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Silver(I)-Mediated Phosphorylation/Cyclization Cascade of *N*-Cyanamide Alkenes for Divergent Access to Quinazolinones and Dihydroisoquinolinones

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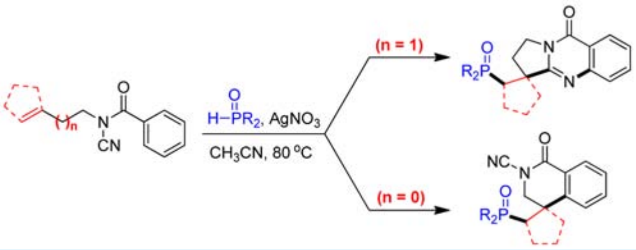
Ⓢ *Supporting Information*

ABSTRACT: A silver(I)-mediated phosphorylation/cyclization radical cascade of *N*-cyanamide alkenes has been developed. The addition of in situ generated phosphorus radical to *N*-cyanamide alkenes triggers the cascade, resulting in late-stage cyclization toward divergent access to 4-quinazolinones and dihydroisoquinolinones. Both terminal and internal *N*-cyanamide alkenes are applicable in this protocol, and the cyclizations are consistent with Baldwin's rule.



Organophosphorous compounds have gained considerable attention because of their wide application in organic synthesis, medicinal chemistry, and material science.[1] Therefore, various synthetic methodologies have been developed for introducing the phosphorus group into organic molecules.[2] Traditional methods rely on the reaction of organometallic reagents with electrophilic phosphorus reagents such as $(EtO)_2P(O)Cl$. Recently, the transition-metal-catalyzed coupling reaction has become a direct approach to phosphorus compounds. For example, Toste developed a dual gold and photoredox catalytic strategy for C−P cross-coupling.[3] Yu reported an elegant work of Pd(II)-catalyzed phosphorylation of aryl C−H bonds.[4] More recently, Lei and co-workers invented a copper-catalyzed radical/radical $C(sp^3)$−P cross-coupling toward phosphorylation of aryl ketone *O*-acetyloximes,[5] while Studer reported a radical C−P and C−C coupling of phosphorus radical with isonitriles to generate phenanthridines.[6] On the other hand, Duan and Miura have respectively established the radical phosphorylation/cyclization of alkynes for accessing benzo[*b*]phosphole oxides.[7] Meanwhile, Gu developed a nice work of catalyst-free synthesis of phosphinic amides.[8]

In recent times, the transition-metal-catalyzed phosphorylation of alkenes has acted as a powerful tool to forge $C(sp^3)$−P bonds. For example, Li established a silver-catalyzed radical phosphonofluorination of unactivated alkenes.[9] Liang,[10] Yang,[11] and Nevado[12] have independently developed silver-catalyzed C−P functionalization of alkenes toward late-stage annulations cascade for access to heterocycles. Thus, the development for phosphorylation/cyclization of unactivated alkenes toward diversified construction of heterocycles is still interesting and important.

In the course of our interest in heterocycle synthesis,[13] we proposed that the phosphorylation/radical cyclization of unactivated alkenes would probably lead to divergent synthesis. Herein, we describe a silver-mediated phosphorylation/cyclization cascade of *N*-cyanamide alkenes for divergent and expedient synthesis of phosphorus 4-quinazolinones and dihydroisoquinolinones (Figure 1).

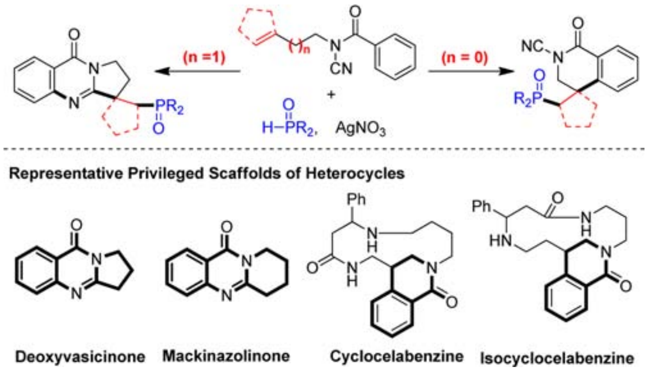


Figure 1. Silver(I)-mediated heterocycle synthesis.

Lacôte, Malacria, and Fensterbank revealed that *N*-cyanamide was a good radical cyclization group in quinazolinone synthesis.[14] Therefore, we commenced our study by investigating *N*-cyanamide olefin **1a** and diphenylphosphine oxide **2a** in the presence of $AgNO_3$ (Table 1), and **1a** was easily synthesized from acylamide butene and cyanogen bromide. Gratifyingly, when **1a** was subjected to reaction with **2a** catalyzed by 20% $AgNO_3$ at 80 °C in CH_3CN under argon, 4-quinazolinone product **3a** was observed and isolated in 41%

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Table 1. Optimization of the Reaction Conditions[a]

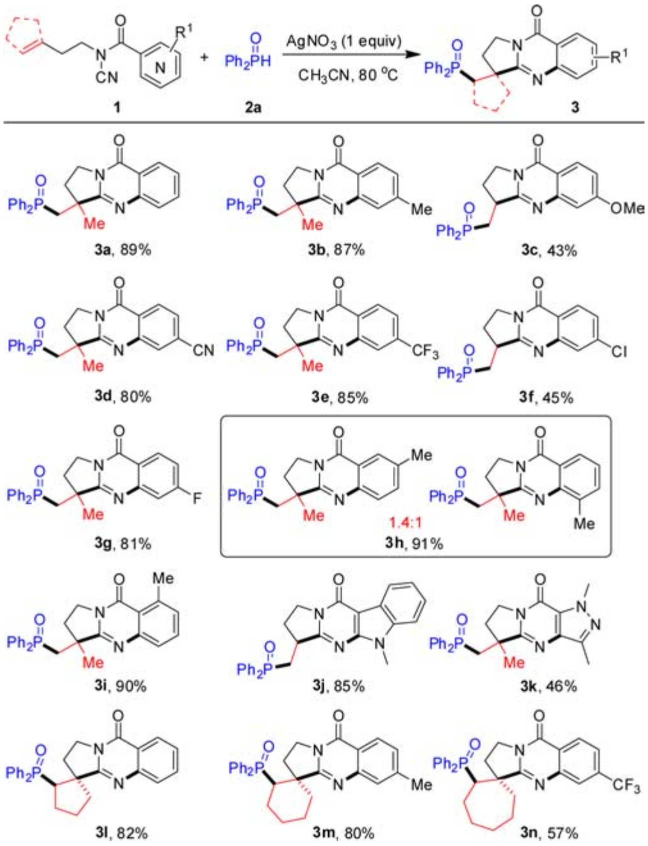
entry	Ag(I) salt	additive	temp (°C)	yield[b] (%)
1	$AgNO_3$ (0.2 equiv)		80	41
2	$AgNO_3$ (0.2 equiv)	$K_2S_2O_8$ (2.0 equiv)	80	27
3	$AgNO_3$ (0.2 equiv)	$Mg(NO_3)_2$ (0.5 equiv)	80	30
4	AgOAc (0.1 equiv)	$Zn(NO_3)_2$ (0.5 equiv)	80	35
5	$AgNO_3$ (0.5 equiv)		80	48
6	$AgNO_3$ (1.0 equiv)		80	89
7[c]	$AgNO_3$ (1.0 equiv)		80	50
8	$AgNO_3$ (1.0 equiv)		50	32

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol) in 2 mL of solvent under argon for 10 h. [b] Isolated yields are given. [c] Reaction was conducted under air.

yield (entry 1). The formation of **3a** indicated an olefin phosphorylation/cyclization cascade, and this finding encouraged us to further optimize the reaction conditions. We attempted to add $K_2S_2O_8$, $Mg(NO_3)_2$, and $Zn(NO_3)_2$ to the reaction as additives and found they were inferior and decreased the yields (entries 2−4). Gratifyingly, when the loading of $AgNO_3$ was increased to 50%, the yield of **3a** could be improved to 48% (entry 5). Moreover, the yield could be ultimately improved to 89% when 1 equiv of $AgNO_3$ was used (entry 6). It should be noted that the argon protection was crucial and the yield would decrease to 50% when the reaction was conducted under air (entry 7), while decreasing the temperature to 50 °C would also lead to a lower yield (entry 8).

With the optimized conditions in hand, various substrates were employed to test the generality (Scheme 1). Those *para*-substituted *N*-acylcyanamide butenes were found to be applicable in this process and could generate the phosphorus 4-quinazolinones in moderate to good yields (**3a**−**g**), with a broad functional group tolerance. Surprisingly, the electronic property (rich and deficient) of the aromatic ring did not show significant effects to the yields. In contrast, the disubstituted terminal alkenes delivered a slightly higher yield than the monosubstituted terminal alkenes, which is attributed to the greater stability of in situ generated tertiary alkyl radical intermediate. Additionally, when the substituent was located on the *meta* position in the aromatic ring, the reaction delivered a 1.4:1 mixture of regioisomers (**3h**). When the *ortho* substitution substrate was subjected to the reaction, the product was formed in excellent yield (**3i**). Interestingly, the heterocyclic moieties, like indole and pyrazole, were amenable to this radical cyclization transformation (**3j**,**k**). Moreover, the more challenged unactivated internal alkenes, like cyclopentene, cyclohexene, and cycloheptene, were also applicable in this protocol to furnish the remarkable spiro phosphorus 4-quinazolinones in good yields (**3l**−**n**). Additionally, the single-crystal X-ray analysis of compound **3d** was obtained to confirm the structure (Figure 2).[15] Interestingly, the dibenzyl phosphonate **2b** and the substituted diphenyl phosphine oxides (**2c**, **2d**) were applicable in this protocol and could also be applied to synthesis of 4-quinazolinone phosphoric acid **3p** in good yields to demonstrate the synthetic utility (Figure 3).

Scheme 1. Synthesis of 4-Quinazolinones[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $AgNO_3$ (0.2 mmol) in 2 mL of CH_3CN at 80 °C under argon for 10 h.

Figure 2. ORTEP representation of the X-ray crystal structure of **3d**.

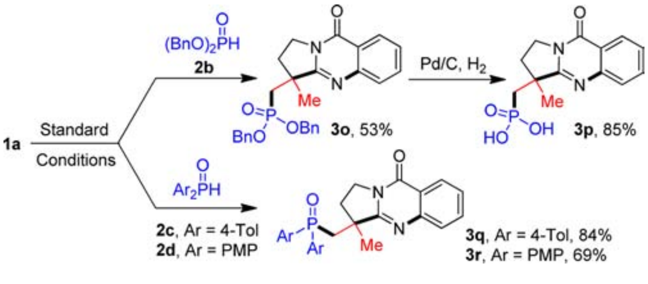


Figure 3. Scope of phosphine oxide.

When propene contained *N*-acylcyanamides were subjected to the reaction conditions, we found another phosphorylation/cyclization occurred to form dihydroisoquinolinone products. This cyclization cascade excludes the involvement of cyanide group, and the generality is shown in Scheme 2.[16] A variety of *N*-cyanamide terminal alkenes tethered with *para*-substituted *N*-acylcyanamides reacted smoothly to furnish the phosphorus dihydroisoquinolinones in synthetically useful yields (**5a**−**g**), and a broad range of substituents were well tolerated. The

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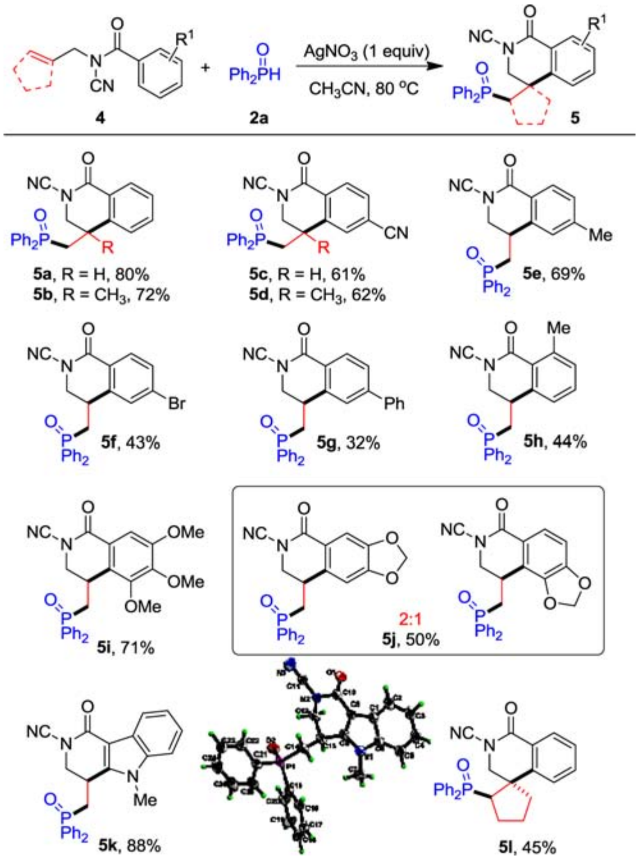
Scheme 2. Synthesis of Dihydroquinolinones[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), AgNO$_3$ (0.2 mmol) in 2 mL of CH$_3$CN at 80 °C under argon for 10 h.

ortho- and poly-substituents were also applicable in this protocol (**5h** and **5i**). When the substituent was placed on the *meta* position, the reaction afforded a 2:1 mixture of regioisomers (**5j**). Additionally, the heterocyclic moieties and internal alkenes like cyclopentene were also amenable to this cyclization cascade. Moreover, the structure was unambiguously confirmed by single-crystal X-ray analysis of compound **5k**.[17]

Next, control experiments were conducted to probe the reaction mechanism. When radical scavengers like TEMPO and BHT were added to the reaction, we were surprised to find that there were no products formed (see the Supporting Information), indicating a free radical might be involved in these cyclizations. On the basis of these results and past literature, a plausible mechanism is proposed in Figure 4.[10−12,14,18] At the beginning, the diphenylphosphine oxide **2a** was oxidized by AgNO$_3$ to radical species **A**, which is trapped by olefin (**1** or **4**) to form **B** with the formation of P−C bond. Then the divergent cyclization emerged at this moment. The butene (**1**) generated intermediate **B** follows an *exo-dig* cyclization to afford iminyl radical **C**, followed by aromatic substitution to give aryl radical **D**. **D** is then oxidized by Ag(I) to produce the 4-quinazolinones products **3** and release Ag(0). In the presence of NO$_3^-$ and H$^+$, partial Ag(0) could be reoxidized to Ag(I) to allow this cascade. With respect to olefin **4**, the in situ generated intermediate **B** takes a direct aromatic substitution rather than the unfavored 4-*exo-dig* addition for generation of **E**. **E** is then oxidized by Ag(I) to furnish **5** and release Ag(0), part of which could be reoxidized to Ag(I).

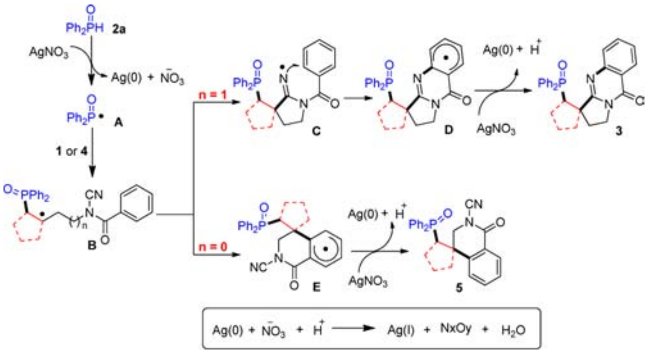


Figure 4. Proposed mechanism.

Baldwin's rule is definitely well obeyed in this divergent cyclization process.

In summary, a Ag-mediated divergent phosphorylation/cyclization cascade of *N*-cyanamide alkenes were developed. This protocol is featured with mild conditions and broad scope for accessing phosphorus-incorporated heterocycles with the achievement of molecular complexity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00481.

Full experimental procedures and spectra data (PDF)
X-ray data for compound **3d** (CIF)
X-ray data for compound **5k** (CIF)

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Notes

The authors declare no competing financial interest.

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