$P(RNCH_2CH_2)_3N$-Catalyzed 1,2-Addition Reactions of Activated Allylic Synthons

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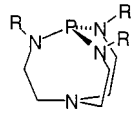
Activated allylic compounds of the type $RCH{:}CHCH_2Z$ (Z = CN, CO_2Me) react efficiently with aromatic aldehydes in the presence of 20−40 mol % of $P(R'NCH_2CH_2)_3N$ at −94 to −63 °C. Both R = H and R = Me lead exclusively to α-addition products. When R = H and Z = CN, an allylic transposition occurs to afford a Baylis−Hillman product as the only product.

Introduction

The formation of C−C bonds is of significant utility in organic synthesis for facilitating the assembly of building blocks into larger molecules.[1] Among organic transformations that proceed through C−C bond formations are reactions such as aldol condensation,[2] the Henry reaction,[3] Knoevenagel condensation[4] and the Baylis−Hillman reaction,[5] all of which (except the Baylis−Hillman reaction) proceed through the addition of anions derived from compounds bearing an activating (electron withdrawing) group and/or a halogen. Stabilized allylic anions have also been used for the construction of C−C bonds.[6] Since the resonance forms of the allylic anion place the negative charge in both the α and γ positions,[6] it is not uncommon to observe both α- and γ-alkylation products in reactions of such ambident anions.[6] γ-Addition of allylic anions has been traditionally achieved via the use of Grignard reagents of the type $RCH{:}CHCH_2{-}MgX$.[7] Since Grignard reagents attack carbonyl groups, the use of carbonyl-functionalized Grignard reagents is therefore not possible. This is also true for allyl barium reagents commonly used for α-addition of allylic anions to carbonyl compounds.[8] Hence, commonly used functionalized allylic anions employed for C−C bond formation are those that possess heteroatoms such as silicon, oxygen, sulfur, nitrogen, or a halogen.[6] Allylic anions stabilized by a strong electron withdrawing group, such as SO, SO_2, or $P(O)R_2$, have also been utilized.[6] However, it should be noted that substrates bearing these functionalities are less prone to nucleophilic addition reactions at the activating group and are employed to a lesser extent in organic synthesis than substrates containing nitrile[9] or ester[10] functionalities.

Subsequent to the synthesis of bases of type **1** first synthesized in our laboratories,[11] we have found that these compounds act as superior catalysts and reagents for a variety of reactions. For example, we have used



1a = Me
1b = i-Pr
1c = i-Bu

them successfully for the synthesis of β-nitroalkanols,[12] β-hydroxy nitriles,[13] silylated alcohols,[14] glutaronitriles,[15]

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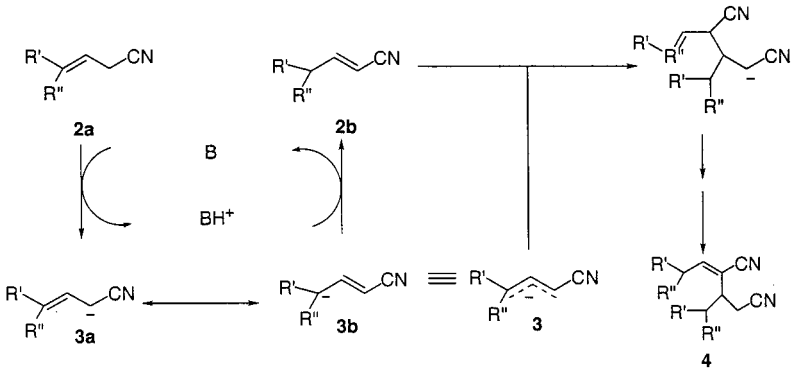
Scheme 1



oxazolines,,[16] a novel ylide,[17] α,β-unsaturated nitriles,[18] and homoallylic alcohols.[19]These nonionic bases have also been used successfully in the promotion of Michael addition reactions,[20] oxa-Michael addition reactions,[20] Knoevenagel condensations,[21] and Wittig olefination reactions.[22] We previously reported that β,γ-unsaturated nitriles undergo dimerization reactions to afford glutaronitriles as the only products.[15] We postulated a mechanism for that reaction in which we assumed that the pathway involves the formation of an allylic anion that either deprotonates the protonated base to form an α,β-unsaturated nitrile or undergoes a Michael-type addition to an already formed α,β-unsaturated nitrile (Scheme 1). Scheme 1 suggests that the resonant allylic anions **3a** and **3b** are sufficiently stable to persist in the reaction mixture until they add to an α,β-unsaturated nitrile molecule. Although we have recently been able to utilize bases of type **1** for the isomerization of methylene-interrupted double bonds[23] (a process that involves the formation of allylic anions), and for the dimerization of allylic cyanides,[15] all our attempts to utilize anions of type **3** in other syntheses have heretofore failed.

As a continuation of our previous work on glutaronitrile synthesis,[15] we report here the first proazaphosphatrane-catalyzed reaction of activated allylic compounds to produce either a Baylis−Hillman product or a β,γ-unsaturated 1,2-addition product, depending on the type of allylic compound employed. To our knowledge, there have been only a few reports in which allylic cyanides and esters of the type used here have been utilized in 1,2-addition to aldehydes.[24] The authors of one of the reports achieved such a reaction in the presence of cadmium chloride and obtained a mixture of α- and γ-addition products,[24a] which contrasts our observations in which exclusive α-addition is encountered. The other reactions were achieved using a variety of lithium bases such as PhSLi,[24b] LDA,[24c,e] or *t*-BuLi[24d] or other alkali metal bases such as NaHMDS[24c] or KHMDS.[24c]

Results and Discussion

Attempted reaction of allyl cyanide with benzaldehyde at room temperature in the presence of 10−20 mol % of **1a** or **1b** consistently produced in our hands the corresponding glutaronitrile as the only product.[15] We also observed no evidence for the reaction of allyl cyanide with benzaldehyde in the presence of 20 mol % of either **1a** or **1b** in THF upon reducing the temperature to −20 °C, although an undetermined amount of the corresponding glutaronitrile[15] was observed. However, in the presence of 20 mol % of **1a** in THF and by reducing the temperature to −63 °C, we were able to observe the formation of the corresponding Baylis−Hillman product in 32% conversion as shown by ^{1}H NMR analysis of the reaction mixture. Increasing the amount of this base to 30 mol % led to an increase in the conversion to the Baylis−Hillman product to about 64% under the same conditions. With 40 mol % of **1b**, complete conversion was observed and an 88% isolated yield of the Baylis−Hillman product **7a** was realized. Reactions employing **1a** or **1c** afforded inconsistent but low conversions, and therefore only **1b** was henceforth used in this study. Interestingly, the Baylis−Hillman product we observe stems from allylic transposition. It is worth comparing this result to that recently reported by Yamamoto and co-workers in which α,β-unsaturated esters were deprotonated by lithium 2,2,6,6-tetramethylpiperidide (LTMP), followed by treatment with a carbonyl substrate in the presence of aluminum *tris*(2,6-diphenylphenoxide) (ATPH) to afford a γ-addition product with retention of both the position and geometry of the double bond.[25]

The Baylis−Hillman reaction has been of interest to researchers for decades.[26] Generally, high pressure is required to induce this reaction between an α,β-unsatu-

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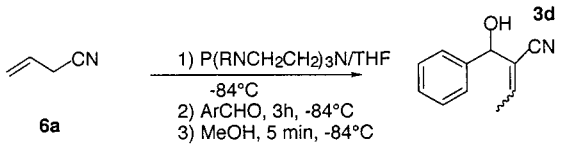
Table 1. Reactions of Allylic Compounds with Aldehydes

aldehyde	allylic compound	reaction conditions	product	% yield
PhCHO **5a**	**6a**	-63°C, 3h 40 mol% **1b**	**7a**	88
5b	**6a**	-63°C, 3h 40 mol% **1b**	**7b**	93
5c	**6a**	-63°C, 3h 40 mol% **1b**	—	—
PhCHO **5a**	**6b**	-94 °C, 3h 40 mol % **1b**	**7c**	94
5b	**6b**	-78°C, 3h 40 mol% **1b**	**7d**	87
5d	**6b**	-94 °C, 3 h 40 mol % **1b**	**7e**	91
PhCHO **5a**	**6c**	-63°C, 3h 20 mol% **1b**	**7f**	88
5d	**6c**	-63°C, 3h 30 mol% **1b**	**7g**	88
5b	**6a**	-63°C, 3h 30 mol% **1b**	**7h**	88
PhCHO **5a**	**6d**	-84°C, 3h 40 mol% **1b**	**7i**	87
5b	**6d**	-78°C, 3h 40 mol% **1b**	**7j**	83
5d	**6d**	-84°C, 3h 40 mol% **1b**	**7k**	95
MeCHO **5e**	**6d**	-78°C, 3h 25 mol% **1b**	**7l**	84
PhCHO **5a**	$PhSO_2CH_2CHCH_2$ **6e**	-78°C, 3h 25 mol% **1b**	**7m**	63
5f	**6a**	-94 °C, 3 h 40 mol % **1b**	**7n**	0

Scheme 2



88% *E*:*Z* = 78:22

rated compound and a carbonyl compound in the presence of an amine such as DABCO, and lengthy periods of time (1−4 weeks) are usually required.[27] The reaction shown in Scheme 2 affords this product under very mild conditions and very short reaction times. Furthermore, this reaction is successful with aromatic aldehydes that have generally led to unreliable results under typical Baylis−Hillman conditions.[28] Unlike the nucleophilic pathway that has been proposed for traditional Baylis−Hillman reactions,[27] the reaction shown in Scheme 2 is proposed to proceed through an allylic anion produced by the deprotonation of allyl cyanide by the proazaphosphatrane (Scheme 3). The allylic anion thus produced could add to the aldehyde to afford an intermediate alkoxide anion which is sufficiently basic to deprotonate allyl cyanide, thus possibly facilitating a catalytic reaction. However, it seems more likely that the alkoxide undergoes a facile 1,3-proton shift, giving a terminal carbanion that deprotonates either allyl cyanide or the protonated base **1**H^+ with resultant regeneration of the prozazphosphatrane base that then re-enters the catalytic cycle in Scheme 3. This mechanism is supported by the observation that a reaction mixture monitored by ^{31}P NMR spectroscopy at −50 °C revealed the existence of both the free base and its protonated form **1b**H^+. This observation is in accord with our previous study showing that a reaction mixture containing **6a** and **1b** in CD_3CN at room temperature contained both the free base and its protonated form in addition to deuterium scrambling.[15]

Since several Baylis−Hillman adducts and their derivatives have recently been found to be efficient antimalarial agents,[29] our protocol offers an easy route to a variety of Baylis−Hillman adducts that could be screened for antimalarial activity. Our methodology is characterized by faster rates compared with the most recently

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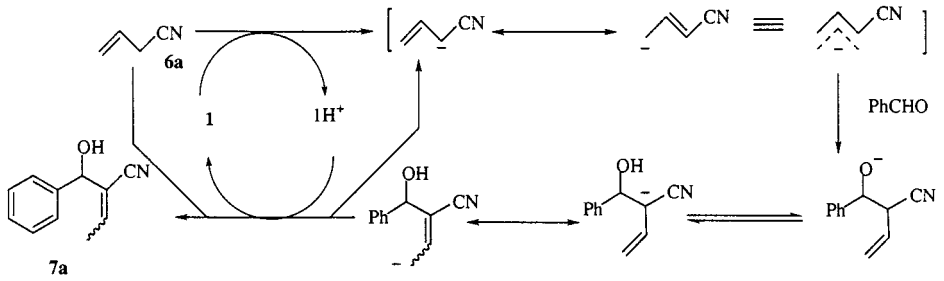
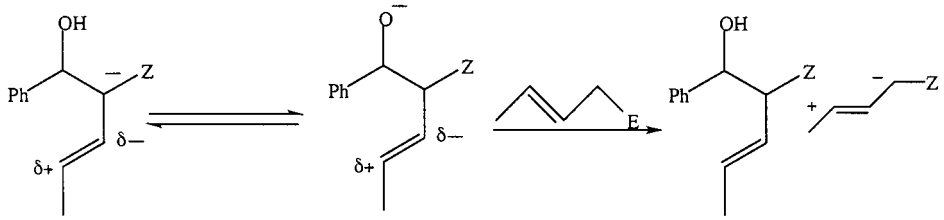
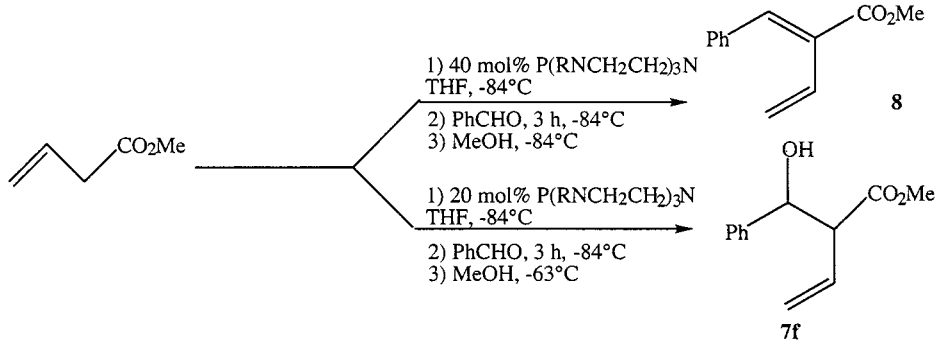
Scheme 3



Scheme 4



Scheme 5



reported variations of the Baylis−Hillman reaction, such as a DABCO-catalyzed reaction in the presence of $LiClO_4$ (20−48 h, 0 to −25 °C, 35−85% yield),[30] a chalcogeno-Baylis−Hillman reaction that requires a 2-fold excess of the α,β-unsaturated compound in addition to 1.5 equiv of DBU, or 2 equiv of Et_2NH to which is also added other reagents such as Me_2S or Ti(O-*i*-Pr)$_4$.[31] Our reaction was equally successful with *p*-chlorobenzaldehyde, affording the corresponding Baylis−Hillman product **7b** in 93% yield (Table 1). However, aliphatic aldehydes such as pivalaldehyde and *n*-butyraldehyde led only to complicated reaction mixtures which upon workup were observed to contain small amounts of unreacted aldehydes and unidentified substances.The higher homologue of allyl cyanide, namely, (*E*)-pentenenitrile (**6b**) also underwent an α-addition reaction under similar conditions to afford the novel unsaturated β-hydroxy nitrile **7c** shown in Scheme 4 and Table 1. The assumption that an allylic anion is also formed in this reaction is justified by ^{31}P NMR observations on this reaction made in experiments analogous to those described above. We observe no detectable amounts of γ-addition products in our reactions. The reactions of *p*-chlorobenzaldehyde and of *p*-fluorobenzaldehyde with **6b** followed a similar course, affording the corresponding β-hydroxy β′,γ′-unsaturated nitriles **7d** and **7e** in 87% and 91% yields, respectively (Table 1). Noteworthy here is the formation of a highly functionalized system in a single step. Reactions of allylic anions reported in the literature are generally devoid of selectivity and usually give rise to a mixture of the α- and γ-addition products.[6]

Compounds analogous to **7c** (e.g., **7i** discussed below) have been prepared by others through a multistep procedure that utilizes aluminum turnings, mercuric chloride, and sulfur-containing intermediate compounds.[32] Another method for preparing these compounds is to react an α,β-unsaturated ester with carbonyl compounds in the presence of LDA and HMPA (a well-known carcinogen).[33] The unsaturated alcohol products (e.g., **7c**−**7l** in Table 1) are useful intermediates for the synthesis of substituted tetrahydrofurans through base-promoted electrophilic cyclizations.[33,34] The formation of **7c**−**7l** (as a 1:1 mixture of diastereomers) is assumed to originate from polarization of the double bond by the methyl group, a process that places a partial negative charge adjacent to an anionic carbon, thus favoring a 1,3-proton shift and the subsequent deprotonation reaction shown in Scheme 4.

This result was sufficiently intriguing that we decided to explore its extension to other activated allylic compounds. Thus, methyl 3-butenoate reacted with benzaldehyde under the conditions shown in Scheme 5 to

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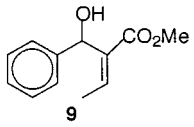
afford an unsaturated ester, **8**, arising from α-addition followed by dehydration. However, this product proved to be unstable and underwent further transformations to unidentified products. Upon reducing the amount of base to 20 mol %, unsaturated aldol products **7f**, (Scheme 5) **7g**, and **7h** (Table 1) were isolated upon reacting **6c** with benzaldehyde, 4-fluorobenzaldehyde, and 4-chlorobenzaldehyde, respectively. All attempts to form the corresponding Baylis−Hillman product **9** were fruitless.

However, by using 30 mol % of **1b** and by carrying out the reaction of PhCHO with **6c** for 6 h at −78 °C, a (7:3:2) mixture of three products i.e., **7f**, **8**, and the desired Baylis−Hillman product **9** was observed upon analyzing the reaction mixture by ^{1}H NMR spectral integration.



9

Neither of the diastereomers of **7f** could be separated from the reaction mixture, because **9** and both diastereomers of **7f** always eluted together. The reactions of **6c** with aliphatic aldehydes (pivalaldehyde, *n*-butyraldehyde, and isobutyraldehyde) were not successful under the above conditions. Only complicated reaction mixtures containing some unreacted starting aldehyde and unidentified material(s) were observed in all three cases. Reactions employing the higher homologue methyl *trans*-3-pentenoate (**6d)** afforded only an incomplete reaction in the presence of 20 mol % of **1a**. In the presence of 40 mol % of **1b**, the reactions of each of the arylaldehydes benzaldehyde, 4-chlorobenzaldehyde, 4-fluorobenzaldehyde, and acetaldehyde with **6d** afforded the corresponding β-hydroxy unsaturated esters **7i**, **7j**,**7k**, and **7l** in high yields (Table 1). The reaction of benzaldehyde with phenyl allyl sulfone gave the α-adduct **7m** with no allylic transposition to the corresponding Baylis−Hillman product. The inability of *p*-nitrobenzaldehyde to react under our conditions to give **7n** in Table 1 while disappointing is in accord with previous reports from our laboratories in which this substrate had been found to form a greenbluish complex in the presence of bases of type **1**.[14,19] This result may also be associated with nucleophilic attack on the nitro group which interrupts the course of the reaction. The relatively lower reactivities of *p*-chlorobenzaldehyde and *p*-fluorobenzaldehyde relative to benzaldehyde are also consistent with observations made on other reactions promoted by bases of type **1** which we reported previously.[13,19] However, the origin of this result is not clear at this point.

Experimental Section

All reactions were conducted under nitrogen. The aldehydes and allylic compounds were used as received without further purification. The bases were prepared according to our previously reported procedures.[11]

General Procedure for the Reaction of Allylic Compounds with Aldehydes. Nitrogen was admitted to a small evacuated flask and then 2.00 mL of dry THF was added followed by 2.00 mmol of the allylic substrate. The reaction mixture was then stirred at the required temperature (Table 1) for 10 min. A solution of proazaphosphatrane base **1b** (Table 1) in 2 mL of THF was added dropwise over 5 min and the resulting solution was stirred for an additional 5 min. This was followed by the dropwise addition of a solution of 2.0 mmol of the aldehyde in 0.75 mL (2 mL in the case of **5b**) of dry THF over a period of 2−3 min. The reaction mixture was then stirred for the time periods specified in Table 1, at the end of which time the mixture was quenched by the addition of 1 mL of MeOH followed by stirring for 5 min. The crude mixture was immediately loaded onto a small silica gel column and flashed off with 5% MeOH in ether. The volatiles were removed under vacuum and the crude product was fractionated on a silica gel column with 60−75% ether in hexane. None of the product diastereomers could be separated by column chromatography except for those of the β-hydroxy esters **7i**−**7k**.

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

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