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ARTICLE TYPE

A Silver-Initiated Free-Radical Intermolecular Hydrophosphinylation of Unactivated Alkenes

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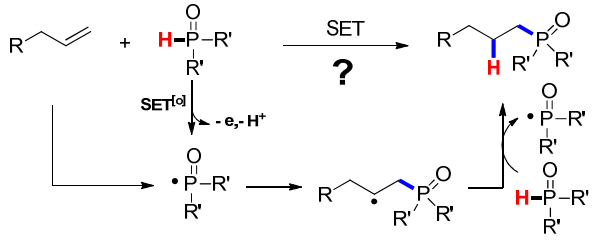
A scalable, operationally easy intermolecular hydrophosphinylation of various unactivated alkenes with H-P(O) compounds via an Ag(I)-initiated free radical process was developed. Mechanistic studies including electron-spin-resonance (ESR) and radical clock experiments suggest that atom transfer processes were involved in this system.

As a large class of important and valuable building blocks, organophosphorus compounds are widely applied in synthesis of pharmaceuticals, agrochemicals and materials.[1] In the past decades, considerable advances have been made to construct C-P bonds.[2] Among them, one of the most atom-economical and attractive strategies is the direct hydrophosphinylation of alkenes.[3] The free-radical strategies for the addition of a P-H or (O)P-H bond to alkenes represent one of the most important methods to form a C-P bond.[4] Although this radical addition using peroxide,[5] AIBN,[6] Et_3B,[7] air/nitrogen,[8] and organic dye/photoirradiation[9] etc as the radical initiators has been achieved, more efficient and practical strategies are still highly desirable.

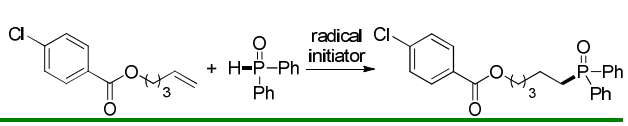
As our continuous investigations on the C-C bond formation via free-radical processes,[10] we began to question whether a C-P bond could be formed via a single-electron-transfer (SET) process. As demonstrated in Scheme 1, single-electron oxidation of the secondary phosphine oxide followed by a deprotonation would generate a P-centered free radical. Addition of the phosphinyl radical to an olefin followed by hydrogen abstract from the phosphine oxide would lead to the product by hydrophosphinylation of alkene and regenerate the phosphinyl radical. Fortunately, we successfully accomplished an Ag(I)-initiated intermolecular hydrophosphinylation of a wide range of unactivated alkenes with phosphites (Scheme 1).



Scheme 1. Free Radical Hydrophosphinylation of Alkene via SET.

Initially, a series of experiments were carried out to test the hypothesis for hydrophosphinylation of unactivated alkenes with phosphites through a one-electron transfer process. It can be seen from Table 1 that the desired product was isolated in nearly quantitative yield by using catalytic amount of AgF (20 mol%), which was more efficient than other silver salts such as Ag_2CO_3, $AgNO_3$, and AgOAc etc (Table 1, entries 1-7). Further optimization of the typical reaction conditions indicated that the solvent, concentration as well as the temperature also affected the reaction efficiency (entries 8-12). Furthermore, addition of persulfates such as $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ could slightly raise the yield of the product (entries 13 and 14).

Table 1. Modification of the typical reaction conditions. [a]

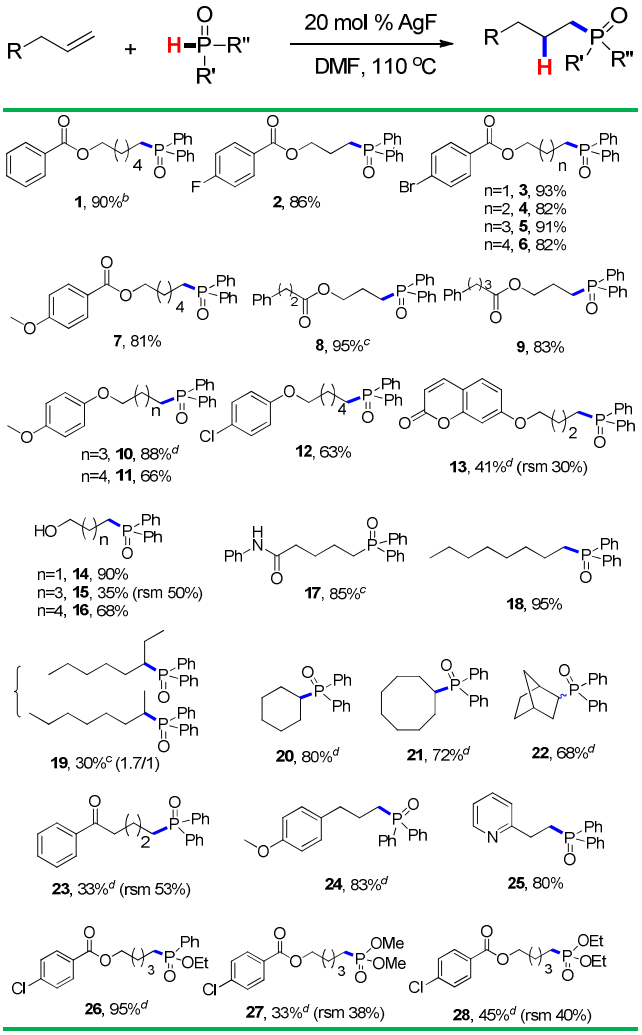


entry	radical initiator (mol %)	solvent (mL)	T (°C)	yield (%)[b]
1	-	DMF (2)	110	-
2	Ag_2CO_3(20)	DMF (2)	110	63
3	$AgNO_3$(20)	DMF (2)	110	26
4	AgOAc (20)	DMF (2)	110	50
5	**AgF (20)**	**DMF (2)**	**110**	**96**
6	AgF (5)	DMF (2)	110	46
7	AgF (10)	DMF (2)	110	70
8	AgF (20)	DMSO (2)	110	16
9	AgF (20)	CH_3CN (2)	110	95
10	AgF (20)	DMF (1)	110	60
11	AgF (20)	DMF (3)	110	81
12	AgF (20)	DMF (2)	80	20
13[c]	AgF (20)	DMF (2)	110	97
14[d]	AgF (20)	DMF (2)	110	98

[a] Reaction conditions: pent-4-en-1-yl 4-chlorobenzoate (1 equiv, 0.25 mmol), diphenylphosphine oxide (4 equiv, 1.0 mmol), 24 h, unless otherwise noted. [b] Isolated yields. [c] $K_2S_2O_8$(3 equiv, 0.75 mmol) was added. [d] $(NH_4)_2S_2O_8$(3 equiv, 0.75 mmol) was added.

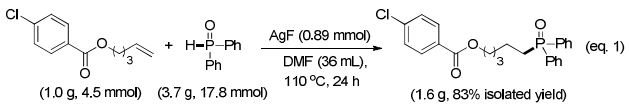
The substrate scope and functional group tolerance were demonstrated in Scheme 2. A wide range of terminal and internal unactivated alkenes are compatible to this system (entries **1**-**25**). Various functional groups such as ester, halogen, ether, hydroxyl, amide and ketone etc can all be well-survived. It is noteworthy

that the free radical addition didn't happen at the internal C=C double bond but the terminal one when 7-(but-3-en-1-yloxy)-2H-chromen-2-one was used as the substrate (entry **13**). (*E*)-Oct-2-ene afforded a regio-isomers with the ratio of 1.7/1 (entry **19**). 2-Vinylpyridine also gave the corresponding product **25** in high yield. However, styrene and its derivatives are not effective in this system. Notably, H-phosphinates and H-phosphonates are proven to be effective substrates (entries **26**-**28**). For example, ethyl phenylphosphinate afforded the desired product in 95% yield (entry **26**). Addition of the dimethyl phosphonate and diethyl phosphonate to pent-4-en-1-yl 4-chlorobenzoate gave the corresponding products in 33% and 45% yields, respectively (entries **27** and **28**). Obviously, H-phosphonates afford relatively low yields of the desired products, which might be due to the stability of the P-centered radicals. Finally, this reaction can be easily scaled up to gram level, which suggests that it can be potentially applied in chemical industry (equation 1).

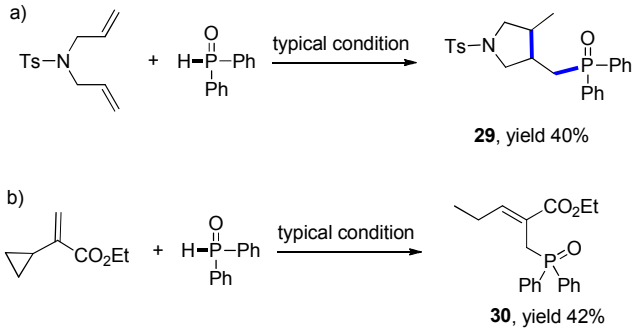


[a] Reaction conditions: alkene (1 equiv, 0.25 mmol), organophosphorus compounds (4 equiv, 1.0 mmol), AgF (20 mol%, 0.05 mmol), DMF (2 mL), 110 °C, 24 h, unless otherwise noted. [b] Isolated yields. [c] $K_2S_2O_8$(3 equiv, 0.75 mmol) was added. [d] $(NH_4)_2S_2O_8$(3 equiv, 0.75 mmol) was added.

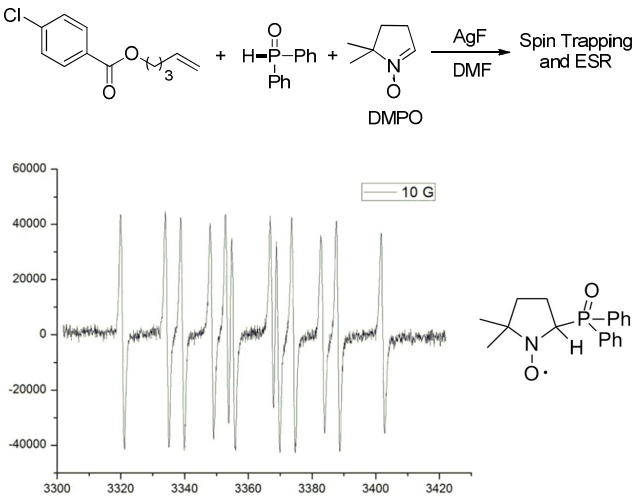
Scheme 2. AgF-Promoted Hydrophosphinylation of Alkenes with H-P(O). [a]



Mechanistic studies including radical clock and ESR were carried out to confirm the previously proposed free radical process. As depicted in Scheme 3, ((4-methyl-1-tosylpyrrolidin-3-yl)methyl)diphenylphosphine oxide was obtained in 40% yield, which might proceed a radical addition/cyclization cascade process (Scheme 3a). In addition, ethyl 2-cyclopropylacrylate led to a ring opening product 30 in 42% yield (Scheme 3b). Furthermore, a series of experiments were designed to get evidences of key radical intermediates through spin trapping technology and ESR. As a result, the ESR signal of a P-centered radical species (g = 2.0060, a_N = 1.411 mT; a_H = 1.888 mT; a_P = 3.475 mT) was observed by using 5,5-dimethyl-1-pyrroline N-oxide (DMPO) as a radical spin trap (Scheme 4). Overall, the proposed free radical addition mechanism is supported by these studies.



Scheme 3. Radical clock experiments.



Scheme 4. ESR studies. ESR spectrum of a solution of pent-4-en-1-yl 4-chlorobenzoate (5.0×10^{-2} mol/L), diphenylphosphine oxide (0.2 mol/L), AgF (1.0×10^{-2} mol/L), and DMPO (6.0×10^{-2} mol/L) in DMF (2 mL), 110 °C for 2.5 h.

In summary, a silver(I)-triggered free radical intermolecular C-P bond formation has been developed. A variety of alkyldiphenylphosphine oxides, alkyl phosphinates as well as alkyl phosphonates can be facilely prepared via addition of H-P(O) compounds with unactivated alkenes by using this strategy.

The features of wide substrate scope, completely *anti*-Markovnikov addition and scalability make this methodology attractive to organophosphorus synthetic chemistry. Radical clock and ESR studies support the free-radical addition pathway.

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