Nitrogen Pronucleophiles in the Phosphine-Catalyzed γ-Addition Reaction

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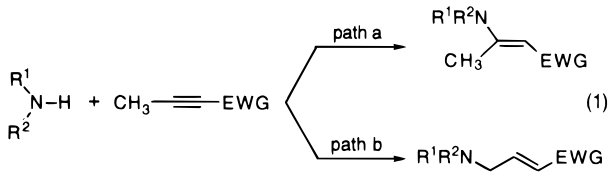
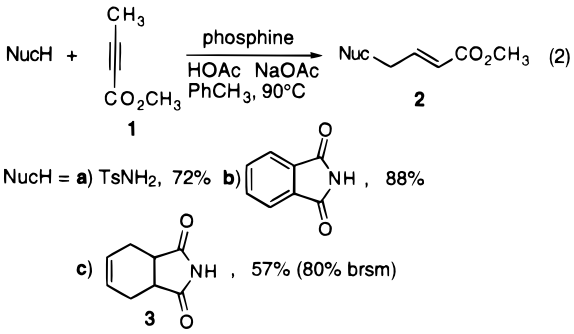
Received May 13, 1997

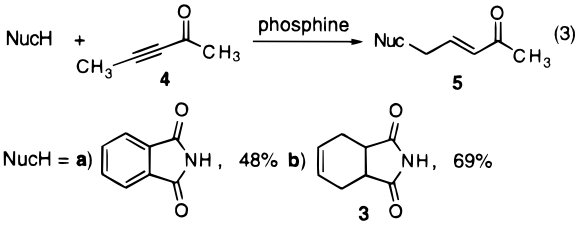
The conjugate addition of nucleophilic species to the β-carbon of α,β-unsaturated systems is a fundamental concept in synthetic organic chemistry.[1] A significant improvement in synthetic design would occur if we could alter the reactivity of Michael acceptors so that 1,4 addition could be circumvented in favor of other useful transformations. Our discovery of phosphine's ability to induce addition of carbon and oxygen pronucleophiles to the 4-position of alkynoates led us to test this new reactivity paradigm with nitrogen-based nucleophiles (eq 1).[2,3] Despite our previous successes, a fear existed that the excellent donor properties of nitrogen in conjugate additions would result in undesired Michael addition products (path a), as opposed to γ-addition mediated by the phosphine-catalyzed process (path b). However, we have found that under our phosphine-catalyzed conditions Michael addition processes are entirely subverted in favor of the desired manifold with a variety of nitrogen nucleophiles, including hydroxamic acid esters, providing an entry into tripeptide structural mimics.



In order to test the feasibility of these processes, methyl 2-butynoate (**1**) was reacted with a number of nitrogen pronucleophiles using our phosphine catalysis system, which also involves a general acid−base catalyst (eq 2). For example, an equimolar mixture of **1** with *p*-toluenesulfonamide with 50% acetic acid and 50% sodium acetate using 10% triphenylphosphine (tpp) in toluene at 90 °C produced the adduct **2a** in 72% yield.[4] The structure of compound **2a** is clearly established by the presence of the new olefinic resonances in the ^{1}H NMR spectrum [(δ 6.75 (dt, J = 15.7, 5.2 Hz, 1H); 5.94 (dt, J = 15.7, 1.86 Hz, 1H)]. The use of 5% of the bidentate phosphines bis(diphenylphosphino)methane (dppm) or 1,2-bis(diphenylphosphino)ethane (dppe) as catalyst led to a much lower recovery of **2**, 28% and 39%, respectively. The use of a larger amount (15%) of 1,3-bis(diphenylphosphino)propane (dppp) with acetic acid−sodium acetate catalyzed the condensation of **1** with phthalimide or tetrahydrophthalimide **3** yielding compounds **2b** and **2c** in 88% and 57% (81% brsm), respectively.

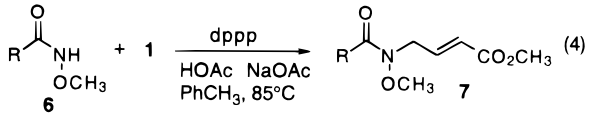


The competition between Michael addition versus phosphine-controlled γ-addition was examined further using 3-butyn-2-one (**4**), a more reactive substrate (eq 3). Reaction between **4** and *p*-toluenesulfonamide using either tpp or dppp gave only polymeric material. The condensation between phthalimide and **4** using either 10% tpp or 15% dppp gave the adduct **5a** in 48% yield. The more nucleophilic imide **3** combines with **4** yielding product **5b** in 69% with tpp as the catalyst.



Satisfied that competitive Michael addition was not a significant problem, we shifted our attention to the nucleophilic partner in these reactions. Although *p*-toluenesulfonamide and phthalimide function well under our conditions, we sought a nitrogen pronucleophile which would allow us more synthetic flexibility. The esters of hydroxamic acids are an interesting class of nitrogen pronucleophiles which could meet the criteria of our phosphine-catalyzed addition reaction. Not only are these compounds conveniently made using standard amino acid coupling technology, they represented a set of nitrogen acids with approprate pK_a combined with small steric constraints.[5]

To this end, we tested the reaction between *N*-methoxypentanamide (**6a**) and **1** using 15% dppp with our acetic acid/sodium acetate buffer system in toluene at 85 °C (eq 4). Gratifyingly, the adduct **7a** was produced in 60% yield. Because our interest lay in nucleophiles containing a branch at the α-position of the hydroxamic acid ester, we submitted *N*-methoxyisobutyramide (**6b**) to these same conditions. A 33% yield of the desired product **7b** was recovered. At this same time, our interest in nucleophiles derived from amino acids had led us to examine the alanine derivative **6c** as well. Under similar conditions as described above, a 39% yield of the desired compound **7c** was observed.

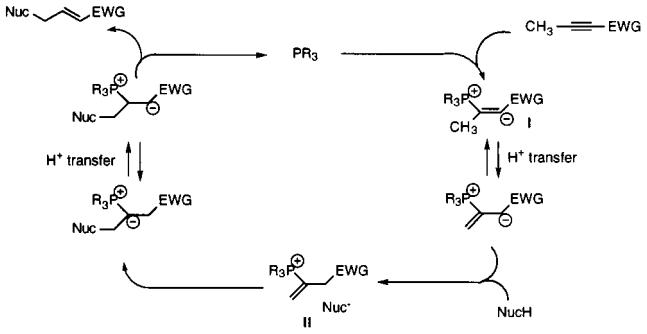


R = a) ^{n}CH$_3$CH$_2$CH$_2$CH$_2$, 60% b) (CH$_3$)$_2$CH, 33%
c) 39%

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.1, pp 1−67.
(2) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167.
(3) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819.
(4) This compound has been fully characterized spectroscopically and its elemental composition established by combustion analysis or high-resolution mass spectrometry.
(5) The pK_a of *N*-methoxyacetamide was established to be between 16.9 and 17.1 (depending on the indicator) in DMSO. See Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T.-Y.; Satish, A. V.; Whang, Y. E. *J. Org. Chem.* **1990**, *55*, 3330.

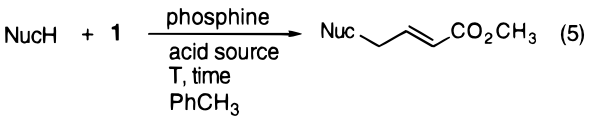
S0022-3263(97)00848-7 CCC: $14.00

Scheme 1. Mechanistic Rationale of the Phosphine-Catalyzed Addition Reaction



Our efforts to improve the efficiency of this process is outlined below (eq 5, Table 1). Using the simpler

Table 1

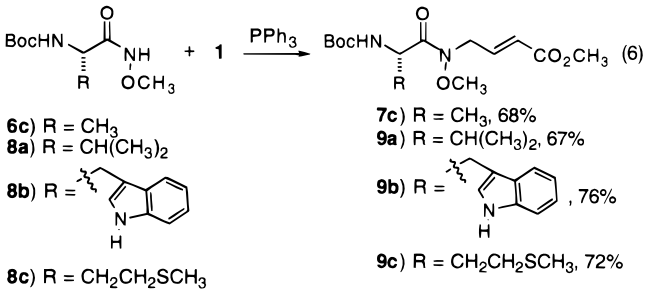


entry	NucH	phosphine[a]	acid source[b]	T (°C)	t (h)	% yield
1	**6b**	10% dppp	HOAc−NaOAc	90	5.5	35
2	**6b**	15% dppp	HOAc−NaOAc	90	2	33
3	**6b**	20% dppp	HOAc−NaOAc	90	2	42
4	**6b**	10% PPh_3	HOAc−NaOAc	85	3.5	21
5	**6b**	10% PPh_3	HOAc−NaOAc	110	10	61
6	**6c**	10% dppp	HOAc−NaOAc	85	18	39
7	**6c**	10% dppp	PhOH	85	18	25
8	**6c**	10% dppp	PhOH−NaOPh	85	18	14
9	**6c**	10% dppp	HOAc−TMG	85	18	−
10	**6c**	10% dppba	HOAc−NaOAc	85	18	−
11	**6c**	10% PPh_3	HOAc−NaOAc	110	18	68

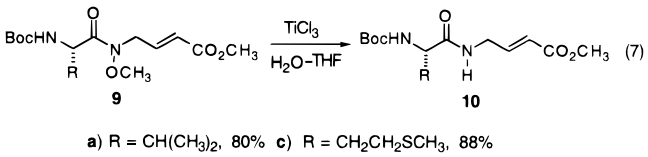
[a] dppba = 2-(diphenylphosphino)benzoic acid. [b] 50 mol % each was used for each reagant. TMG = tetramethylguanidine.

nucleophile **6b**, neither the variation of the amount of the phosphine catalyst (entries 1−3), nor the use of a mono- or bidentate phosphine (entries 1 and 4) appreciably affected the outcome of the reaction. The combination of the use of tpp as catalyst at a higher temperature did have a significant effect on the reaction, providing **7b** in 61% yield. Concurrently, alternative acid sources in the reaction between **1** and **6c** were found not to dramatically affect the course of the reaction (entries 6−9), except the use of tetramethylguanidine (TMG) as cobase in entry 9 resulted in a complete inhibition of reaction. The inclusion of an internal acid source in the phosphine as in 2-(diphenylphosphino)benzoic acid (dppba) resulted in no reaction (entry 10). However, the use of the triarylphosphine catalyst in combination with a higher reaction temperature as in entry 5 gave the desired adduct **7c** in 68%, a very acceptable result (entry 11). The yields obtained are reflective of the conversion of these processes, and not byproduct formation. Specifically, the formation of Michael addition products was not observed.

With these new conditions available, this γ-addition process was tested using other hydroxamic acid ester derivatives of amino acids with **1** (eq 6). The sterically encumbered valine derivative **8a**, like hydroxamic acid ester **6c**, smoothly reacts with **1** (10% tpp, 100 °C) to give the desired compound **9a** in 67% yield. Using 15% dppp at 85 °C, as before, yielded **9a** in only 23% yield. The tryptophan derivative **8b** also combines easily with **1** using tpp at 110 °C to give the desired product **9b** in 76% yield. The divalent sulfur moiety contained in **8c** also poses no problem with these same conditions, providing the substituted amide **9c** in 72% yield.



The cleavage of the N−O bond in these compounds gives entry into vinylogous glycine derivatives. Vinylogous amino acids have been used as structural mimics of peptidal compounds, serving as tripeptide equivalents.[6] The cleavage of the N−O bond is readily accomplished using titanium(III) chloride in combination with a proton source such as water. As an illustration, compounds **9a** and **9c** were subjected to $TiCl_3$ in wet THF at room temperature to give the demethoxylated compounds **10a** and **10c** in 80% and 88% yields, respectively (eq 7).



The ability of phosphines to act as a "nucleophilic trigger" and modify the reactive manifold of ynoate systems is truly remarkable. The mechanistic rationale for this process is outlined in Scheme 1. Although vinylphosphonium intermediate **I** could, after protonation, serve as a Michael type acceptor for an appropriate nucleophile, the thermodynamically more stable intermediate **II** is invariably the dominant reactive intermediate using methyl 2-butynoate as the acceptor. After nucleophilic addition to vinylphosphonium species **II** (or its enol), and proton transfer, the phosphine is ejected to reinititate a new catalytic cycle.

The synthetic power of these phosphine-catalyzed reactions is wondrous, especially when their simplicity is also considered. The use of an activating methoxy substituent on an amide nitrogen to provide a nucleophilic partner for the formation of these 1:1 adducts reveal the utility of this atom economical process.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health. Mass spectra were graciously provided by the Mass Spectrometry Facility, University of California, San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Sample experimental procedures and spectral data for **2a**−**c**, **5a**,**b**, **7a**−**c**, **9a**−**c**, **10a**,**c** (5 pages).

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(6) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568.