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Phosphoramidites Are Efficient, Green Organocatalysts for the Michael Reaction. Mechanistic Insights into the Phosphorus-Catalyzed Michael Reaction of Alkynones and Implications for Asymmetric Catalysis

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Hexamethylphosphorous triamide (HMPT) and other phosphoramidites and phosphites have been found to be efficient catalysts for the Michael reaction of alkenones and alkynones with malonates, α-cyano esters, β-keto esters, and nitro compounds. The relatively nontoxic, easily hydrolyzed HMPT catalyzes the Michael reaction within seconds at room temperature in the absence of a solvent, and the reaction is worked up simply by removing the catalyst in vacuo. The Michael reactions of alkynones, unlike those of alkenones, are shown to be irreversible. The implications for asymmetric catalysis are discussed.

Since its discovery in the 1880s,[1] the Michael reaction has become one of the premier methods for the synthesis of densely functionalized quaternary centers.[2] Its complete atom economy, wide substrate scope, susceptibility to many classes of catalysts, and easily accessible starting materials render it one of the most modern of classical reactions. Asymmetric Michael reactions of prochiral nucleophiles, on the other hand, remain difficult to execute via either stoichiometric or catalytic approaches, despite recent advances.[3]

We have spent much time exploring the double Michael reaction of tethered diacids (compounds consisting of two carbon acids connected by a tether) with alkynones to give a variety of highly functionalized and substituted carbocyclic and azacyclic compounds.[4] The stereochemistry-determining step for most of these double Michael reactions is the intermolecular Michael reaction of an α-cyano ester to an ethynyl ketone. An asymmetric double Michael reaction, then, requires a catalyst for rendering this step asymmetric. Unfortunately, the Michael reactions of α-cyano esters are among the most difficult to render asymmetric.[5]

We have recently found that the double Michael reactions of certain tethered diacids with 3-butyn-2-one proceed far more cleanly when basic catalysts are replaced with Ph_3P.[6] Although we are by no means the first to find that phosphines catalyze the Michael reaction,[7] we may be the first to apply them to the Michael reaction of alkynones. We have proposed two catalytic cycles for the phosphine-catalyzed Michael reaction of carbon acids with 3-butyn-2-one (Schemes 1 and 2). Both involve an enolate−β-phosphonio enone ion pair,[8] but in catalytic cycle 1, the "direct addition" mechanism (Scheme 1), the enolate attacks 3-butyn-2-one, whereas in catalytic cycle 2, the "addition−elimination" mechanism (Scheme 2), the enolate attacks the β-phosphonio enone in an addition−elimination process.[9] (Catalytic cycle 1 is directly analogous to the one generally written for alkenones.) In catalytic cycle 2, the C−P bond is intact during the C−C bond-forming, stereochemistry-determining step (assuming a prochiral enolate), and the phosphine resides near the nascent stereocenter, raising the intriguing possibility that a chiral, enantiopure phosphine catalyst might induce asymmetry in the Michael reaction.

(1) Komnenos, T. *Ann. Chem.* **1883**, *218*, 145. Michael, A. *J. Prakt. Chem. (Leipzig)* **1887**, *35*, 349.

(2) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179. Martin, S. F. *Tetrahedron* **1980**, *36*, 419. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1992. Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315.

(3) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388. Leonard, J.; Díez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, *2051*, 1. Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.

(4) Grossman, R. B. *Synlett* **2001**, 13. Hughes, F., Jr.; Grossman, R. B. *Org. Lett.* **2001**, *3*, 2911.

(5) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057. Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295. Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439. Inagaki, K.; Nozaki, K.; Takaya, H. *Synlett* **1997**, 119. Stark, M. A.; Jones, G.; Richards, C. J. *Organometallics* **2000**, *19*, 1282. Motoyama, Y.; Koga, Y.; Kobayashi, K.; Aoki, K.; Nishiyama, H. *Chem.—Eur. J.* **2002**, *8*, 2968.

(6) Grossman, R. B.; Pendharkar, D. S.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7178.

(7) White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, 3597.

(8) We note that any enolate−β-phosphonio enone ion pair may be in equilibrium with a phosphorane containing a P−O bond.

(9) A mechanism similar to the latter was written for the phosphine-catalyzed addition of an alcohol to an acetylenic ester. Wende, M.; Meier, R.; Gladysz, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 11490.

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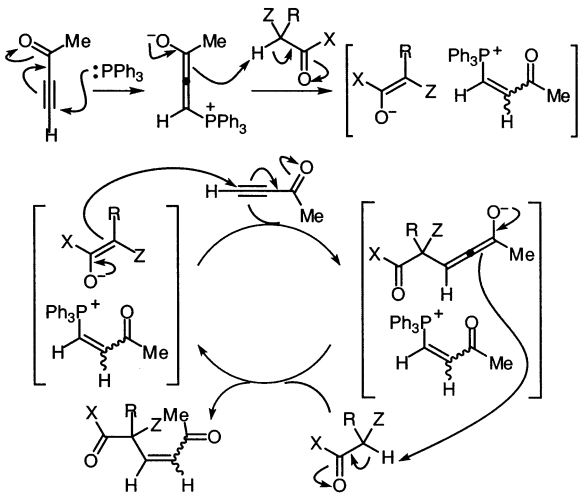
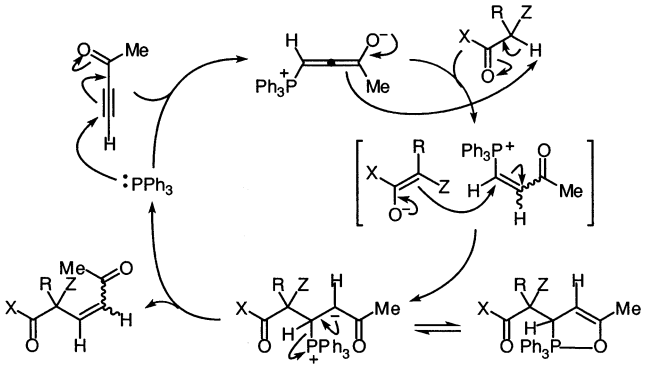
SCHEME 1. Catalytic Cycle 1: Direct Addition[a]



[a] X = OEt or alkyl, Z = electron-withdrawing group, R = alkyl.

SCHEME 2. Catalytic Cycle 2: Addition−Elimination[a]



[a] X = OEt or alkyl, Z = electron-withdrawing group, R = alkyl.

Although chiral monophosphines are well-known,[10] their syntheses are often difficult, multistep endeavors. We felt that our chances of discovering a successful asymmetric phosphorus-based catalyst for the Michael reaction would be enhanced if we could search for it by combinatorial methods, and it occurred to us that, for several reasons, chiral phosphites, phosphoramidites, phosphonites, and phosphonamidites would be excellent compounds among which to execute a combinatorial search for a catalyst.[11] Before we could execute this search, however, we first needed to establish whether these compounds catalyzed the Michael reactions of alkynones at all.

Results

Nonasymmetric Catalysis. We have found that phosphites, phosphonites, and phosphoramidites catalyze the Michael reaction of various α-cyano esters and β-keto esters with electrophilic alkynes to give the corresponding adducts with 63−86% isolated yields (Table 1). The best catalyst by far is $(Me_2N)_3P$ (HMPT), but other viable catalysts include $(MeO)_3P$ and $PhP(OMe)_2$. The reaction is fastest in polar solvents such as DMF and CH_3CN and at higher concentrations, suggesting that the rate-limiting step is the addition of the P nucleophile to the electrophilic π bond to give a zwitterion.

Mixtures of *E* and *Z* Michael adducts are obtained from electrophilic alkynes. When 3-butyn-2-one is the electrophile (entries 1−12), the *Z* isomer predominates in every case but one (entry 11). In the one case where the *E* isomer predominates, we have resubjected the *Z* isomer to the reaction conditions and found that it isomerizes smoothly to the *E* isomer, presumably by an addition−rotation−elimination mechanism. We attribute the lability of this adduct to the small steric bulk and potent electron-withdrawing ability of the γ-cyano groups. Other adducts fail to isomerize under the reaction conditions. When ethyl propiolate is the electrophile, the *E* isomer always predominates (entries 13−16). We have resubjected the *Z* isomer of one of these adducts to the reaction conditions; conversion to the *E* isomer is not observed.

The kinetic *Z* selectivity of the butynone reactions can easily be understood. If catalytic cycle 1 is operative, irreversible protonation of allenolate **A** from the less hindered face provides a *Z* Michael adduct directly (Scheme 3a). If catalytic cycle 2 is operative, on the other hand, the irreversible protonation of β-phosphonio allenolate **B** from the less hindered face provides β-phosphonio enone **C** with a predominantly *Z* configuration (Scheme 3b). This compound combines with the enolate of the nucleophile to give a β-phosphonio enolate **D** as conformer **D1**; minimal bond rotation to conformer **D2** and elimination of the P catalyst then provides the Michael adduct, which will have the same configuration as **C** if intermediate **D** is short-lived.[12]

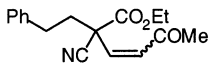
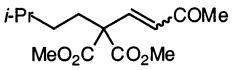
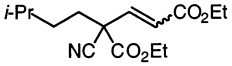
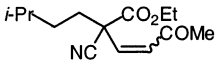
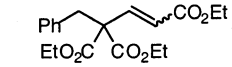
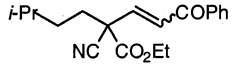
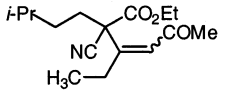
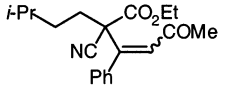
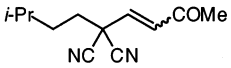
The *E* selectivity of the ethyl propiolate reaction is less easily understood. If catalytic cycle 2 is operative, intermediates **D** may be expected to have a shorter lifetime when X^2 = OEt than when X^2 = Me, and this argument would suggest that the reaction should again favor the *Z* isomer. However, it is possible that when X^2 = OEt, the reversible protonation of β-phosphonio enolate **D** to β-phosphonio ester **E** may compete with elimination, thereby allowing elimination to occur from the more thermodynamically favorable conformer **D3** after reconversion to the β-phosphonio enolate (Scheme 3b). On the other hand, if catalytic cycle 1 is operative, perhaps allenolate **A** interacts more strongly with the phosphonium counterion when X^2 = OEt than it does when X^2 = Me, leading to a later TS for proton transfer and hence an enhanced selectivity for the *E* isomer.

HMPT is a particularly efficient catalyst for the Michael reaction of both alkynyl electrophiles (Table 1, entries 1, 5−8, 11, 13, 14, 16−18, and 20) and vinyl electrophiles (Table 2). In many cases, the Michael reaction of α-cyano esters, β-keto esters, malonates, or nitro compounds proceeds within seconds at room temperature or 0 °C in the absence of solvent and in the presence of 5−10 mol % HMPT. The monoalkylation of

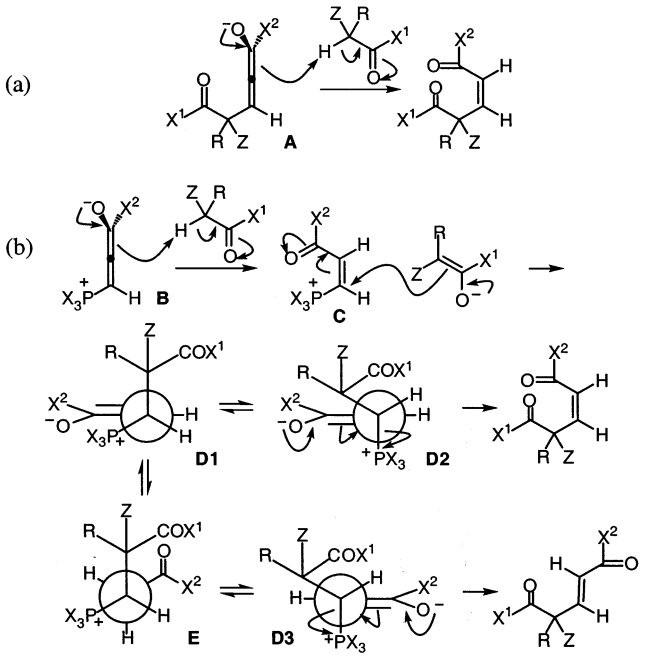
(10) Zhang, X. *Enantiomer* **1999**, *4*, 541.
(11) Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315. Komarov, I. V.; Börner, A. *Angew. Chem., Intl. Ed.* **2001**, *40*, 1197. Denney, D. Z.; Chen, G. Y.; Denney, D. B. *J. Am. Chem. Soc.* **1969**, *91*, 6838. Nielsen, J.; Dahl, O. *J. Chem. Soc., Perkin Trans. 2* **1984**, 553. Delapierre, G.; Brunel, J. M.; Constantieux, T.; Buono, G. *Tetrahedron: Asymmetry* **2001**, *12*, 1345.

(12) Patai, S.; Rappoport, Z. In *The Chemistry of Alkenes*; Patai, S., Ed.; Wiley: New York, 1964; Chapter 8, p 469.

TABLE 1. Phosphorus-Catalyzed Michael Reactions of Alkynyl Electrophiles

entry	Michael adduct	catalyst (10%), conditions	E/Z	yield (%)	entry	Michael adduct	catalyst (10%), conditions	E/Z	yield (%)
1		$(Me_2N)_3P$, CH_3CN, rt	30/70	83	12		$(Me_2N)_3P$, CH_3CN, rt	–	0
2		$(MeO)_3P$, CH_3CN, rt	30/70	79	13		$(Me_2N)_3P$, CH_3CN, rt	75/25	89
3		$(MeO)_3P$, CH_3CN, rt	45/55	63	14		$(Me_2N)_3P$, neat, rt	55/45	88
4		$PhP(OMe)_2$, CH_3CN, rt	25/75	12	15		Et_3N, CH_3CN, rt	75/25	95
5		$(Me_2N)_3P$, CH_3CN, rt	30/70	89	16		$(Me_2N)_3P$, neat, rt	85/15	79
6		$(Me_2N)_3P$, neat, 10 °C	30/70	88	17		$(Me_2N)_3P$, CH_3CN, rt	65/35	79
7		$(Me_2N)_3P$, CH_2Cl_2, rt	45/55	83	18		$(Me_2N)_3P$ (30%), CH_3CN, rt	60/40 or 40/60	87
8		$(Me_2N)_3P$, $CHCl_3$, rt	45/55	79	19		Et_3N (30%), CH_3CN, rt	–	7 (GC/MS)
9		Et_3N, CH_3CN, rt	30/70	89	20		$(Me_2N)_3P$ (30%), CH_3CN, rt	78/22 or 22/78	77
10		$i\text{-}Pr_2NEt$, CH_3CN, rt	25/75	85	21		Et_3N (30%), CH_3CN, rt	–	0
11		$(Me_2N)_3P$, CH_3CN, rt	75/25	75					

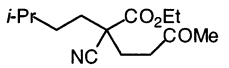
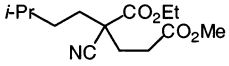
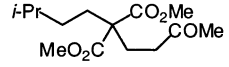
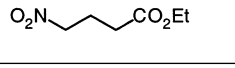
SCHEME 3. Origin of Selectivity for *Z* and *E* Isomers of Michael Adducts[a]



[a] X^1 = OEt or alkyl, X^2 = OEt or Me, Z = electron-withdrawing group, R = alkyl.

CH_3NO_2 with methyl acrylate in 57% yield (Table 2, entry 7) is an especially significant result, because under other Michael reaction conditions it is difficult to prevent the initial adduct from undergoing a second Michael reaction.[13] The high vapor pressure of HMPT makes it possible to remove it from the solventless reaction mixture simply by applying a vacuum. When an alkenone is the electrophile, the product is obtained in >95% pure form, but when an alkynone is the electrophile, filtration through silica gel or distillation to remove polymerized alkynone is required. If a solvent is desired, HMPT allows the use of more nonpolar solvents (CH_2Cl_2, $CHCl_3$) than

TABLE 2. Phosphorus-Catalyzed Michael Reactions of Vinyl Electrophiles

entry	Michael adduct	catalyst (10%), conditions	yield
1		$(Me_2N)_3P$, CH_3CN, rt	77
2		$(Me_2N)_3P$, neat, rt	96
3		Et_3N, neat, rt	65 (25 SM)
4		$(Me_2N)_3P$, CH_3CN, rt	99
5		$(Me_2N)_3P$, neat, rt	99
6		$(Me_2N)_3P$, CH_3CN, rt	81
7		$(Me_2N)_3P$, CH_3NO_2, rt	57

(13) Kisanga, P. B.; Ilankumaran, P.; Fetterly, B. M.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555.

$(MeO)_3P$ does (CH_3CN, DMF). HMPT is relatively nontoxic, easily hydrolyzed, and inexpensive. It is slowly oxidized by air to the much more toxic HMPA, but an atmosphere of N_2 prevents this eventuality. Moreover, although HMPA is much less volatile than HMPT, there has been no sign of it in the NMR spectra of the crude products. As a result, the color of the HMPT-catalyzed Michael reaction can be nonhyperbolically described as a very deep green. Phosphite and phosphonite catalysts are less efficient than HMPT (Table 2, entries 2−4). In these cases, Arbuzov or elimination reactions may destroy the catalyst before the Michael reaction is complete.

There are some limitations to the HMPT-catalyzed Michael reactions. Polymerization of 3-butyn-2-one is faster than its reaction with a substituted malonate derivative (Table 1, entry 12), the reaction of diethyl isopropylmalonate and methyl vinyl ketone fails to proceed to completion, and ethyl *trans*-crotonate is unreactive toward an α-cyano ester. These limitations are easily understood in terms of the absolute and relative rates of the steps in catalytic cycle 1 and other competing reactions.

Although many HMPT-catalyzed Michael reactions are catalyzed equally well by tertiary amines (Table 1, cf. entries 5−8 and 11 to 9, 10, and 15), HMPT catalyzes some Michael reactions that are not catalyzed by Et_3N (Table 1, entries 18−21). For example, ethyl 2-cyano-5-methylhexanoate undergoes Michael reactions with 3-hexyn-2-one and 4-phenyl-3-buten-2-one in the presence of 30 mol % HMPT but not 30 mol % Et_3N. The powerfully nucleophilic HMPT can add to the hindered electrophile at a reasonable rate, and the resulting allenolate is an excellent and irreversible base, providing a high equilibrium concentration of enolate. By contrast, in the amine-catalyzed reaction, the amine does not add to the electrophile at a reasonable rate, so it acts solely as a base, and the enolate is probably reprotonated by the ammonium counterion faster than it adds to the electrophile.

Asymmetric Catalysis. All attempts to induce asymmetry in the Michael reaction of alkynyl electrophiles by using chiral analogues of HMPT as catalysts met with abject failure. The electrophile was 3-butyn-2-one or ethyl propiolate, and the nucleophile was an α-cyano or β-keto ester bearing a configurationally pure menthyl group in the alcohol portion (see Supporting Information). The menthyl groups exerted no facial bias on the Michael reaction of the intermediate enolate, but they allowed the diastereoselectivity of the reaction to be determined easily. A variety of chiral phosphoramidites were examined; several catalyzed the reaction efficiently, but none gave any diastereoselectivity in the reaction under a variety of reaction conditions.

The complete lack of asymmetric induction with chiral phosphoramidites and phosphites suggests that catalytic cycle 1 is operative. In fact, the similarity of the *E*/*Z* ratios when tertiary amines and HMPT are used to catalyze the nonasymmetric Michael reaction also suggests that HMPT serves merely to generate a counterion. We hypothesize that phosphoramidites are such powerful nucleophiles that the elimination part of catalytic cycle 2 is simply too slow. Even assuming that catalytic cycle 1 is operative, it remains somewhat surprising that the chiral β-phosphonio enone counterion exerts absolutely no asymmetric influence in the C−C bond-forming step by an ion-pairing effect.[14]

Conclusion

HMPT is a very effective organocatalyst for the Michael reaction of good carbon acids. Its reactivity, low cost, lack of toxicity, and volatility allow it to be favorably compared with other phosphorus-based catalysts for the Michael reaction.[7,13] Even though chiral phosphoramidites do not induce asymmetry in the Michael reactions of alkynones, we believe that the irreversibility of these Michael reactions provides new opportunities for the development of asymmetric Michael reactions, for example, by a chiral auxiliary or phase-transfer catalysis approach.[14] Experiments in this regard are ongoing and will be reported in due course.

Typical Experimental Procedure for the HMPT-Catalyzed Michael Reaction

Ethyl 2-Cyano-5-methyl-2-(3-oxobutyl)hexanoate. Methyl vinyl ketone (2.0 mL, 24 mmol) was added dropwise to a stirred solution of ethyl 2-cyano-5-methylhexanoate[15] (3.67 g, 20 mmol) and HMPT (182 μL, 1 mmol). (Caution: HMPT is slowly oxidized by air to HMPA, a known carcinogen. Precautions should be taken to avoid protracted exposure of HMPT to air.) After 10 min, the reaction mixture was directly concentrated under reduced pressure to give the title compound (96% yield, 100% pure by GC−MS).

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Supporting Information Available: Substrates and catalysts used in the asymmetric catalysis experiments, analytical data for all new compounds, and some experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.
(15) Hessler, J. C. *J. Am. Chem. Soc.* **1913**, *35*, 990.