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Highly Regio- and Stereoselective Nickel-Catalyzed Addition of Dialkyl Phosphites to Ynamides: an Efficient Synthesis of β-Aminovinylphosphonates

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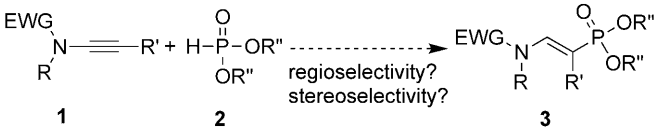
Abstract: A highly regio- and stereoselective, nickel(II)-catalyzed procedure for the hydrophosphonylation of ynamides has been developed. This protocol provides a straightforward and efficient entry to a series of β-aminovinylphosphonates that can easily be prepared in good yields from a wide range of ynamides and dialkyl phosphites as well as useful insights into the reactivity of ynamides under nickel catalysis.

Keywords: aminophosphonates; hydrophosphonylation; nickel catalysis; ynamides

Functionalized vinylphosphonates are especially useful small organic molecules and have received considerable attention over the past decade.[1] Among all the methods available for their preparation, the transition metal-catalyzed hydrophosphonylation of alkynes is certainly one of the most efficient to date and has been widely studied recently.[2] However, examples of addition to internal alkynes are still limited, suffer from low regioselectivity and have not been applied to heteroatom-substituted alkynes. Our interest in the chemistry of ynamides[3,4] and aminophosphonates[5] led us to consider the possibility of a metal-catalyzed addition of dialkyl phosphites **2** to ynamides **1** (Scheme 1), which would provide an efficient access to β-aminovinylphosphonates **3**,[6] molecules that have not received much attention and for which there is no general synthesis to date despite their synthetic usefulness[7] and their potential in medicinal chemistry.[8]

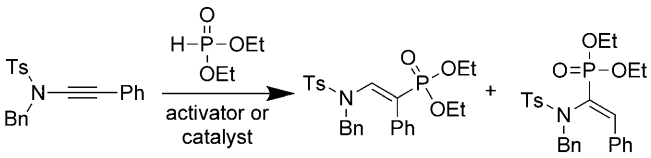


Scheme 1. Regio- and stereoselective addition of dialkyl phosphites to ynamides.

Herein, we describe the successful nickel-catalyzed hydrophosphonylation of ynamides, which yields densely functionalized β-phophoryloxy-enamines with high levels of regio- and stereoselectivities.

To test our hypothesis, ynamide **4**, readily prepared by our alkynylation procedure with vinyl dibromides,[3a,b] was reacted with diethyl phosphite in the presence of various activators or transition metal catalysts: results from these studies are shown in Table 1. After checking that the reaction could not be mediated by simple Brønsted acids (entry 1) or radical initiators (entry 2), the activity of a set of representative catalysts with potential for activating the triple bond of the starting ynamide was evaluated. Quite surprisingly, most catalysts with high affinities for π-electrons such as silver, gold, copper or platinum complexes (entries 3–8) failed to promote the reaction and the starting ynamide was completely recovered, which might be due to a too strong complexation of the metal center with diethyl phosphite. While palladium tetrakistriphenylphosphine, which has been demonstrated to be a quite efficient catalyst for the hydrophosphonylation of alkynes,[2] only gave minor amounts of the α-isomer **6**, the use of nickel(II) bromide turned out to be a lot more efficient since the expected β-aminovinylphosphonate **5** could be isolated in 71% yield with complete regio- and stereocon-

Table 1. Screening of catalysts for the hydrophosphonylation.

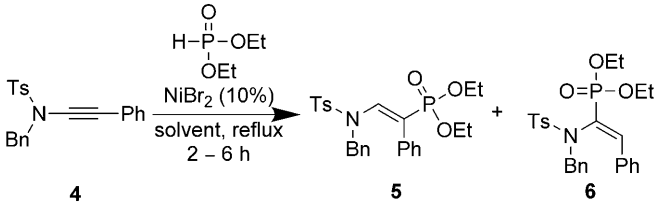


4 5 6

Entry	Activator or Catalyst	**5**:**6**[a]	*E*-**5**:*Z*-**5**[a]	Yield[g]
1	TfOH[b,c]	NR[f]	–	–
2	AIBN[d,e]	NR[f]	–	–
3	$AgPF_6$[b,e]	NR[f]	–	–
4	AgOTf[d,e]	NR[f]	–	–
5	AuCl[b,e]	NR[f]	–	–
6	$Cu(OTf)_2$[b,e]	NR[f]	–	–
7	CuI[d,e]	NR[f]	–	–
8	$PtCl_2$[d,e]	NR[f]	–	–
9	$[Rh(OAc)_2]_2$[d,e]	NR [f]	–	–
10	$Pd(PPh_3)_4$[d,e]	>5:95	>5:95	10%
11	$NiBr_2$[d,e]	>95:5	>95:5	71%

[a] Measured by ^{31}P NMR analysis of crude reaction mixtures.
[b] Reaction performed in DCM at room temperature.
[c] 1 equiv. of activator used.
[d] Reaction performed in refluxing toluene.
[e] 10 mol%.
[f] No reaction.
[g] Yield of pure, isolated product.

Table 2. Solvent optimization.



4 5 6

Entry	Solvent	**5**:**6**[a]	*E*-**5**:*Z*-**5**[a]	Yield[c]
1	DMSO	NR[b]	–	–
2	DMF	NR[b]	–	–
3	ethanol	NR[b]	–	–
4	acetonitrile	NR[b]	–	–
5	THF	>95:5	>95:5	45%
6	toluene	>95:5	>95:5	75%

[a] Measured by ^{31}P NMR analysis of crude reaction mixtures.
[b] No reaction.
[c] Yield of pure, isolated product.

trol.[5a,9] Interestingly, the selectivity observed in favour of the β-isomer is complementary to the one observed in the thermal addition of diethyl phosphite to ynamines where the α-isomer is formed predominantly.[10] Attempts at lowering the catalyst loading resulted in a more sluggish reaction and lower yields (57% yield with 5 mol% $NiBr_2$, 6% yield with 2 mol% $NiBr_2$).

In an effort to further improve the yield of the hydrophosphonylation reaction and to check whether the selectivity could be modified, we briefly examined the used of various solvents (Table 2). While the use of highly polar solvents such as DMF, DMSO, ethanol or acetonitrile completely inhibited the reaction, THF and toluene were found to be the most efficient ones, the last one being superior in terms of yield of isolated product, which might simply be due to a combination of its higher boiling point and its poor ability to chelate the nickel(II) catalyst.

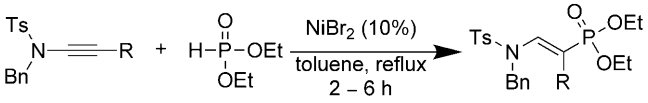
With these optimized conditions in hand, the scope of the reaction was next investigated with regard to the substituent on the triple bond of the ynamide: results from these studies are shown in Table 3. A variety of aminovinylphosphonates could be obtained in reasonable to good yields, even on a multigram scale (Table 3, entry 1), with complete regio- and stereocontrol, the *E*-β-isomer being exclusively formed in all cases.[5a,9] The reaction was found to be compatible with a variety of aromatic groups, including heteroaromatics (Table 3, entries 7 and 8), and the presence of electron-withdrawing (Table 3, entries 3–5) or donating (Table 3, entry 2) groups had virtually no effect on the reaction. The lower yields observed with substrates possessing an ester in the *ortho* position, an aromatic chloride or a pyridine ring might be due to competitive addition of the ester to the activated triple bond, insertion into the C–Cl bond/competitive Tavs' reaction[11] or catalyst poisoning, respectively.

Notably, the presence of an additional double bond was tolerated (Table 3, entry 10) and the corresponding aminodienylphosphonate was isolated in good yield as a single regio- and stereoisomer.

The hydrophosphonylation of alkyl-subtituted ynamides (Table 3, entries 11–13) was, however, found to be more difficult, even though the reaction was still highly selective. In these cases, the corresponding aminovinylphosphonates could be isolated in modest yields, which might be due to the unstability of the starting materials.

The scope of the reaction was also investigated with respect to the nature of the electron-withdrawing group of the ynamide (Table 4). The reaction was found to be compatible with all classes of ynamides including yne-sulfonamides, yne-amides, yne-carbamates and yne-oxazolidinones. In addition, the presence of bulky substituents on the ynamide (Table 4, entries 4 and 7) did not inhibit the reaction or affect its selectivity and the corresponding densely substituted aminovinylphosphonates could still be obtained in synthetically useful yields. Besides the fact that no traces of the regio- or stereoisomers could be detected in all these reactions, this hydrophosphonylation

Table 3. Scope and limitations: substitution of the ynamide.



regioisomeric ratio > 95/5
dr > 95/5

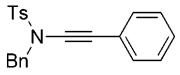
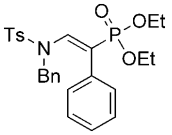
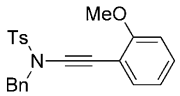
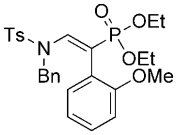
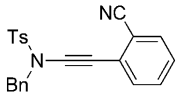
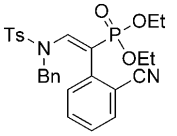
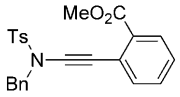
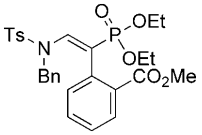
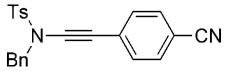
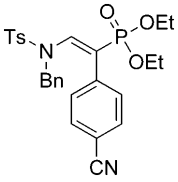
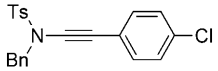
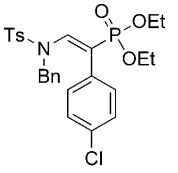
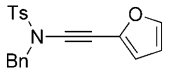
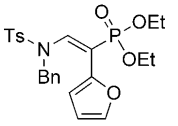
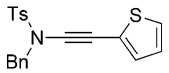
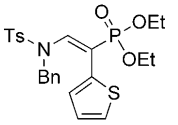
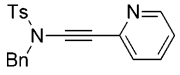
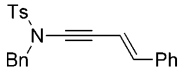
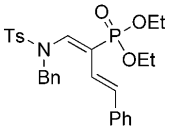
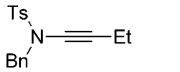
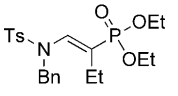
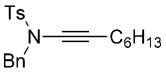
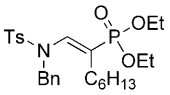
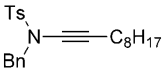
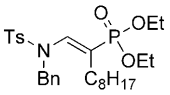
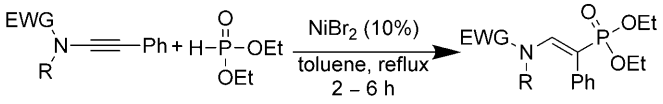
Entry	Ynamide	2-Amino-1-alkenylphosphonate	Yield[a]
1			71%, 75%[b]
2			61%
3			74%
4			35%
5			61%
6			27%
7			86%
8			69%
9		–	NR[c]
10			64%
11			20%

Table 3. (Continued)

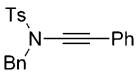
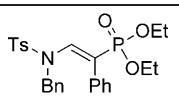
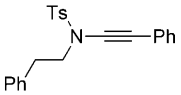
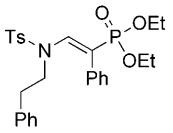
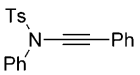
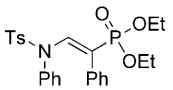
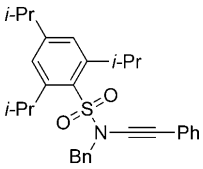
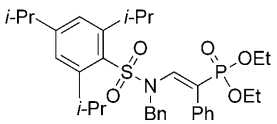
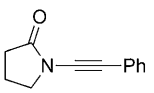
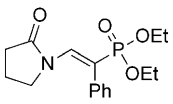
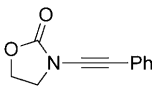
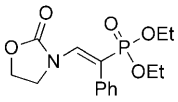
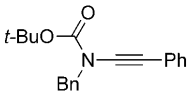
Entry	Ynamide	2-Amino-1-alkenylphosphonate	Yield[a]
12			24%
13			32%

[a] Yield of pure, isolated product.
[b] Reaction performed on a 4-gram scale.
[c] No reaction.

Table 4. Scope and limitations: hydrophosphonylation of representative ynamides.

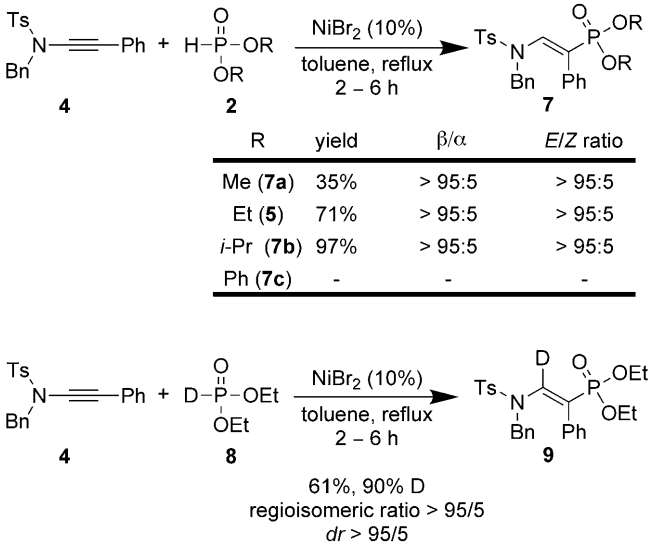


regioisomeric ratio > 95/5
dr > 95/5

Entry	Ynamide	2-Amino-1-alkenylphosphonate	Yield[a]
1			71%
2			61%
3			53%
4			48%
5			73%
6			94%
7			87%

[a] Yield of pure, isolated product.

procedure also seems to be highly selective for the ynamide and no over-hydrophosphonylation, which would yield to the formation of amino-bisphosphonates, could be evidenced.



R	yield	β/α	*E*/*Z* ratio
Me (**7a**)	35%	> 95:5	> 95:5
Et (**5**)	71%	> 95:5	> 95:5
i-Pr (**7b**)	97%	> 95:5	> 95:5
Ph (**7c**)	-	-	-

Scheme 2. Scope and limitations with representative dialkyl phosphites.

Finally, the hydrophosphonylation of ynamide **4** with other dialkyl phosphites **2** was also evaluated to further test our procedure (Scheme 2). Other dialkyl phosphites such as dimethyl or diisopropyl phosphite were found to perform well under our hydrophosphonylation conditions, the former being a little superior in terms of yield. Only diphenyl phosphite did not participate in the reaction since starting ynamide was completely recovered from the crude reaction mixture. The use of deutero-diethyl phosphite **8**[12] was equally efficient, yielding the deuterated aminovinylphosphonate **9** in good yield and selectivities.

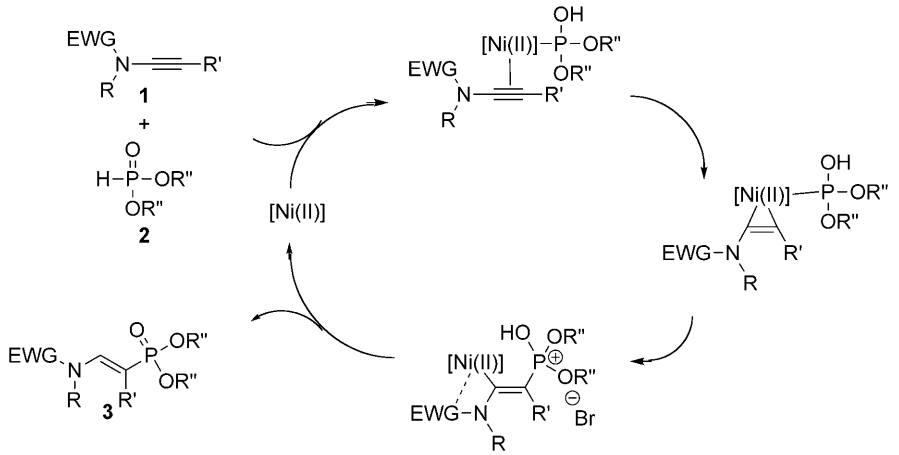
The mechanism of this novel nickel(II)-catalyzed hydrophosphonylation reaction is unlikely to proceed similarly to that of the palladium(0)[2a] or nickel(0)[2c] version which involve oxidative addition into the P–H bond followed by hydrometallation and reductive elimination. This reaction pathway would mostly afford the α-isomer, due to chelation of the metal center to the electron-withdrawing group after the hydrometallation step, as shown in related hydrostannylation reactions.[13] In our case, the nickel(II)[14] catalyst most probably simply acts as a strong Lewis acid: coordination to the electron-rich triple bond of the ynamide **1** would facilitate an inner-sphere addition of dialkyl phosphite (Scheme 3). This would account for both the observed stereoselectivity and the strong solvent effect since a polar, coordinating solvent probably prohibits chelation of the ynamide. The complete regioselectivity of this step would finally be due chelation of the nickel catalyst to the electron-withdrawing group, a phenomenon that has been involved in a number of processes with ynamides.[15] Proton transfer from the resulting vinyl-nickel complex would finally produce the β-aminovinylphosphonate **3** and regenerate the nickel catalyst.

In conclusion, we have developed a highly efficient nickel(II)-catalyzed hydrophosphonylation of ynamides. This procedure affords β-aminovinylphosphonates with complete regio- and stereocontrol and provides useful insights into both the reactivity of ynamides in transition metal-catalyzed processes and hydrophosphonylation of alkynes. Applications of this reaction to other heteroatom compounds and selective preparation of α-aminovinylphosphonates from ynamides are under way and will be reported in due course.

Experimental Section

General Procedure for the Nickel-Catalyzed Hydrophosphonylation

To a solution of ynamide (11.90 mmol) and dialkyl phosphite (35.70 mmol) in toluene (40 mL) was added nickel(II)



Scheme 3. Possible mechanism for the nickel(II)-catalyzed hydrophosphonylation reaction.

bromide (1.19 mmol). The reaction mixture was refluxed for 2–6 h, cooled to room temperature, diluted with ethyl acetate and hydrolyzed with 1M HCl. Purification by flash chromatography on silica gel afforded the desired aminovinylphosphonates.

Acknowledgements

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