$P(RNCH_2CH_2)_3N$: Efficient Catalysts for Transesterifications, Acylations, and Deacylations

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Extremely strong nonionic superbases of the type $P(RNCH_2CH_2)_3N$ catalyze the transesterification of carboxylic acid esters with high selectivity and yields at 25 °C. These bases also catalyze the deacetylation of alcohols under mild conditions in quantitative yields. Using enol acetates as acylating agents, primary and secondary alcohols are efficiently protected as acetates through the action of these catalysts. Substituents such as epoxide, carbamate, acetal, oxazoline, nitro, and alkynyl functionalities are tolerated under the reaction conditions. N-Protected peptides undergo clean transesterification without significant racemization, making this methodology potentially very useful.

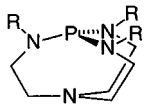
Introduction

Transesterifications are important transformations in organic synthesis in industrial as well as in academic laboratories. For example, methyl esters produced by the transesterification of naturally occurring oils and fats can be used as diesel alternatives.[1] There are many catalysts available for transesterification,[2] and the most common procedure is to reflux the ester with a catalytic amount of $Ti(O\text{-}i\text{-}Pr)_4$ in an alcohol solvent.[3] Other Lewis acid catalysts[4] such as $BuSn(OH)_3$,[4a] $Al(OR)_3$,[4b] and $[SCNBu_2SnOSnBu_2SCN]_2$[4c] also catalyze this conversion. Alternatively, ionic as well as nonionic bases (e.g., NaOMe,[5] DMAP,[6] and DBU/LiBr[7]) can be employed as catalysts for this reaction. Transesterifications, catalyzed by $Ti(O\text{-}i\text{-}Pr)_4$ and $BuSn(OH)_3$, require higher reaction temperatures and acidic conditions. A 50 mol % excess of DBU in the DBU/LiBr catalyst systems is required for efficient transesterifications, DMAP is effective only with enolizable keto esters, and NaOMe causes racemization of amino acid derivatives. Such drawbacks experienced with these catalysts make worthwhile the search for new catalysts that operate under milder conditions.

The acyl group is a common alcohol-protecting group that can be introduced in several ways.[8] The most common method involves the reaction of an alcohol with acetic anhydride in the presence of pyridine.[8] For acid- or base-sensitive alcohols, however, such procedures do not work very well. Transesterification using vinyl acetate offers an alternate route that is very mild[8] and which can be effected selectively using $Cp_2^*Sm\cdot thf$[9] or $[ClBu_2SnOSnBu_2Cl]_2$ as catalysts.[10] Enzymes and acids are also catalysts for this reaction. Even though $Cp_2^*Sm\cdot thf$ and $[ClBu_2SnOSnBu_2Cl]_2$ catalyze acylations very efficiently, the reductive nature of low valent samarium and the Lewis acidity of tin halides pose threats for nitro, epoxide, and amine functionalities that may be present.

The deacylation of protected alcohols is an important strategy in synthesis.[8] K_2CO_3/MeOH has been a widely used reagent system, but recently DIBAL-H has been shown to effect clean deacylation[11] for pivaloate esters. Though the latter procedure is effective, the reagent is pyrophoric and must be handled carefully.

Earlier we reported that the commercially available nonionic base **1a** is a superior catalyst for the trimerization of isocyanates[12] and for the protective silylation of alcohols,[13] a promoter for acylation of hindered alcohols,[14] and an effective reagent for dehydrohalogenations,[15] the selective C-monoalkylation of active methylene compounds,[16] and the synthesis of pyrroles[17] and α,β-unsaturated nitriles.[18] Here we report that **1a** and in certain instances **1b** are efficient transesterification, acylation, and deacylation catalysts.



1a, R = Me
1b, R = *i*-Pr

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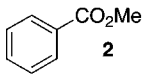
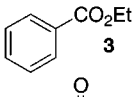
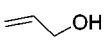
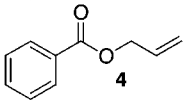
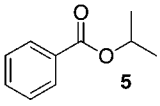
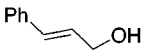
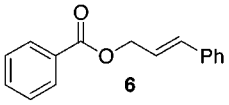
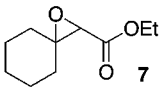
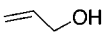
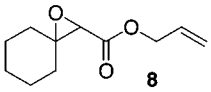
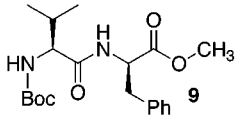
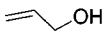
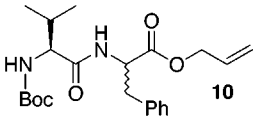
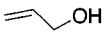
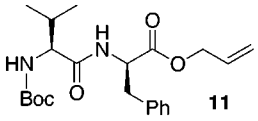
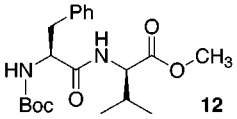
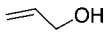
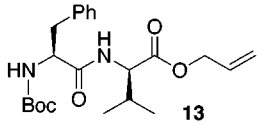
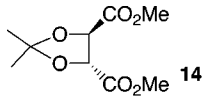
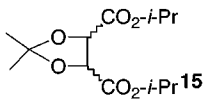
Table 1. Transesterification of Esters by Alcohols Catalyzed by Superbases[a]

substrate	alcohol	product	time (hrs)	yield (%)
 **2**	EtOH	 **3**	4	89
2		 **4**	4	82
2		 **5**	8.5	85
2		 **6**	24	91
2		no reaction	24	—
 **7**		 **8**	5	91
 **9**		 **10**	17	96
9		 **11**	4	96[b]
 **12**		 **13**	13	100
 **14**		 **15**	18	95[c]
14		**15**	21	81

[a] Catalyst **1a** was used (10 mol %) unless otherwise stated. [b] Catalyst **1b** was used (15 mol %). [c] Catalyst **1b** was used (10 mol %).

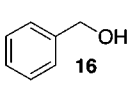
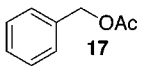
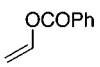
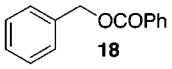
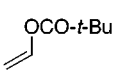
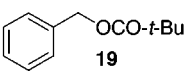
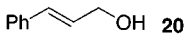
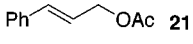
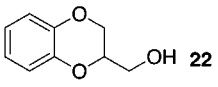
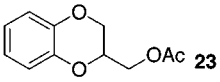
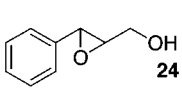
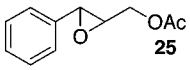
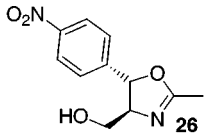
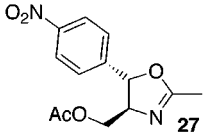
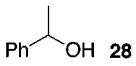
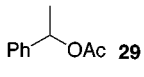
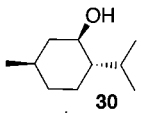
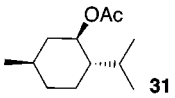
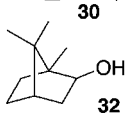
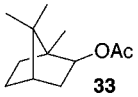
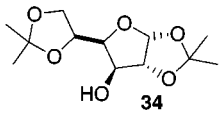
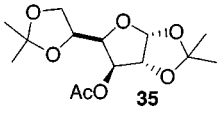
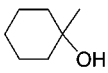
Results and Discussion

Methyl benzoate (**2**) was examined as a model substrate as a ca. 0.2 M solution in EtOH containing (10 mol %) of **1a**. After 4 h at rt, the methyl ester was completely converted into its ethyl analogue (**3**) which was isolated in 89% yield (Table 1). Encouraged by this result, several alcohols as well as several esters as substrates for transesterification were studied in an effort to elucidate the scope and limitations of this reaction. The results are summarized in Table 1. Allyl alcohol gave allyl benzoate **4** in 82% yield whereas isopropyl alcohol, a secondary alcohol, took somewhat longer (8.5 h) to give the isopropyl benzoate **5** in 85% yield. For cinnamyl alcohol, the procedure was slightly modified. Thus, a 1:1 mixture of cinnamyl alcohol and methyl benzoate was refluxed in THF, and the methanol formed was trapped by molecular sieves placed between the flask and the condenser, giving cinnamyl benzoate **6** in 91% yield. When *tert*-butyl alcohol was used as the exchanging alcohol, no reaction was observed even after 24 h. In this case, only starting material was recovered, probably because this reaction is thermodynamically and kinetically unfavored owing to the steric hindrance of the *tert*-butyl group. To assess the selectivity of catalyst **1a** in transesterification reactions, an ester with a sensitive functional group was chosen. Thus when epoxy ester **7** was treated with allyl alcohol in the presence of 10 mol % of **1a**, the corresponding allyl ester **8** was obtained in 91% yield. This selectivity cannot be achieved by the conventionally used catalyst Ti(O-i-Pr)$_4$, which is known to catalyze ring opening of epoxides by alcohols.[19] Moreover, allyl esters could not be made using Ti(O-i-Pr)$_4$ as a catalyst since allyl alcohols are not stable under the conditions employed.[3]

Our initial success with simple esters prompted us to turn our attention to amino acid esters, because esters

(19) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

Table 2. Acylations of Alcohols with Enol Esters Catalyzed by Nonionic Superbases 1a[a]

Substrate	enol ester	Product	Time (hrs)	Yield (%)
 **16**		 **17**	2	99
16		 **18**	5.5	99
16		 **19**	5.5	99
 **20**		 **21**	2	98
 **22**		 **23**	2	99
 **24**		 **25**	4	98
 **26**		 **27**	24	76
 **28**		 **29**	24	66[b]
28		**29**	41	91
 **30**		 **31**	14	97[c]
 **32**		 **33**	16	96[c]
 **34**		 **35**	17	92[c]
 **36**		no reaction	24	—[c]

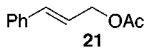
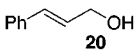
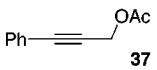
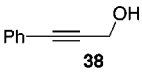
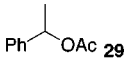
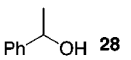
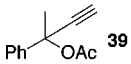
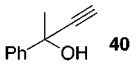
[a] Catalyst **1a** was used (10 mol %) unless otherwise stated. [b] Catalyst **1b** was used as catalyst and 15% of the alcohol was recovered. [c] The temperature was 50 °C.

are very useful protecting groups in peptide synthesis. Boc-Val-Phe-OMe (**9**) was used as a substrate and allyl alcohol was chosen as the solvent since peptide allyl esters are frequently utilized. When **1a** was used as a catalyst, the reaction was over in 17 h, and the allyl ester **10** was isolated in 96% yield. Unfortunately, however, the product was found by ^{1}H NMR spectroscopy to be a 55:45 mixture of epimers at the phenyl alanine residue. We believed that a more basic and more bulky catalyst such as **1b** might solve the problem of epimerization. Indeed when **1b** was used as a catalyst, the reaction was over in 4 h, the product **11** was isolated in 96% yield, and it was obtained in high diastereomeric purity (98:2). It was also found in this case that a longer reaction time (12.5 h) was not beneficial because a mixture (84:14) of epimeric products was formed. When the less racemization-prone valine ester **12** was the substrate, the allyl ester **13** was obtained in quantitative yield without racemization using the less basic and less bulky catalyst **1a**. On the other hand, when the acetonide of dimethyl tartrate **14** was subjected to similar transesterification conditions with catalysts **1a** or **1b** in the presence of isopropyl alcohol, the optical activity was completely lost in diisopropyl ester **15**, though it was obtained in 95% yield. In all cases, yields and selectivities are comparable to those realized with DBU/LiBr and similar substrates.[7] However, catalysts **1a** and **1b** are more efficient because the amount used is 10−15 mol % whereas the DBU/LiBr system utilizes 50 mol % of DBU and 500 mol % of LiBr. Moreover, our reactions are carried out under milder conditions (room temperature) whereas other catalysts such as Ti(O-*i*-Pr)$_4$ and BuSn(OH)$_3$, require reflux temperatures, and racemization of amino acid esters occurs when NaOMe is the catalyst.[5]

The results of our alcohol acetylations with vinyl esters in the presence of **1a** and **1b** are summarized in Table 2. Using **1a** as the catalyst in the presence of 5 equiv of vinyl acetate and benzyl alcohol as the substrate, complete acetylation occurred after 2 h at room temperature to give benzyl acetate in 99% yield. Similarly, other vinyl esters such as vinyl benzoate and vinyl pivaloate gave the corresponding esters **18** and **19**, respectively, in very high yields. Cinnamyl alcohol **20** gave cinnamyl acetate **21** in excellent yield, and the acid-sensitive alcohol **22** was acetylated in 99% yield. Although **22** can be acetylated using **1a** with acetic anhydride, the reaction requires a molar equivalent of **1a**.[14] To determine the selectivity of **1a** in acylation reactions, alcohol **24** was selected because of the presence of the epoxy group which is susceptible to reduction, for example with SmI_2.[20] The reaction was very clean, and the epoxy acetate **25** was isolated in 98% yield. Using the nitro-substituted oxazoline methanol **26** as the substrate, the reaction was slow but the corresponding acetate **27** was obtained in 76% yield. This selectivity is advantageous because nitro groups are reduced by low valent samarium reagents[21] that catalyze acylation reactions. When [ClBu$_2$SnOSnBu$_2$Cl]$_2$ was used as a catalyst for substrate **26**, we observed no formation of product **27**. This may be due to the Lewis acidity of the Sn(IV) reagent which may form a complex with the oxazoline nitrogen. However, when the secondary alcohol **28** was treated under our conditions, the reaction gave a mixture of at least four products. Thus although 85% of the alcohol had reacted, the acetylated product **29** was obtained in only 66% yield. It is known that isopropenyl acetate is a better reagent for transesterification than vinyl acetate.[9] Thus when vinyl acetate was replaced with isopropenyl acetate, the acylated product **28** was afforded in 91% yield. For more hindered alcohols such as **30**, **32**, and **34**, the reaction mixture was heated to 50 °C, and the corresponding acetates were isolated in excellent yields. When the tertiary alcohol **36** was subjected to the same transesterification conditions, no product was detected. Though our methodology is not effective for acylating tertiary alcohols, it is very sucessful and highly selective for primary alcohols, including acid-sensitive primary alcohols such as **22**, **24**, and **26**, and for hindered alcohols exemplified by **30**, **32**, and **34**. Hence, our approach offers substantial advantages over catalysts such as Cp$_2$*Sm·thf and [ClBu$_2$SnOSnBu$_2$Cl]$_2$.

The results of deacylation reactions using **1a** are given in Table 3. By dissolving cinnamyl acetate **21** in MeOH in the presence of 10 mol % of **1a** and stirring for 20 min at room temperature, cinnamyl alcohol **20** was obtained in quantitative yield. Similarly the propargyl alcohol **37** was obtained from the corresponding acetate **38** in comparable yield. This reaction is very selective because the reactive acetylene is not affected. In contrast, DIBAL-H is known to react with acetylenes.[22] The secondary alcohol acetate **29** took somewhat longer to react but the yield of the alcohol **28** was virtually quantitative. Though the reaction was slow, the tertiary ester **39** gave rise to the tertiary alcohol **40** in 96% yield, and no side reactions such as elimination were detected.

Table 3. Deprotection of Acetates Catalyzed by 1a

substrate	product	time (min)	yield (%)
 **21**	 **20**	20	100
 **37**	 **38**	20	100
 **29**	 **28**	220	99
 **39**	 **40**	41 hrs	96

In summary we have shown that the transesterification of a variety of esters with different alcohols can be efficiently achieved using the commercially available[23] nonionic superbase **1a**, or its analogue **1b** which is easily made using our published procedure.[24] Product yields are high and are comparable to those achieved with conventional procedures. Chemoselectivity is higher than with catalysts such as Ti(O-i-Pr)$_4$, NaOMe, and DMAP. Moreover **1a** and **1b** are found to be good catalysts for selective acylation and deacylation reactions, and hence the procedures described here should find ready application in organic synthesis. Extension of our transesterification conditions for the cleavage of peptides from Wang resin is currently in progress.

Experimental Section

Although **1a** is commercially available,[23] we synthesized it according to our previously published procedure, and its analogue **1b** was also synthesized according to one of our previous reports.[24] All reactions were carried out in air.

A general procedure for the transesterification of esters with alcohols and for the deacylation of esters with methanol is now given. To a stirred solution of **1a** or **1b** (10−15 mol %) in the alcohol (5 mL), 1 mmol of ester was added at room temperature. The mixture was stirred for the time given in Table 1 and 2 and then the alcohol was evaporated in vacuo. The residue was dissolved in diethyl ether and passed through a pad of silica. Solvent evaporation under vacuum gave the product which was found to be pure by ^{1}H NMR analysis.

A general procedure for the acylation of alcohols with vinyl or isopropenyl acetate follows. To a stirred solution of **1a** or **1b** (10 mol %) in dry THF (1 mL), 1 mmol of alcohol was added followed by 5 equiv of vinyl acetate or isopropenyl acetate at room temperature. The mixture was stirred for the time given in the Table **3**, and then the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel using 0−20% ethyl acetate in hexane as eluent.

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

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