evaluated. No reaction occurred in the case of a monosubstituented olefin ($R^2 = H$). However, a series of α-substituted olefins bearing different functional groups, such as phenyl (**2v**), benzyl (**2w**), ester (**2x**), and phthalimide (**2y**) groups can still provide the desired products in moderate to good yields. Notably, the product of **2y** can be easily to converted into spiropyrrolidinyloxoindoles such as horsfiline.[13] α,β-disubstituted arylacrylamide was also subjected to the process, thus affording the spirooxindole **2z** with 82 % yield and moderate diastereoselectivity. Finally, both diethyl phosphite

and ethyl phenylphosphinate could be used as substrates, thus generating the corresponding products in 83% and 43% yields (**2aa**, **2bb**), both of which can undergo various functional groups conversions through cross-coupling reactions.[14] The reaction can also be effectively scaled up with similar efficiency (see the Supporting Information).

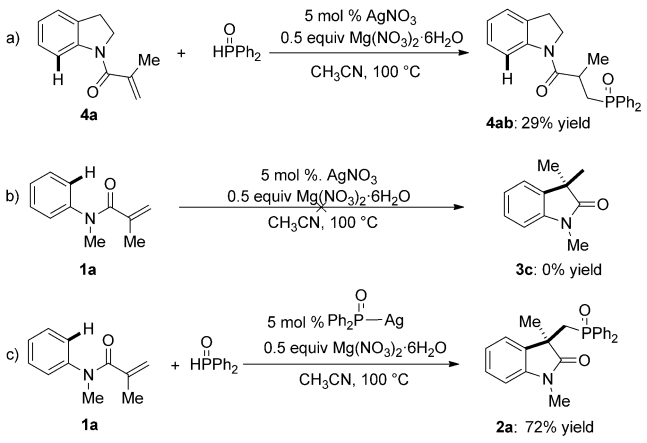
To obtain larger rings and to determine whether the Michael addition occurred during the phosphorylation of the alkene, we selected **3d** as a substrate for the reaction and the six-membered-rings product **2dd** was obtained in 63% yield. This result also excluded the Michael addition in this transformation [Scheme 2, Eq. (1)]. In addition, we introduced



Scheme 2. $AgNO_3$-catalyzed carbon phosphorylation of alkenes.

a stereogenic center at the α-position of the carbonyl group and set out to obtain the optically pure product **2ee**, but a low d.r. value was observed [Scheme 2, Eq. (2)].

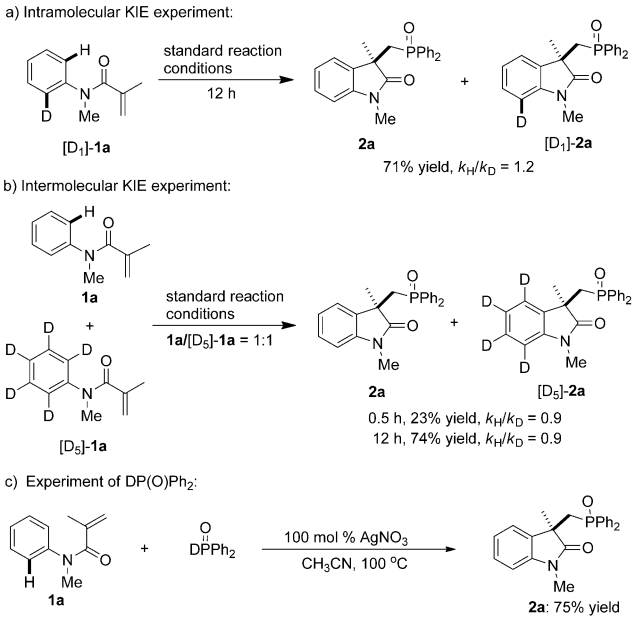
While investigating the scope with respect to the substrates, the arylacrylamide **4a** reacted with $Ph_2P(O)H$ under the optimal reaction conditions and only hydrophosphorylation of the alkene occurred to give the uncyclizated product **4ab** in 29% yield (Scheme 3). This result suggests that $AgNO_3$ coordinates to **4a** and leads to alkene addition. In contrast, a pioneering report shows that $AgNO_3$ can react with $Ph_2P(O)H$ to form the complex of $Ph_2(O)PAg$ (**2A**).[15] Two experiments were performed to collect additional



Scheme 3. Investigation of phosphorylation and cyclization.

evidence in this regard. As a unique substrate, **1a** worked in the presence of 5 mol% $AgNO_3$ and 0.5 equivalents $Mg(NO_3)_2{\cdot}6H_2O$ in CH_3CN at 100 °C. C–H functionalization did not occur and the cyclization product **3c** was not detected (Scheme 3). However, **2A** catalyzed a carbon phosphorylation reaction of **1a** under the optimized reaction conditions to give **2a** in 72% yield (Scheme 3). Thus, we conclude that the first step is phosphorylation with $AgNO_3$ and the formation of the $Ph_2(O)PAg$ is the key step in this transformation.

A detailed mechanism for this novel transformation is unknown. To collect data on the catalytic procedure, the intramolecular and intermolecular kinetic isotope effect (KIE) experiments were carried out with the deuterium-labeled substrates [D_1]-**1a** and [D_5]-**1a** (Scheme 4a and b).

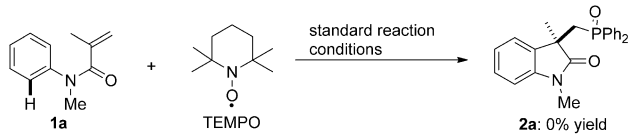


Scheme 4. Deuterium-labeled carbon phosphorylation of alkenes.

Two secondary kinetic isotope effects were observed (the intramolecular $k_H/k_D = 1.2$, and intermolecular $k_H/k_D = 0.9$). First, the intermolecular one indicates that the C–H bond is broken after the turnover-limiting step. In addition, the observation of the intramolecular kinetic isotope effect of 1.2 indicates that C–C bond formation occurs before C–H cleavage.[16] [D_1]Diphenylphosphine oxide was also examined in the presence of 100 mol% $AgNO_3$ and **2a** was obtained in 75% yield and no other deuterium-labeled product was observed. This result illustrates that $Ph_2P(O)H$ first reacts with $AgNO_3$ and forms **2A**. Simultaneously, the pH value of the reaction solution changes and also indicates that the HNO_3 is produced (see the Supporting Information).

Some metal-catalyzed carbon phosphorylation reactions of alkenes with diphenylphosphine oxide $Ph_2P(O)H$ and H-phosphonates $(RO)_2P(O)H$ are well known to proceed by a radical process,[17] so our carbon phosphorylation reaction of alkenes may proceed by a radical pathway. The preliminary mechanistic studies support this assumption. Chemical trapping of radicals using TEMPO (2,2,6,6-tetramethyl-1-piper-

idinyloxy, a well-known radical-trapping reagent) was recently also shown to be invaluable in elucidating the mechanism of the phosponyl radical.[17d,e] As illustrated in Scheme 5, the addition of 1.0 equivalents of TEMPO suppressed the carbon phosphorylation process, thus suggesting that this transformation might involve a radical process.

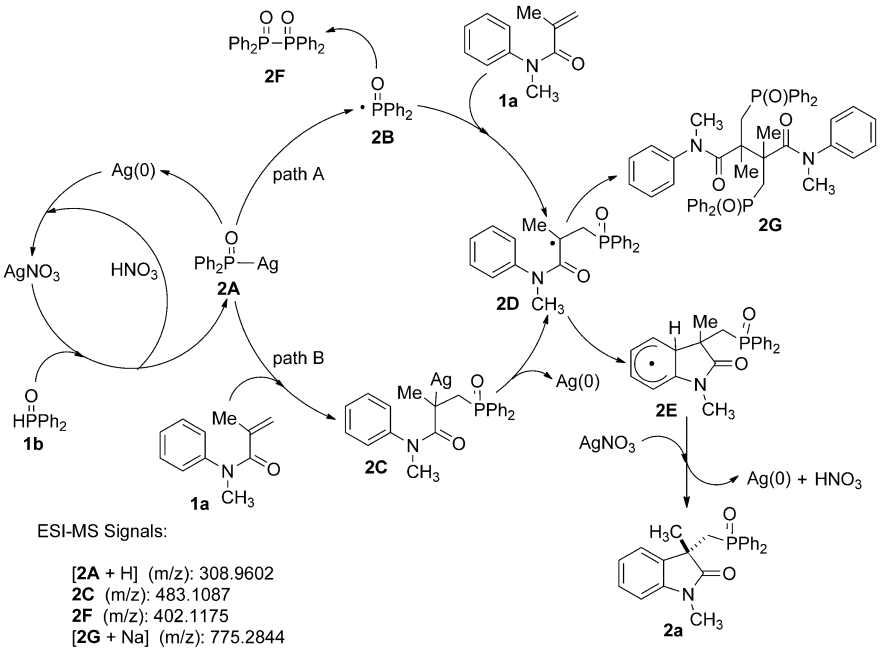


Scheme 5. TEMPO-trapped carbon phosphorylation of alkene.

To further understand the catalytic cycle of the carbon phosphorylation, the model reaction was monitored by mass spectrometry experiment. First, the ESI/MS showed a peak at *m*/*z* 308.9602, which corresponds to $[\mathbf{2A}+\mathrm{H}]^+$ (Scheme 6). The signal might mean that $AgNO_3$ can easily react with diphenylphosphine oxide to form the intermediate **2A**. In contrast, a signal at *m*/*z* 483.1087 may be the silver(I) species **2C** which results from the addition of **1a** with **2A**. In the standard catalytic reaction, we were delighted to see two signals at *m*/*z* 402.1175 and 775.2844, which are related to the masses of the radical dimmers of **2F** and **2G**, respectively.[18] The above observations provide support for this transformation possibly involving the intermediates **2A**, **2C**, **2F**, and **2G** (Scheme 6).

On the basis of the above experiments, we propose a tentative pathway for this transformation (Scheme 6). First, diphenylphosphine oxide reacts with $AgNO_3$ to form the intermediate **2A** under the reaction conditions. It may also proceed by a pathway involving a silver-promoted generation of the phosphoryl radical **2B** (Scheme 6, path A),[19] which then adds to **1a** to give the alkyl radical **2D**.[17d] Another possibility for the formation of the alkyl radical **2D** is the addition of **2A** to **1a** to form the silver(I) species **2C**, which was oxidized to the alkyl radical **2D** (Scheme 6, path B). The resulting alkyl radical **2D** participates in an intramolecular radical substitution reaction. Addition of the radical to the aromatic ring to generate the intermediate **2E** with a subsequent single-electron transfer (SET) from **2E** to silver(I) would release the product along with HNO_3 and silver(0).[19] In the presence of HNO_3, the silver(0) was oxidized to silver(I).

In summary, we have developed a highly efficient protocol for the preparation of various diphenylphosphoryl oxindoles by silver-catalyzed difunctionalization of alkenes through a carbon phosphorylation and C–H functionalization cascade process. A cheap, nontoxic silver salt is employed in catalyzing the hydrophosphorylation of alkenes for the first time. Further studies on the clarification of the reaction mechanism and application to other substrates are underway.



Scheme 6. Proposed mechanisms of $AgNO_3$-catalyzed carbon phosphorylation of arylacrylamide.

Experimental Section

General Procedures for silver-catalyzed carbon phosphorylation of substrates: In a Schlenk tube, **1a** (0.30 mmol), $HP(O)Ph_2$ (0.6 mmol), $AgNO_3$ (0.015 mmol), and $Mg(NO_3)_2{\cdot}6H_2O$ (0.15 mmol) were added and charged with Ar three times. Anhydrous CH_3CN (3 mL) was then added. The mixture was allowed to stir at 100 °C for 12 h (monitored by TLC). After the substrate was consumed, the reaction was cooled to room temperature and *t*BuONa (1.2 mmol) was added. The mixture was stirred for an additional 10 min at room temperature. The solvent was then removed under vacuum and the resulting residue was purified by column chromatography on silica gel (eluent: hexanes/ethylacetate 1:1) to give the product **2a**.

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