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Manganese(III) Acetylacetonate-Mediated Phosphorylation of Enamides at Room Temperature

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Abstract. A highly *Z*-selective phosphorylation by Manganese(III) acetylacetonate-mediated cross-dehydrogenative-coupling of enamides and phosphine oxides has been developed under mild conditions. The reaction shows broad substrate scope and functional group compatibility. DFT studies revealed that the formation of *Z*-products is presumably due to the presence of an intramolecular hydrogen bond. *β*-Aminophosphine could be readily obtained by reduction and hydrolysis of the product.

Keywords: phosphorylation; *Z*-selective; Manganese-mediated; cross-dehydrogenative-coupling; room temperature

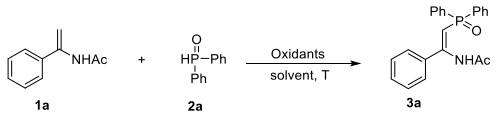
Enamines are of important organic compounds which are widely used in organic synthesis.[1] Over the past decade, enamides have also been involved in a variety of new synthetic transformations including asymmetric synthesis [1c,1e-f] and C-H bond activation. [2] Since the pioneering work reported by Loh and co-workers on the Pd(II)-catalyzed arylation of cyclic enamines through C-H activation, [2a] a lot of novel C-H functionalizations of enamines had been realized. However, to be our best knowledge, the phosphorylation of enamides through C-H activation had not been yet reported. *β*-phosphorylated enamides are useful building block which could be easily transformed into α-phosphorylated ketones. [3] They could also be potentially applied to asymmetric hydrogenation to obtain chiral *β*-aminophosphine oxide.

In the past decades, transition-metal-catalyzed cross-coupling reactions have emerged as a powerful strategy for the construction of C-P bond. [4] In particular, cross-dehydrogenative-coupling reactions between C-H and P-H bond have drawn much attention due to atom and step economy. [5] The phosphonation of arenes with dialkyl phosphites was first reported by Ishii and coworkers using Mn(II) catalyst with Co(II) as co-catalyst under oxygen atmosphere. [5m] Zhang and co-workers developed a protocol of $Mn(OAc)_3$-promoted regioselective phosphonation of heterocycles. [5n] Tan and co-workers recently described the silver-catalyzed phosphorylation of styrenes to synthesize the vinylphosphonates. [6] As part of our program devoted to the study of C-H bond activation of enamides, [7] we decided to explore the utilization of enamides as the suitable building block for the preparation of *β*-phosphorylated enamides by direct cross-coupling of C(sp2)-H with P-H bond. However, the initial attempt to achieve the cross-coupling of enamides with phosphine oxides failed by using Tan's method due to the rapid decomposition of enamides under their reaction conditions. Herein, we would like to communicate the direct *Z*-selective phosphorylation by $Mn(acac)_3$-mediated oxidative coupling of enamides and phosphine oxides under mild conditions.

We commenced our study with the coupling of enamide **1a** and diphenylphosphine oxide **2a** by Tan's method (5 mol% $AgNO_3$, 2 equiv. $K_2S_2O_8$, 0.4 equiv. TEMPO). Unfortunately, no desired product was observed and the drastic decomposition of enamide **1a** was observed. To our delight, 57% yield of desired product **3a** was obtained by using $Pd(OAc)_2$ (10 mol%) as catalyst and AgOAc (2.0 equiv.) as the oxidant in CH_3CN at 80 °C (Table 1, entry 1). A control experiment revealed that the reaction could also undergo smoothly in the absence of $Pd(OAc)_2$ (Table 1, entry 2). Wu and co-workers examined the activity of Mn(III) as an oxidant for P-H/aryl C-H coupling.[7m] Therefore the more cheaper manganese salts were exploited as the promoter and $Mn(acac)_3$ gave the best result, providing the product **3a** in 78% yield (Table 1, entries 3-7). The solvent had significant impact on the reaction. Among the solvents examined, toluene was regarded as the optimal candidate to afford the target product **3a** in the 81% yield (Table 1, entries 8-12). Even at room temperature, the reaction could also smoothly proceed, giving the product in 86% yield. (Table 1, entry 13). The product could also be observed as the

intermediate by couplings of phosphine oxides with oximes using copper catalyst and ligand. [3] We have also tried this reaction using a catalytic amount of $Mn(acac)_3$ in presence of O_2 or air, but the yield of product is not satisfactory. It should also be pointed out that the C-C coupling products reported by Li's group [8] between acetylacetone, which was the by-product in our reaction, and enamides were not observed in our reaction conditions.

Table 1. Optimization of the Reaction Conditions [a,b,c)]

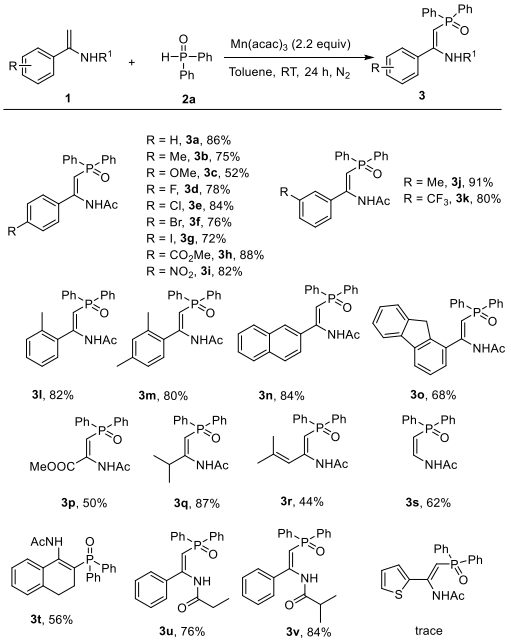


1a 2a 3a

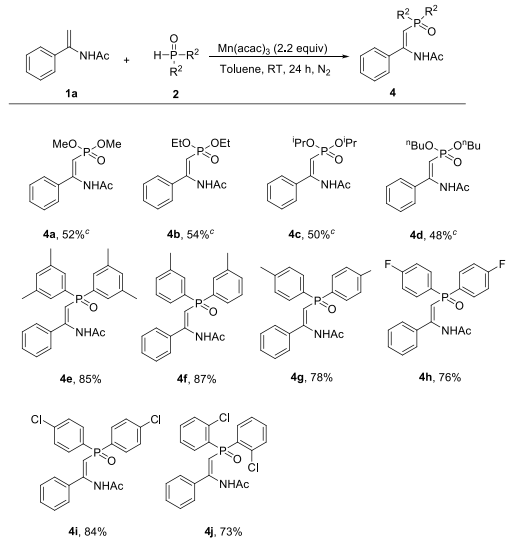
Entry	Oxidant	Solvent	T/°C	Yield/%
1	AgOAc	CH_3CN	80	57[c]
2	AgOAc	CH_3CN	80	60
3	$Mn(OAc)_3{\cdot}2H_2O$	CH_3CN	80	53
4	$Mn(acac)_3$	CH_3CN	80	78
5	$Mn(OAc)_2$	CH_3CN	80	23
6	Ag_2CO_3	CH_3CN	80	55
7	$AgNO_3$	CH_3CN	80	37
8	$Mn(acac)_3$	Toluene	80	81
9	$Mn(acac)_3$	DCE	80	56
10	$Mn(acac)_3$	MeOH	80	31
11	$Mn(acac)_3$	THF	80	42
12	$Mn(acac)_3$	DMF	80	trace
13	$Mn(acac)_3$	Toluene	rt	86

[a)] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), oxidants (2.2 equiv.), in solvent (2.0 mL), under N_2 atmosphere for 24 h. [b)] Isolated yield. [c)] with 10 mol % $Pd(OAc)_2$

With the optimized conditions in hand, we next investigated the scope of enamides in this reaction as summarized in Scheme 1. The transformation exhibited broad substrate scope and a variety of substituent groups at the para position of the phenyl ring were well tolerated under the standard conditions to deliver the corresponding products **3a**-**3i** in good to excellent yields. In addition, both ortho and meta-substituted enamides smoothly afforded the products **3i**-**3m** in excellent yields, revealing that the steric hindrance had negligible effect on the reaction. Naphthyl enamide and fluorenylenamide participated in the reaction to give the corresponding **3n**-**3o** in high yields. Electron-deficient enamide showed good reactivity to give the product **3p** in good yield. Alkyl enamide **1q** could afford the phosphorylation product **3q** in high yield. Alkenyl substituted enamide provided the product **3r** in moderate yield with high selectivity. The less stable *N*-vinylacetamide could tolerate the reaction conditions to give the desired product **3s** in 62% yield. The cyclic enamide participated in the reaction to give the phosphorylation product **3t** in 56% yield. To our disappointment, heterocyclic enamides, such as **1w**, could not efficiently participate in the reaction to get the desired product. Enamides with different acylation substituents proceeded well to afford the corresponding products **3u**-**3v** in excellent yields. The reaction showed high *Z*-selectivity. Only *Z*-products were observed in the reaction in contrast to *E*-selectivity obtained in the phosphorylation of styrenes. The DFT studies demonstrated that the energy of product *Z*-**3a** with phenyl group is lower than that of its *E* isomer by 2.0 kcal/mol, and this value increased to 4.1 kcal/mol for the product **3s** without phenyl group. This result is consistent with Chang's report, [9] implicating that an intramolecular hydrogen bond had significant impact on the formation of *Z*-products. (see the Supporting Information).

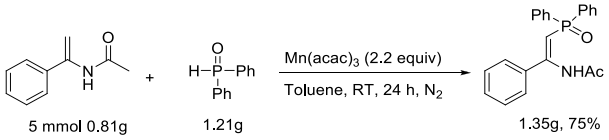


Scheme 1. Scope of Enamides [a,b)] [a)] **1** (0.2 mmol), **2a** (0.24 mmol), $Mn(acac)_3$ (2.2 equiv.), Toluene (2.0 mL), under N_2 atmosphere for 24 h. [b)] Isolated yield.



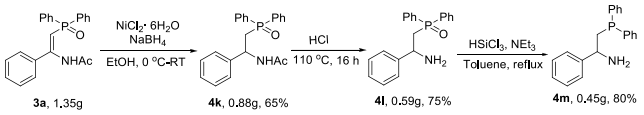
Scheme 2. Scope of Phosphine Oxides and Phosphonates [a,b,c)] [a)] **1a** (0.2 mmol), **2** (0.24 mmol), $Mn(acac)_3$ (2.2 equiv.), Toluene (2.0 mL), under N_2 atmosphere for 24 h. [b)] Isolated yield. [c)] At 80 °C

The scope of phosphine oxides **2** using **1a** as the coupling partner was further examined and the results are listed in Scheme 2. Dialkyl phosphonate could participate in the reaction, affording the corresponding *β*-aminophosphonate **4a**-**4d** in moderate yields under higher temperature. Both electron-rich and electron-deficient substituents on the aryl groups were well tolerated in this reaction to give the product **4e**-**4j** in good to excellent yields.



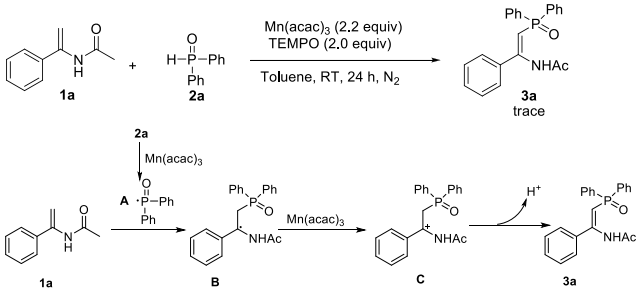
Scheme 3. Gram-Scale Synthesis of 3a

With the aim of evaluating the practicality of this reaction, a gram-scale experiment was performed with **1a** (0.81g) and **2a** (1.21 g), affording the corresponding product **3a** in 75% yield.



Scheme 4. Synthetic Approach toward Derivatization of 3a

To further demonstrate the synthetic utility of the method, a synthetic approach toward *β*-aminophosphine ligand was shown in Scheme 4 from **3a** through reduction of double bond, hydrolysis of amide and reduction of phosphorus-oxygen double bond. This method provides a novel strategy to access *β*-aminophosphine ligand.



Scheme 5. Mechanism Investigation

To elucidate the mechanism of the current reaction, 2.0 equivalents of radical inhibitor 2,2,6,6-tetramethylpiperidine oxide (TEMPO) was added to this reaction system under standard conditions. It was found that the addition of TEMPO completely inhibited the reaction, and traces of **3a** was detected (Scheme 5). The result suggested that the reaction may involve a radical pathway. Based on the result and literature reports, [5*m*-*p*,10] a mechanistic pathway is proposed as shown in Scheme 5. The reaction of phosphine oxide **2a** with Mn(III) salt generates phosphorous radicals **A**, which reacts with enamide **1a** to produce intermediate **B**. Subsequently single electron oxidation by Mn(III) leads to the formation of cationic intermediate **C**, which delivers the product **3a** by elimination of a proton.

In summary, a novel approach to access *β*-phosphorylated enamides via $Mn(acac)_3$-mediated oxidative coupling of enamides with phosphine oxide has been developed under mild reactions. The reaction showed high *Z*-selectivity and broad substrate scope. The product could be further reduced and hydrolyzed to get important *β*-aminophosphine derivative.

Experimental Section

To a sealed tube with a stir bar were added N-(1-phenylvinyl)acetamide (**1a**, 32.2 mg, 0.20 mmol), diphenylphosphine oxide (**2a**, 48.5 mg, 0.24 mmol), $Mn(acac)_3$ (0.44 mmol, 155 mg), in toluene (2.0 mL) under nitrogen. The reaction mixture was stirred at RT (25 °C) for 24 h, then filtered through a pad of celite, and then washed with CH_2Cl_2. Organic solvents were removed under reduced pressure and the crude reaction mixture was purified by column chromatography with n-hexane/EtOAc/MeOH as an eluent to give the desired product.

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