$P(RNCH_2CH_2)_3N$: Efficient 1,4-Addition Catalysts

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The 1,4-addition of primary alcohols, higher nitroalkanes, and a Schiff's base of an α-amino ester to α,β-unsaturated substrates produces the corresponding products in moderate to excellent yields when carried out at −63 to 70 °C in the presence of catalytic amounts of the nonionic strong bases $P(RNCH_2CH_2)_3N$ (R = Me, *i*-Pr, *i*-Bu) in isobutyronitrile. Diastereoselectivity for the anti form of the product is high in the case of the Schiff's base in the absence of lithium ion. These catalysts are easily removed from the product by either column filtration through silica gel or via aqueous workup.

Introduction

Michael addition is one of the most efficient and effective routes to the formation of C−C bonds.[1] This reaction is widely applied in organic synthesis,[2] and several new versions of the reaction have recently been introduced.[3] Michael addition reactions of electron-deficient alkenes have been used to produce difunctionalized synthons that have been used extensively in organic synthesis.[2] 1,5-Diketones (prepared by Michael addition of α-nitroketones to α,β-unsaturated ketones)[4] have been used to prepare 2-cyclohexenones,[5] and β-nitroketones can be reduced to β-aminoketones.[1,6] Alternatively, the nitro group can be removed[7] leaving behind a β-alkyl substituent on the carbonyl product.

The commonly employed anionic alkyl synthons for Michael addition are those derived from nitroalkanes,[8] ethyl cyanocarboxylates,[9] and malonates.[10] Such Michael donors have been extensively studied, and their limitations (such as double additions,[11] requirement for a large excess of the nitroalkane,[12] restrictions in the types of Michael acceptors[13] tolerated, and the low to moderate product yields encountered[10b]) have been largely overcome by newer methodologies.

The newer approaches are by no means devoid of drawbacks, however. Among recent developments are the use of Amberlyst A-27,[14] and sodium hydroxide solution in the presence of cetyltrimethylammonium chloride (CTACl) as a cationic surfactant.[15] However, the Amberlyst A-27[14] process requires reaction times ranging from 4 h (for MVK) to 25 h for the reactions of higher nitroalkanes with β-substituted methyl vinyl ketones. The sodium hydroxide method[15] affords only modest product yields in the reaction of secondary nitroalkanes, even with MVK.[15] The yields in both processes range from moderate to high for most substrates. Michael addition reactions of higher nitroalkanes to α,β-unsaturated carbonyl compounds generally require lengthy reaction times and yields are only moderate. Although reactions employing alumina are rapid, 4 equiv of the rather expensive higher nitroalkanes are required.[7b]

Oxa-Michael addition reactions have been reported, and the protected β-hydroxy carbonyl compounds so produced are of significant importance in organic synthesis.[16] Reports describing such reactions include descriptions of UV irradiation of cycloalkenones in methanol to produce the β-methoxy cyclic ketones;[16] reactions promoted by NaOMe,[17a] KH,[17b] and potassium *t*-butoxide;[17c] and the cyanoethylation of alcohols by a Mg−Al hydrotalcite prepared in a process requiring 450 °C for up to 12 h.[18a] Several other catalysts have also been used for the cyanoethylation of alcohols, but their utility has not been extended to other α,β-unsaturated

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(1) Reviews: (a) Ono, N.; Kaji, A. *Synthesis* **1986**, 693. (b) Rosini, G.; Ballini, R. *ibid.* **1988**, 833. (c) Tamura, R.; Kamimura, A.; Ono, N. *Ibid.* **1991**, 423.

(2) Angelo, J.; Revial, G.; Costa, P. R. R.; Castro, R. N.; Antunes, O. A. C. *Tetrahedron Asymmetry* **1991**, *2*, 199. (b) Hagiwara, H.; Okamoto, T.; Harada, N.; Uda, H. *Tetrahedron*, **1995**, *51*, 9891. (c) Seebach, D.; Colvin, E. W.; Leher, F.; Weller, T. *Chimia* **1979**, *33*, 1.

(3) Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J. S. *Synth. Commun.* **1998**, *28*, 653. (b) Yamagushi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223. (c) Hanyuda, K.; Hirai, K.; Nakai, T. *Synlett.* **1997**, 31.

(4) Ono, N.; Miyake, H.; Kaji, H. *J. Chem. Soc., Chem. Commun.* **1983,** 875.

(5) Grieco, P. A.; Pogonowski, C. S. *Synthesis* **1973**, 425.

(6) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 2, pp 321−340.

(7) Ono, N.; Miyake, H.; Tamuta, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*,1705. (b) Bryce, M. R.; Gardiner, J. M.; Horton, P. J.; Smith, S. A. *J. Chem. Res., Synop.* **1989**, *1*, 1.

(8) Wada, M.; Tsuboi, A.; Nishimura, K.; Erabi, T. *Nippon Kagaku Kaishi* **1987**, *7*, 1284. *Chem. Abstr.* **1987**, *108*, 149866.

(9) Ranu, B. C.; Saha, M.; Bahr, S. *Synth. Commun.* **1997**, *27*, 621.

(10) Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Tetrahedron Lett.* **1997**, *38*, 6557. (b) Ranu, B. C.; Hamada, A. *Tetrahedron* **1992**, *48*, 1327.

(11) Pollini, G. P.; Barco, A.; De Giuli, G. *Synthesis* **1972**, 44. (b) Bergbreiter, D. E.; Lalonde, J. J. *J. Org. Chem.* **1987**, *52*, 1601.

(12) Clark, J. H.; Cork, D. G.; Gibbs. H. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2253.

(13) Ballini, R.; Petrini, M.; Rosini, G. *Synthesis* **1987**, 711.

(14) Ballini, R.; Marziali, P.; Mozzicafreddo, A. *J. Org. Chem.* **1996**, *61*, 3209.

(15) Ballini, R.; Bosica, G. *Tetrahedron Lett.* **1996**, *37*, 8027.

(16) Grangier, G.; Trigg, W. J.; Lewis, T.; Rowan, M. G.; Potter, B. V. L.; Blagbrough, I. S. *Tetrahedron Lett.* **1998**, *39*, 889. (b) Noyori, R.; Kato, M. *Bull. Chem. Soc. Jpn.* **1974**, *46*, 1460.

(17) Titova, T. F.; Krysin, A. P.; Shakirov, M. M.; Mamatyuk, V. I. *J. Org. Chem. USSR (Engl. Transl.)* **1984**, *20*, 294. (b) Duffy, J. L.; Kurth, J. A.; Kurth, M. J. *Tetrahedron Lett.* **1993**, *34*, 1259. (c) Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *J. Chem. Soc., Chem. Commun.* **1997**, 1831.

(18) Kumbhar, P. S.; Sanchez-Valente, J.; Figueras, F. *Chem. Commun.* **1998**, *10*, 1091. (b) Kabashima, H.; Hattori, H.; *Catal. Today* **1998**, *44*, 277. (c) Che, R.; Wei, R.; Liang, Y.; Zheng, S.; Yang, P.; Cui, Y. *Lizi Jonhuan Yu Xifu* **1995**, *11*, 18. *Chem. Abstr.* 124: 263979.

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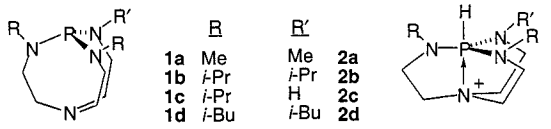
compounds.[18b,c] Recently, vanadium complexes have been reported to induce hydroalkoxylation of α,β-unsaturated ketones and epoxides.[19] However, the use of transition metals introduces environmental concerns. To our knowledge, no general reaction has been reported in which β-alkoxy ketones can be prepared via Michael addition. Thus, there still exists a need for new methodologies for the preparation of β-alkoxy ketones.

Michael addition reactions of Schiff's bases of α-amino esters have long been known to constitute a convenient method for functionalizing α-amino esters at the α position.[20] However, this transformation has a propensity to undergo a competing cycloaddition.[20b] The ratio of Michael addition to cycloaddition product has been found to depend on the metal ion employed to chelate the enolate produced upon deprotonation. Although the use of DBU in this reaction has been observed to give an α-functionalized α-amino ester as the exclusive product,[21] a stoichiometric amount of LiBr is required to provide sufficient cation concentration for chelation. It is worth noting that a weaker base such as triethylamine produces only the cycloadduct even in the presence of LiBr.[22]

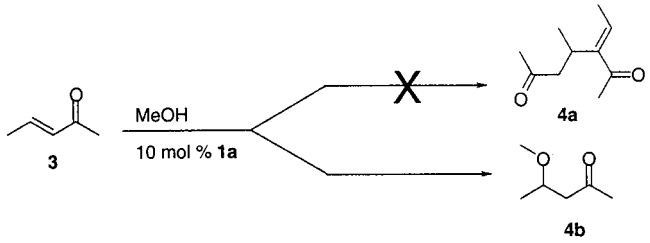
We have previously reported that the proazaphosphatranes **1a**,[23a] **1b**,[23b] and **1c**[23c] are exceedingly strong



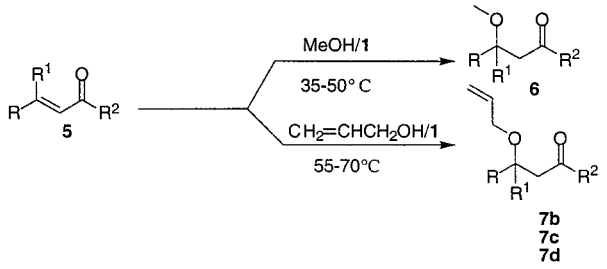
nonionic bases[23d] for the catalytic deprotonation of activated methyl and methylene groups. Thus, they deprotonate nitroalkanes, acetonitrile, alkyl halides, and carboxylic acid esters, leading to efficient preparations of nitro alcohols,[24] α,β-unsaturated nitriles,[25] β-hydroxy nitriles,[26] glutaronitriles,[27] alkenes[28] and α,β-unsaturated esters,[29] for example. In such reactions, bases of type **1** are protonated to form the corresponding cations **2a**−**d**.

We report herein the use of **1a**−**c**[23] and the most recently synthesized member of this family **1d**[30] as catalysts for the 1,4-addition of alcohols, nitroalkanes, and a Schiff's base of an α-amino ester to α,β-unsaturated carbonyl compounds. We also show that these catalysts effect the hydroalkoxylation of α,β-unsaturated ketones

Scheme 1



Scheme 2



a: R = R¹ = H, R² = Me
b: R = H, R¹, R² = $(CH_2)_3$
c: R = R¹ = R² = Me
d: R = H, R¹ = Me, R² = Et
e: R = R¹ = H, R² = OMe
f: R = Me, R¹ = H, R² = OEt
g: R = H, R¹ = Ph, R² = Me
h: R = H, R¹ = CO_2Me, R² = OMe
i: R = H, R¹ = Me, R² = OMe

in a most efficient manner and that they are very efficient catalysts in the absence of any metal ion for the Michael addition of a Schiff's base of an α-amino ester.

Results and Discussion

Hydroalkoxylation of α,β-Unsaturated Carbonyl Compounds. We first observed a Michael addition reaction promoted by bases of type **1** when we attempted to dimerize (*E*)-3-penten-2-one (**3**) in the presence of 10 mol % of **1a** in methanol (Scheme 1) in analogy to the dimerization of α,β-unsaturated nitriles previously reported from our laboratories under similar conditions.[27] Although none of the expected dimer (**4a**) was observed, we were able to isolate 20−30% of the corresponding β-methoxy ketone **4b**. When the reaction was repeated with MVK (**5a**) and with 2-cyclohexen-1-one (**5b**), we isolated the respective β-methoxy compounds in 33% (**6a**) and 24% (**6b**) yield (Scheme 2). Catalysts **1a** and **1b** each afforded similar yields within experimental error. We determined earlier that the protonation of proazaphosphatranes of type **1** to form cation **2** is slow and incomplete in alcohols at room temperature[23a,29] In the present work, hydroalkoxylation reactions utilizing 10 mol % of **1a** or **1b** at this temperature led to substantial substrate oligomerization with only 20−30% of hydroalkoxylation product that was observed to flow through the chromatography column. At 50 °C all of **1a** and **1b** is rapidly protonated, substantial hydromethoxylation of MVK and of 2-cyclohexenone occurred in 10−15 min, and additional hydromethoxylation occurred over an additional 15 min at room temperature to afford the corresponding β-methoxy ketones in 65% and 76% yield, respectively. Base **1c** afforded a lower yield (52−61%) probably owing to its relative instability to oligomeriza-

(19) Nikitin, A. V.; Kholuiskaya, S. N.; Rubailo, V. L. *J. Chem. Biochem. Kinet.* **1997**, *3*, 37. (b) Nikitin, A. V.; Kholuiskaya, S. N.; Rubailo, V. L. *J. Chem. Res., Synop.* **1994**, *9*, 358.
(20) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277. (b) Bey, P.; Vevert, J. P. *J. Org. Chem.* **1980**, *45*, 3249. (c) Stork, G.; Leong, A. Y. W.; Touzin, A. M. *ibid.* **1976**, *41*, 3491.
(21) Yamamoto, H.; Kanemasa, S.; Wada, E. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2739. (b) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411.
(22) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384.
(23) Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75. (b) Wroblewski, A.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69. (c) D'Sa, B. A.; Verkade, J. G. *Phosphorus, Sulfur, Silicon* **1997**, *123*, 301. (d) Kisanga, P.; Verkade, J. G.; Schwesinger, R. *J. Org. Chem.* **2000**, *65*, 5431.
(24) Kisanga, P.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 4298.
(25) D'Sa, B.; Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961.
(26) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090.
(27) Kisanga, P.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1998**, *63*, 10057.
(28) Arumugam, S.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827.
(29) Kisanga, P.; D'Sa, B.; Verkade, J. G. Tetrahedron 2001, *57*, 8047.
(30) Kisanga, P.; Verkade, J. G. *Tetrahedron*, **2001**, *57*, 467.

Table 1. The Reaction of α,β-Unsaturated Carbonyl Compounds with Alcohols in the Presence of 1

Michael acceptor	Michael donor	base/mol %	reaction conditions	product	% yield	lit. yield[a]
3-penten-2-one (**3**)	MeOH	**1a**/10	50 °C; 1 h	**4b**	78	NA
MVK (**5a**)	MeOH	**1a**/10	50 °C; 0.5 h	**6a**	65	96[b]
2-cyclohexenone (**5b**)	MeOH	**1b**/20	50 °C; 0.5 h	**6b**	76	71[c]
(*E*)-PhCHCHCOMe (**5g**)	MeOH	**1b**/10	50 °C; 2 h	–	–	–
4-hexen-3-one (**5d**)	MeOH	**1b**/10	50 °C; 0.5 h	**6d**	96	93[d]
4-hexen-3-one (**5d**)	CH_2CHCH_2OH	**1b**/20	70 °C; 3 h	**7d**	71	NA
4-hexen-3-one (**5d**)	Me_3COH	**1b**/20	70 °C; 3 h	–	–	–
2-cyclohexenone (**5b**)	CH_2CHCH_2OH	**1b**/20	70 °C; 3 h	**7b**	58	N A.
mesityl oxide (**5c**)	MeOH	**1b**/10	50 °C; 0.5 h	**6c**	79	70[e]
mesityl oxide (**5c**)	Me_2CHOH	**1b**/20	70 °C; 3 h	–	–	–
mesityl oxide (**5c**)	CH_2CHCH_2OH	**1b**/20	70 °C; 3 h	**7c**	40	NA
MVK (**5a**)	MeOH	**1c**/20	50 °C; 0.5 h	**6a**	61	96[b]
mesityl oxide (**5c**)	CH_2CHCH_2OH	**1d**/20	55 °C; 7 h	**7c**	89	NA
mesityl oxide (**5c**)	CH_2CHCH_2OH	**1d**/20	70 °C; 3 h	**7c**	88	NA
4-hexen-3-one (**5d**)	CH_2CHCH_2OH	**1d**/20	70 °C; 3 h	**7d**	94	NA
mesityl oxide (**5c**)	Me_2CHOH	**1d**/20	70 °C; 3 h	–	–	–
MVK (**5a**)	MeOH	**1d**/10	35 °C; 24 h	**6a**	62	96[b]
MVK (**5a**)	MeOH	**1d**/15	35 °C; 24 h	**6a**	93	96[b]
2-cyclohexenone (**5b**)	MeOH	**1d**/10	50 °C; 3 h	**6b**	89	71[c]

[a] Based on reactions mediated by base. [b] Kabashima, H.; Katou, T.; Hattori, H. *Appl. Catal. A.* **2001**, *214*, 121. [c] Reference 16b. [d] Horiuchi, C. A.; Ochiai, K.; Fukunishi, H. *Chem. Lett.* **1994**, *2*, 185. [e] Lechevallier, A.; Huet, F.; Conia, J. M. *Tetrahedron* **1983**, *39*, 3317.

tion.[23c] Because of its low boiling point (38 °C) MVK was added to the warm mixture of MeOH and catalyst in a septum-sealed tube whose contents were stirred at 50 °C for 10 min, followed by stirring at room temperature for an additional 20 min. When 15 mol % of **1d** was used as the catalyst at 35 °C, an excellent yield of the desired product **6a** was obtained from MVK (**5a**) in 24 h (Table 1). Repetition of this reaction with **1a** and with **1b** at the same temperature resulted in the isolation of only trace amounts of the product **6a** after column chromatography. Subtle differences in reactions catalyzed by proazaphosphatranes have recently been observed by us[29,30a] and a rationale for these differences will be reported in due course. Higher alcohols such as *tert*-butyl alcohol and 2-propanol resisted addition to (*E*)-3-penten-2-one (**3**), 2-cyclohexen-1-one (**5b**), or 4-hexen-3-one (**5d**) when reacted at 50−70 °C in the presence of up to 30 mol % of the proazaphosphtranes **1a**, **1b**, or **1d**.

Allyl alcohol on the other hand reacted at 70 °C over 3 h to afford high yields of β-allyloxy carbonyl products using **1b** or **1d** (Table 1). Hence, mesityl oxide (**5c**) reacted with allyl alcohol in the presence of 20 mol % of **1b** or **1d** at 70 °C to afford **7c** in 40 or 88% yield, respectively, in 3 h. On the other hand, 4-hexen-3-one (**5d**) reacted more efficiently under similar conditions to afford the corresponding β-allyloxy ketone **7d** (Scheme 2) in 71% and 94% yield in the presence of **1b** and **1d**, respectively (Table 1). At the lower temperature of 55 °C, however, allyl alcohol also reacted very efficiently with mesityl oxide (**5c**) in the presence of **1d** to give the corresponding β-allyloxy ketone **7c** in 89% yield. This is probably due to the higher solubility anticipated for **1d** which allows the occurrence of an efficient reaction at this relatively low temperature. Both **1a** and **1b** failed to produce any appreciable amount of the desired product under these mild reaction conditions.

To the best of our knowledge, there is only a single report for the preparation of 4-allyloxy-4-methylpentan-2-one (**7c** in Scheme 2) and its analogues (which are valuable intermediates in ketyl−olefin radical cyclization reactions).[31] This was achieved by treating the corresponding alcohols with $CaSO_4$, allyl bromide, and silver oxide for 10 h to afford the desired β-alkoxy ketone in 44% yield. Although the inability of 4-phenyl-2-but-3-enone (**5g**) to react with methanol or allyl alcohol in the presence of **1b** or **1d** under our conditions is disappointing, this result can be rationalized in terms of the resonance stability of this substrate which would be interrupted by hydroalkoxylation.

α,β-Unsaturated esters [represented by methyl acrylate (**5e**) and (*E*)-ethyl crotonate (**5f**)] reacted with methanol in the presence of 10 mol % of **1d** in 2 h to afford the β-methoxylation products, and in the latter case also the transesterified product. When reacted with 3.0 equiv of methanol in a solvent such as THF or Me_2-CHCN, **5f** gave a 14:15 mixture of MeCH(OMe)CH_2CO_2-Et (**7f**) and MeCH(OMe)CH_2CO_2Me, respectively, in 83% total yield, which were inseparable upon attempted column chromatography. Reducing the amount of methanol below 3.0 equiv afforded total yields that were less than 50%. Hence, hydroxymethoxylation of α,β-unsaturated esters under our conditions is of limited practical utility because of transesterification. Mild conditions for the transesterification of esters in the presence of catalysts of type **1** have been reported previously from our laboratories.[32]

Michael Addition of Nitroalkanes. The Michael addition of the lower nitroalkanes nitromethane or nitropropane to MVK and 2-cyclohexeneonone **5b** catalyzed by **1a**−**d** afforded only modest product yields (Table 2). These reactions required a lower temperature (−63 °C) in order to suppress the competing facile nitroaldol reaction which becomes particularly efficient when the nitroalkane is used as the solvent.[24] By employing the Michael addition of nitromethane to mesityl oxide as a model reaction, we discovered a strong dependency of this transformation on the solvent. Thus, this reaction is influenced more by the solvent than by the proazaphosphatrane base used. Neither **5g** nor **5h** afforded any Michael adduct upon reaction with $MeNO_2$ for up to 24 h with up to 20 mol % of **1b** in *i*-PrCN. Because an increase in the ratio of nitromethane or its use as a solvent led to the formation of nitroaldols from the Michael adduct, we investigated several solvents for the reaction. From the first four entries in Table 2, it is seen

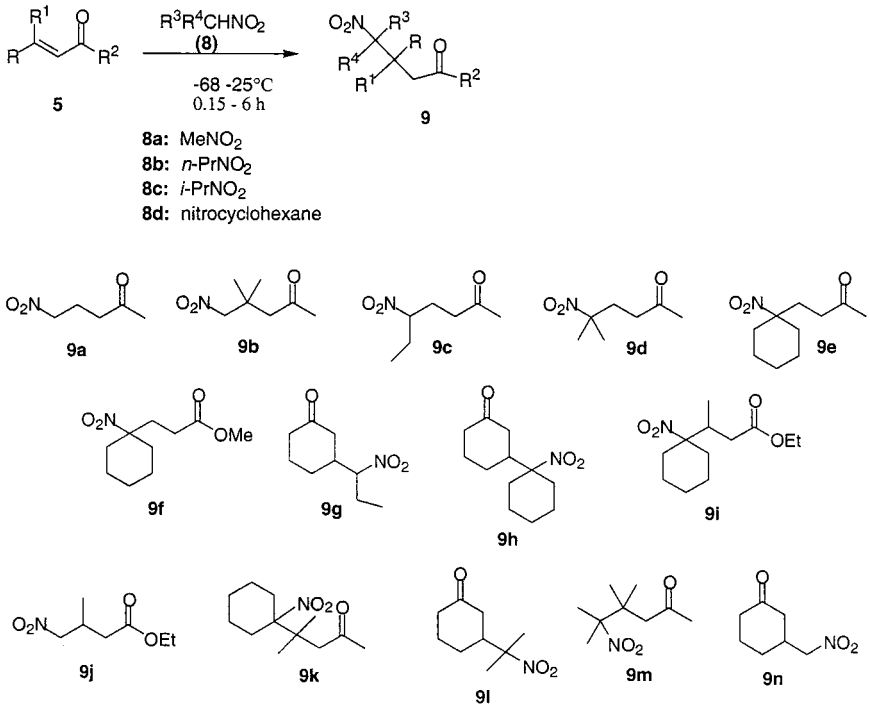
(31) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872.
(32) Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086.

Table 2. The Michael Addition of Nitroalkanes to α,β-Unsaturated Carbonyl Compounds in the Presence of 1

Michael acceptor	Michael donor	base[a]/°C/h.	product	% yield of **9**	lit.[b] yield
mesityl oxide (**5c**)	$MeNO_2$ (**8a**)	**1b**/RT/0.5	**9b**	99	93[c]
mesityl oxide (**5c**)	$MeNO_2$ (**8a**)	**1b**/RT/0.5[d]	**9b**	95	93[c]
mesityl oxide(**5c**)	$MeNO_2$ (**8a**)	**1b**/RT/0.5[e]	**9b**	91	93[c]
mesityl oxide (**5c**)	$MeNO_2$ (**8a**)	**1b**/RT/0.5[f]	**9b**	92	93[c]
2-cyclohexenone (**5b**)	$MeNO_2$ (**8a**)	**1b**/RT/0.5[d]	**9n**	89	99.8[g,8]
MVK (**5a**)	$MeNO_2$ (**8a**)	**1b**/−63/0.15	**9a**	78	98[h]
MVK (**5a**)	*n*-$PrNO_2$ (**8b**)	**1b**/−63/0.15	**9c**	81	95[i]
MVK (**5a**)	*i*-$PrNO_2$ (**8c**)	**1b**/RT/0.25	**9d**	99	95[j]
MVK (**5a**)	nitrocyclohexane (**8d**)	**1b**/RT/0.25	**9e**	93	80[k]
2-cyclohexenone (**5b**)	Me_2CHNO_2 (**8c**)	**1b**/RT/0.5	**9l**	99	100[l]
CH_2=$CHCO_2Me$ (**5e**)	nitrocyclohexane (**8d**)	**1b**/RT/4	**9f**	100	85[m]
(*E*)-ethyl crotonate (**5f**)	nitrocyclohexane (**8d**)	**1b**/RT/4	**9i**	100	NA
2-cyclohexenone (**5b**)	*n*-$PrNO_2$ (**8b**)	**1b**/−63/0.25	**9g**	71	93[i]
(*E*)-ethyl crotonate (**5f**)	$MeNO_2$ (**8a**)	**1b**/−63/0.25	**9j**	99	96[n]
2-cyclohexenone (**5b**)	nitrocyclohexane (**8d**)	**1b**/RT/1	**9h**	99	77[l]
mesityl oxide (**5c**)	nitrocyclohexane (**8d**)	**1d**/RT/1[o]	**9k**	95	NA
MVK (**5a**)	nitrocyclohexane (**8d**)	**1d**/RT/0.25	**9e**	99	80[n]
CH_2:$CHCO_2Me$ (**5e**)	nitrocyclohexane (**8d**)	**1d**/RT/1	**9f**	99	85[m]
(*E*)-ethyl crotonate (**5f**)	nitrocyclohexane (**8d**)	**1d**/RT/1	**9i**	99	NA
mesityl oxide (**5c**)	*i*-$PrNO_2$ (**8c**)	**1d**/RT/0.33	**9m**	99	14[p]

[a] The amount of base used was 10 mol % in isobutyronitrile unless stated otherwise. [b] Based on reactions mediated by bases. [c] Perrin, C. L.; Thoburn, J. D.; Elsheimer, S. *J. Org. Chem*. **1991**, *56*, 7034. [d] The solvent was THF. [e] The solvent was benzene. [f] The solvent was ether. [g] Kabashima, H.; Tsuji, H.; Shibuya, T.; Hattori, H. *J. Mol. Catal. A: Chem*. **2000**, *155*, 23. [h] Reference 33. [i] Mdoe, J. E. G.; Clark, J. H.; Macquarrie, D. J. *Synlett*. **1998**, *6*, 625. [j] Clark, J. H.; Miller, J. M.; So, K. *J. Chem. Soc., Perkin Trans. 1*. **1978**, *9*, 941. [k] Reference 34b. [l] Reference 11b. [m] Bryce, M. R.; Gardiner, J. M.; Horton, P. J.; Smith, S. A. *J. Chem. Res. Miniprint* **1989**, *1*, 116. [n] Floch, L.; Kubán, J.; Gogová, A.; Zálupsky, P.; Jakubík, T.; Prónayová, N. *Molecules* **1996**. *1*, 175. [o] The amount of **1d** used was 20 mol %. [p] Papat, J. B.; Black, D. S. C. *Aust. J. Chem*. **1968**, *21*, 2483.

Scheme 3



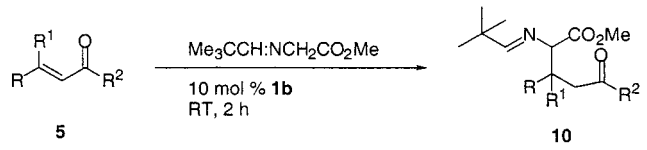
that isobutyronitrile is the best solvent for the Michael addition of nitromethane to mesityl oxide. The same reaction of MVK with nitromethane, however, produced several products including nitroaldols and double Michael addition products as indicated by ^{1}H NMR spectroscopy. This problem was overcome by carrying out the reaction at −63 °C for 10−15 min affording a 78% yield (Table 2). Recently, the same reaction was reported to proceed in 98% yield at a higher temperature (0 °C) in the presence of the less basic charge-neutral catalyst TBD.[33]

Based on the model study using mesityl oxide, the reaction of (*E*)-ethyl crotonate with nitromethane in isobutyronitrile, for example, was found to afford the corresponding Michael adduct **9j** in 99% yield (Table 2) in the presence of **1b**. The same yield was obtained when bases **1a**,**c**,**d** were employed.

Michael additions with higher nitroalkanes, such as 2-nitropropane (**8c**) and nitrocyclohexane (**8d**), proceeded smoothly in 0.15−6 h (Scheme 3). Our methodology constitutes a distinct improvement for Michael addition of nitrocyclohexane (**8d**) to 2-cyclohexenone (**5b**), mesityl oxide (**5c**), or (*E*)-ethyl crotonate (**5f**) which occurs

(33) Simoni, D.; Rondanin, R.; Morini, M.; Baruchello, R.; Invidiata, F. P. *Tetrahedron Lett.* **2000**, *41*, 1607.

Scheme 4



b: R = H, R^1, R^2 = $(CH_2)_3$
c: R = R^1 = R^2 = Me
e: R = R^1 = H, R^2 = OMe
g: R = H, R^1 = Ph, R^2 = Me
h: R = H, R^1 = CO_2Me, R^2 = OMe
i: R = H, R^1 = Me, R^2 = OMe
j: R = H, R^1 = R^2 = Me

Table 3. Michael Addition of Me$_3$CCH=NCH$_2$CO$_2$Me in the Presence of 1b

Michael acceptor	yield (*anti*:*syn*)[a] of **10x**[b]	lit. yield[c]
methyl acrylate (**5e**)	72	NA[d,e]
methyl crotonate (**5i**)	76 (9:1)	77 (single, anti)[e]
mesityl oxide (**5c**)	86	NA
2-cyclohexenone (**5b**)	97 (single)	NA
(*E*)-3-penten-2-one (**3**)	85 (7:1)	80 (single, anti)[e]
dimethyl maleate (**5h**)	94 (single)	99 (single, anti)[e]
(*E*)-4-phenyl-3-buten-2-one (**5g**)	91 (single)	97 (single, anti)[e]

[a] Determined by ^{1}H NMR integration based on a comparison with literature spectra.[22] [b] Where **x** is the letter index of the corresponding Michael acceptor **5** except in the case of the fifth entry where the product is **10j**. [c] Based on reactions mediated by bases. [d] Isolated as a mixture of products. [e] Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411.

quantitatively under mild conditions in 4−6 h (Table 2). Likewise, the Michael addition of 2-nitropropane (**8c**) to **5a**, **5b**, and **5c** occurred quantitatively in 0.5−3 h. Although both DBU and TMG have been reported as catalysts for these transformations,[33] reaction times of up to 48 h are required for either catalyst to afford the Michael adducts in only poor to modest yields.[33] Thus, proazaphosphatranes of type **1** used here serve as superior catalysts for Michael addition of nitroalkanes and especially of higher nitroalkanes.

Michael additions of nitrocycloalkanes to α,β-unsaturated esters afford intermediates that are useful in the synthesis of spirolactams.[7c] Triton B has been used for the Michael additions of nitrocyclohexane to α,β-unsaturated esters to give the corresponding Michael adducts in 64% yield.[7c] Lower yields (70%) and longer reaction times (up to 10 h) were also the case in reactions employing Amberlyst A21.[14] Our methodology gives **9e** in 99% yield in 1 h at room temperature in the presence of **1d**. Our approach also improves on a reported process in which 1-nitrocyclohexene was reacted with α,β-unsaturated esters in methanol in the presence of $NaBH_4$ to afford Michael addition products (e.g. **9f**) in 62−95% yield over 24 h.[34] It is worth mentioning that the procedure and the workup in that reported procedure[34] is cumbersome compared with ours.

Michael Addition of Me$_3$CCH=NCH$_2$CO$_2$Me. The reaction of the title Schiff's base was found to proceed smoothly in the presence of 0.1 equiv of **1b** (Scheme 4 and Table 3). When 10 mol % of **1d** was employed, the conversion obtained for the reaction of methyl acrylate (**5e**) with Me$_3$CCH=NCH$_2$CO$_2$Me was found to be equal to that employing **1b** within experimental error. Although base-catalyzed reactions of this type have been reported previously using Et_3N and DBU, the formation of the Michael adduct rather than cycloaddition product depended on the presence of Li^+.[21,22] The efficiency of bases of type **1** in this reaction is demonstrated by their ability to induce a clean Michael addition of the imine with various α,β-unsaturated compounds in the absence of Li^+. Hence, methyl crotonate (**5i**), methyl acrylate (**5e**), mesityl oxide (**5c**), 2-cyclohexenone (**5b**), (*E*)-3-pentenone (**3**), dimethyl maleate (**5h**), and (*E*)-4-phenyl butenone (**5g**) afforded the corresponding products in 72−97% yield (Table 3).

Chelation has consistently been cited as a possible reason for the higher diastereoselectivities observed in the Michael addition reaction of the *N*-lithiated azomethine ylides (or lithium enolates) produced upon deprotonation of the imines.[21] For reasons that are not presently clear, we observe high diastereoselectivity and high yields (Table 3) with (*E*)-3-penten-2-one (**2**), methyl crotonate (**5i**), dimethyl maleate (**5h**), and (*E*)-4-phenyl-3-buten-2-one (**5g**) despite the absence of a metal ion. It is interesting that the reaction of methyl acrylate with Me$_3$CCH=NCH$_2$CO$_2$Me in the presence of DBU and LiBr reported by other investigators[21] gives only the double Michael adduct in 71% yield whereas our method affords the desired mono adduct in 72% yield.

Conclusions

We have shown that proazaphosphatranes are efficient catalysts for the Michael addition of primary alcohols, higher nitroalkanes and Schiff's bases to α,β-unsaturated carbonyl compounds. However, Michael addition of alcohols to unsaturated esters is hindered by competing transesterification. The Michael addition of nitroalkanes was found to have limited success with nitromethane owing to its nitroaldol reaction with the products formed from MVK and cyclohexenone. Michael addition of the Schiff's base Me$_3$CCH=NCH$_2$CO$_2$Me proceeds smoothly with high diastereoselectivity in the absence of a chelating metal ion. As can be seen from Tables 1−3, to the best of our knowledge our product yields exceed those in the literature by at least 4% in 11 cases, are reasonable to excellent in 14 cases not reported in the literature, are within ±3% in 9 cases and are worse by 4% or more in 8 cases.

Experimental Section

All reactions were conducted under nitrogen. Isobutyronitrile (Aldrich) was dried over 4 Å molecular sieves and stored under nitrogen. The unsaturated compounds (Aldrich) were used as received except in the cases of the Michael donors for synthesizing **9k** and **9l** wherein it was necessary to distill these reagents before use. The melting points of the products are uncorrected. The bases **1a**,[23a] **1b**,[23b] and **1c**[23c] were prepared according to our previously reported methods and Me$_3$CCH=NCH$_2$CO$_2$Me was prepared according to a published procedure.[22]

General Procedure for the Oxa-Michael Addition of Alcohols to α,β-Unsaturated Substrates. The required weight of the proazaphosphatrane **1** was weighed in a small test tube under nitrogen. To this was added 3.0 mL of the alcohol, and then the colorless solution was heated in an oil bath that had been preheated to the required temperature (Table 1) under stirring for 2−3 min. The Michael acceptor (2.00 mmol) was then added in one portion, and stirring was

(34) Andruszkiewicz, R.; Silverman, R. B. *Synthesis* **1989**, 953. (b) Ono, N.; Kamimura, A.; Miyake, H.; Hamamoto, I.; Kaji, A. *J. Org. Chem.* **1985**, *50*, 3692.
(35) Ho, T. L. *Synth. Commun.* **1982**, *12*, 339.

continued for the time periods specified in Table 1. At the end of the reaction time, the reaction mixture was added to 20 mL of brine and then extracted with 3 × 30 mL of ether. The extract was dried over anhydrous sodium sulfate, and the volatiles were removed in vacuo to afford the crude alkoxy ketones that were purified (when necessary) as detailed below. Alternatively, the reaction mixture was allowed to cool to room temperature, loaded onto a small silica gel column, and eluted with 70 mL of 5% methanol in ether. Removal of the volatiles under reduced pressure afforded the crude alkoxy ketones that (when necessary) were also purified. Products requiring purification were purified by elution on a silica gel column using ether in hexane. The ratio of ether was increased in 5% increments and the products eluted at 40% ether in hexane.

General Procedure for the Michael Addition of Nitroalkanes to α,β-Unsatuarated Substrates. The base (0.2 mmol) was weighed into a small test tube under nitrogen, and a small stirring bar was added. To this was added 2.0 mL of the appropriate solvent (Table 2) followed by 2.1 mmol of the Michael donor. The mixture was stirred for 5 min at the temperature given in Table 2 after which 2.0 mmol of the Michael acceptor was added in one portion. After stirring had been continued for the required time, the reaction mixture was loaded onto a small silica gel column and eluted with 5% MeOH in ether. Removal of the solvent under reduced pressure afforded the crude product that was then fractionated on a silica gel column using an eluent system made up of hexane and EtOAc, wherein the EtOAc was increased in concentration by 5% increments. The products eluted with 20% EtOAc in hexane.

General Procedure for the Michael Addition of $Me_3CCH{=}NCH_2CO_2Me$ to α,β-Unsatuarated Substrates. The base (0.2 mmol) was weighed in a small test tube under nitrogen, and a small stirring bar was added. To this was added 2.0 mL of isobutyronitrile followed by 2.1 mmol of the Michael donor. The mixture was stirred for 5 min at room temperature after which 2.0 mmol of the Michael acceptor was added in one portion and stirring was continued for 2 h. The reaction mixture was added to 20 mL of ethyl acetate, and then the mixture was washed with 10 mL of water and 10 mL of brine. The organic layer was dried over anhydrous sodium sulfate, and the volatiles were removed under reduced pressure to afford the Michael adduct. However, these compounds were too labile to be purified by column chromatography. This result is in accord with previous reports by Yamamoto et al.[21a] and Kanemasa and co-workers.[21b] The Michael adducts were essentially NMR-pure, and only the ^1H NMR and ^{13}C NMR spectra were recorded.

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Supporting Information Available: ^1H and ^{13}C NMR and mass spectral data for the products reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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