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Efficient Transesterification/Acylation Reactions Mediated by *N*-Heterocyclic Carbene Catalysts

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Imidazol-2-ylidenes, a family of *N*-heterocyclic carbenes (NHC), are efficient catalysts in the transesterification involving numerous esters and alcohols. Low catalyst loadings of aryl- or alkyl-substituted NHC catalysts mediate the acylation of alcohols with enol acetates in short reaction times at room temperature. Commercially available and more difficult to cleave methyl esters react with primary alcohols in the presence of alkyl-substituted NHC to efficiently form the corresponding esters. While primary alcohols are selectively acylated over secondary alcohols with use of enol esters as acylating agents, methyl and ethyl esters can be employed as protective agents for secondary alcohols in the presence of the more active alkyl-substituted NHC catalysts. The NHC-catalyzed transesterification protocol was simplified by generating the imidazol-2-ylidene catalysts in situ.

Introduction

Specifically designed catalysts have been shown to play a key role in optimizing the efficiency of a wide variety of organic transformations. During the past few decades small molecule synthesis has attracted attention owing to its importance in the synthesis of key intermediates or compounds in pharmaceutical, agrochemical, and fine chemical industries. However, there is a growing interest in finding metal-free catalyzed processes that would provide efficient alternatives to classical organic transformations and result in more economical and environmentally friendly chemistry. To this end, nucleophilic organocatalysts have successfully been employed in diverse organic reactions.[1] Notable examples are the enantioselective pyrrole-catalyzed 1,3-dipolar additions,[2] the Diels−Alder reactions,[3] and the proline-catalyzed Mannich reaction for the enantioselective synthesis of α-

or β-amino acids and β-lactams.[4] Chiral DMAP derivatives also have been efficiently employed as nucleophilic catalysts for the dynamic kinetic resolution of secondary alcohols[5] and nonenzymatic acylation of amines.[6]

The ester moiety represents one of the most ubiquitous functional groups in chemistry, playing a paramount role in biology and serving both as key intermediate and/or protecting group in organic transformations.[7] Usually, esters are synthesized from carboxylic acids and alcohols. However, this reaction requires harsh conditions. As a consequence, efficient methods for the synthesis of esters are in demand. In this context, the base or Lewis acid-catalyzed acylation of alcohols by acetic anhydride or acid halides suffers from poor selectivity between primary and secondary alcohols or cleavage of acid-sensitive functional groups. Lewis acidic catalysts such as $Sc(OTf)_3$ and $Sc(NTf_2)_3$,[8] $TiCl(OTf)_3$,[9] TMSCl and TMSOTf,[10] $La(O^iPr)_3$,[11] $CoCl_2$,[12] $Sn(OTf)_2$,[13] and $TiCl_4/AgClO_4$,[14] and bases such as phosphines[15] or proazaphosphatrane[16] have been used

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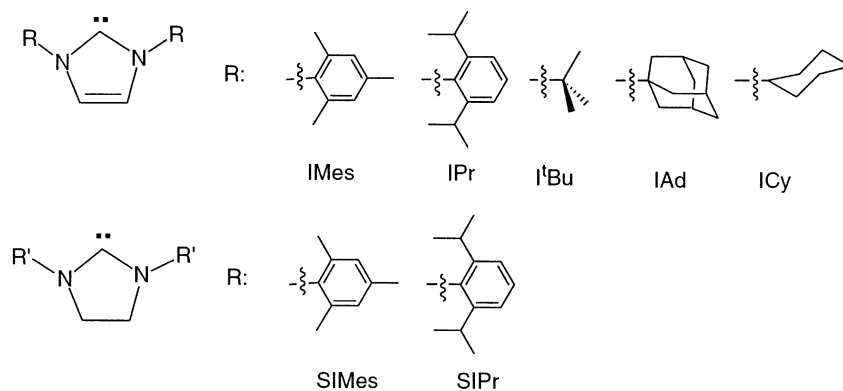
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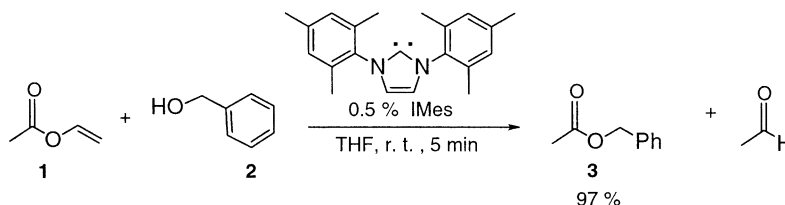(12) Iqbal, J.; Srivastava, R. R. *J. Org. Chem.* **1992**, 57, 2001−2007.

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SCHEME 1. *N*-Heterocyclic Carbene Catalysts

SCHEME 2. IMes-Catalyzed Acylation of Benzyl Alcohol with Vinyl Acetate

as catalysts or stoichiometric reagents to mediate this reaction. However, Lewis acid catalysts lead to cleavage of sensitive functional groups such as acetals, dienes, and epoxides. On the other hand, phosphines suffer from poor air-stability, toxicity, and flammability. Other bases generally lack selectivity between primary and secondary alcohols. Transesterification of an ester by exchange of an alkoxy moiety has been efficiently achieved with use of enol esters as acylating agents.[7] Conversion of the resulting enolate to an aldehyde or ketone subsequently shifts the transesterification equilibrium in the desired direction. Although organometallic catalysts such as Cp*$_2$Sm(thf)$_2$[17] and distannoxanes,[18] or the very basic iminophosphoranes[19] have been employed to this end, they either are limited to nonacid-sensitive substrates[17] or require high catalyst loading and long reaction times.[17−19] Furthermore, readily available methyl esters require harsh conditions to deprotect the alcohol and, at the same time, do not undergo transesterification to higher homologues easily due to the reversibility of the reaction.[7,20] Here, we wish to disclose a versatile and general catalytic method leading to the synthesis of various esters using *N*-heterocyclic carbenes (NHC) or imidazol-2-ylidenes (Scheme 1) as nucleophilic catalysts for the transesterification reaction.

Results and Discussion

We have reported that NHC represent a class of ligands with a considerable stabilizing effect in organometallic systems[21] compared to the widely utilized tertiary phosphines. Their donating properties are comparable to or better than those of the most basic phosphines. In terms of reactivity, NHC behave as nucleophiles due to their lone electron pair.[22] NHC have been shown to efficiently promote organic transformations such as the

benzoin condensation,[23] and ring-opening polymerization of lactones and lactides.[24]

On the basis of our experience with NHC and the fact that transesterification of enol esters can be affected by basic phosphines such as PBu$_3$[15] or iminophosphoranes,[19] we reported[25a] that the NHC IMes catalyzed the reaction of benzyl alcohol with vinyl acetate in THF, with almost quantitative conversion to benzyl acetate in 5 min at rt (Scheme 2). Hedrick reported simultaneously a similar protocol for the NHC-catalyzed transesterification/poly-condensation reactions.[25b]

Acylation of Primary Alcohols with Enol Esters. Once having established that IMes was an excellent catalyst for the transesterification reaction of vinyl acetate with benzyl alcohol, we investigated a variety of challenging alcohol substrates (Table 1). Usaturated alcohols such as substituted 2-propen-1-ol are of interest since their corresponding esters are used as herbicide[26a] or antimycotic agents.[26b,c] Unsaturated alcohols geraniol

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TABLE 1. Acylation of Primary Alcohols with Enol Esters[a]

entry	ester	alcohol	product	IMes (mol%)	time (min)	yield(%)[b]
1	1	4	4a	1	60	99
2	1	5	5a	1	15	96
3	1	6	6a	0.5	15	100
4	7	2	7a	0.5	5	93
5	7	4	7b	2	60	93[c]
6	7	5	7c	d	30	95
7	8	5	5a	1	180	95[c]
8	9	2	9a	5	15	95[c]

[a] Reaction conditions: 1 mmol of benzyl alcohol, 1.1 mmol eof nol ester, 0−5−2 mol % of IMes, room temperature. [b] Isolated yield, average of two runs. [c] 2 mmol of enol ester was used. [d] 2 mmol of vinyl acrylate, 5 mol % of ICy.

and cinnamyl alcohol reacted rapidly with vinyl acetate in the presence of 1 mol % of IMes giving quantitative yields of the desired products (entries 1 and 2). Alcohols bearing acid-sensitive functional groups such as **6**[17,18] led to the corresponding acetate in a very short reaction time and in the presence of only 0.5 mol % of the catalyst (entry 3). Vinyl benzoate presented a similar trend, reacting in a very short reaction time with benzyl alcohol and requiring either higher catalyst loading or slightly longer reaction times for the reaction with more difficult alcohols (entries 4−6), while the sterically hindered isopropenyl acetate required a longer reaction time (entry 7). Acrylic esters can be problematic substrates for transesterification due to side reactions such as decomposition, isomerization, or polymerization. Vinyl acrylate effectively protected benzyl alcohol, albeit with a higher loading of the more active catalyst ICy (entry 8).

Selectivity in protecting a primary alcohol versus a secondary one is very important in natural product synthesis.[7] Selective protection of primary alcohols has been achieved by using organometallic systems such as

distannoxane/enol ester[18] or Sc(OTf)$_3$/Ac$_2$O.[27] Transesterification selectivity under our standard reaction conditions with respect to primary alcohols was confirmed by the inactivity of 2-butanol to acylation with vinyl acetate. Moreover, benzyl alcohol **2** is almost exclusively acylated by vinyl acetate in the presence of 2-butanol with the assistance of the IMes catalyst (Scheme 3).

Influence of the Nucleophile on the Acylation of Benzyl Alcohol with Methyl Acetate. On the basis of the success of acylation of various alcohols with enol esters, we tested the acylation of the commercially available and more challenging substrate methyl acetate using different nucleophiles. Two main factors were identified for biasing the reaction in the desired direction. First, the use of 4 Å molecular sieves to absorb the liberated methanol led to quantitative conversion of benzyl alcohol to benzyl acetate in 1 h with 2.5 mol % of ICy. Second, the nature of the nucleophile also influenced the transesterification equilibrium. Under similar conditions (2.5 mol % of catalyst, 1 mL of methyl acetate, 1 h, molecular sieves) IMes afforded the product in 93% yield, while IPr led to a moderate conversion presumably due

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SCHEME 3. IMes-Catalyzed Selective Acylation of Benzyl Alcohol
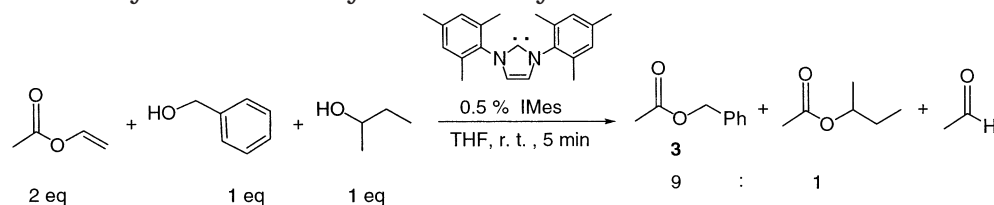
SCHEME 4. Reaction of Methyl Acetate with Benzyl Alcohol Catalyzed by Various Nucleophiles[a,c]
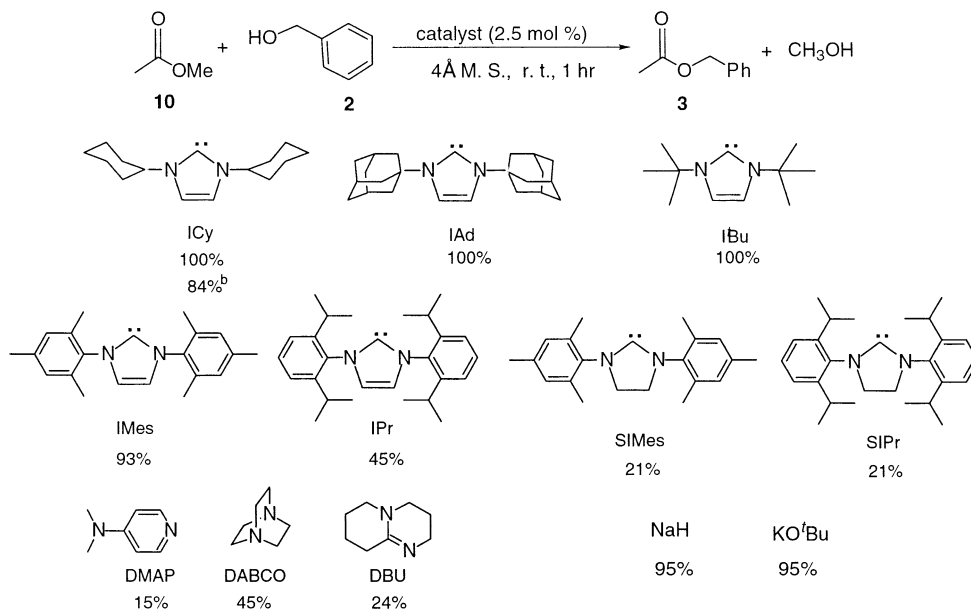
[a] Reaction conditions: (a) 1 mmol of benzyl alcohol, 1 mL of methyl acetate, 2.5 mol % of catalyst, 0.5 g of 4 Å molecular sieves, room temperature, 1 h; (b) without molecular sieves; (c) GC yield, average of two runs.

to its steric bulk. The corresponding aryl-substituted imidazolin-2-ylidenes SIMes and SIPr afforded the products in low yields.[28] The alkyl-substituted ICy, I^{t}Bu, and IAd performed much better in the model reaction affording the product quantitatively (Scheme 4) presumably due to their higher nucleophilicity.[21a] It should also be stated that the pK_a values of two NHC have recently been reported to be in the range of 22−24.[29] Strongly basic amines, such as DMAP,[30] DABCO,[31] and DBU,[32] known to catalyze the acylation of alcohols with acyl chlorides or acid anhydrides, are not effective catalysts for the transesterification of methyl acetate with benzyl alcohol. As expected, the strong inorganic bases NaH and KO^{t}Bu led to high conversions. However, the use of these bases may be problematic for more sensitive substrates.[7,33]

Transesterification of Alkyl Esters with Alcohols. The scope and generality of this NHC-catalyzed transesterification was also expanded to the readily available, but more difficult to react or deprotect methyl esters (Table 2). Methyl acetate not only affected transesterification of benzyl alcohol in excellent yield (entry 1), but also performed well in the reaction with the acid-labile alcohol **6**, affording the product **6a** in 90% isolated yield (entry 2).

During organic transformations, the deprotection of methyl esters is rather difficult, requiring severe cleavage conditions; therefore their conversion to benzyl or allyl esters, which are easily cleaved under mild conditions, is desirable.[34] Various alkyl and aryl methyl esters were converted in high yield and short reaction time to their benzyl homologues with use of our protocol. Activated substrates such as *p*-nitro-substituted substrates can be problematic due to the involvement of this functionality in side reactions.[32] Nonetheless, methyl *p*-nitrobenzoate **16** converted to its benzyl ester **16a** in excellent yield in only 15 min in the presence of 2.5 mol % of ICy (entry 9). Sterically more hindered, acidic and α,β-unsaturated methyl esters underwent clean reaction with benzyl

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TABLE 2. Transesterification of Methyl Esters with Various Alcohols[a]

entry	ester	alcohol	product	ICy (mol%)	time (min)	yield%[a,e]
1	10	2	3	2.5	60	95
2	10	6	6a	2.5	30	90
3	10	11	11a	3.5	60	92[d]
4	10	12	12a	3.5	60	96[d]
5	13	2	13a	2.5	30	95[b]
6	13	12	12b	5	120	89[b]
7	14	2	14a	2.5	180	97[b]
8	15	2	15a	2.5	30	99[b]
9	16	2	16a	2.5	15	96[b]
10	16	12	16b	5	120	88[b]
11	17	2	17a	2.5	30	93[c]
12	18	2	18a	2.5	15	96[b]

[a] Reaction conditions: 1 mmol of alcohol, 1 mL of methyl acetate, 0.5 g of 4 Å molecular sieves, room temperature. [b] 1.5 mmol of alcohol, 1 mmol of methyl ester, 1 mL of THF, 0.5 g of 4 Å molecular sieves. [c] 1 mmol of alcohol, 1 mmol of dimethyl carbonate, 1 mL of THF. [d] GC yield. [e] Isolated yield, average of two runs.

alcohol under our standard conditions (entries 5, 7, and 11).

Since we and others[17–19] have observed that enol esters affect the acylation of primary alcohols selectively, we were interested in examining whether secondary alcohols can be acylated using methyl esters. The acylation of secondary alcohols would be of interest as an alternative to enzymatic transesterification of racemates.[35] Secondary alcohols **11** and **12** underwent acylation successfully with use of various methyl esters (entries 3, 4, 6, 8, and

10). The higher catalyst loadings and the longer reaction times required for these transformations are due to the lower reactivity of the branched alcohols.

Given that methyl esters can be easily activated for transesterification reaction with ICy as the organic catalyst, we further explored the use of ethyl acetate as acylating agent. Ethyl acetate, used commonly as solvent, underwent efficiently transesterification with benzyl alcohol (Table 3, entry 1). The resultant ethyl alcohol was removed from the equilibrium with 5 Å molecular sieves. Similar to methyl acetate, ethyl acetate showed an analogous trend for the acylation of various primary and secondary alcohols, with the requirement of higher catalyst loading in the later case.

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TABLE 3. Acylation of Various Alcohols with Ethyl Acetate as Acylating Agent[a]

entry	alcohol	product	ICy (mol%)	time (min)	yield(%)[c]
1	**2**	**3**	2.5	30	94
2	**4**	**4a**	2.5	30	97
3	**5**	**5a**	2.5	60	93
5	**6**	**6a**	2.5	60	72
6	**21**	**21a**	2.5	180	93[b]
7	**12**	**12a**	3.5	60	90[b]

[a] Reaction conditions: 1 mmol of alcohol, 1 mL of ethyl acetate, 0.5 g of 5 Å molecular sieves, room temperature. [b] GC yield. [c] Isolated yield, average of two runs.

SCHEME 5. Influence of the Use of Molecular Sieves on the Equilibrium
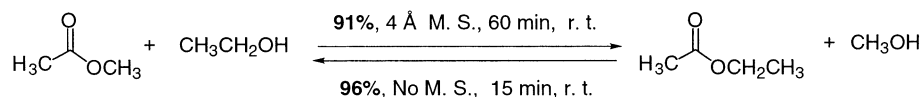
Since transesterification/acylation is an equilibrium process, the judicious choice of alcohol/ester combination can direct the formation of the target ester. Studies have shown that the formation of methyl acetate is thermodynamically favored and therefore methyl alcohol will easily replace/exchange the alkoxy moiety of the reactant ester.[36] On the other hand, higher alkyl alcohol homologues have a lower reactivity with respect to the acylation reaction. The most commonly used method to shift the equilibrium to obtain the desired ester is the removal of the resulting alcohol either under partial vacuum or under azeotropic distillation, which can both be difficult when low boiling point esters or alcohols are targeted.

We were able to shift the equilibrium in the desired direction using the proper catalyst/molecular sieves combination (Scheme 5). Ethanol can be efficiently replaced from ethyl acetate by its lower homologue methanol by using the effective ICy catalyst without the need of molecular sieves. Inversely, the equilibrium of the reaction of methyl acetate with ethyl alcohol can be shifted with the absorbance of the resulting methanol into 4 Å molecular sieves and formation of ethyl acetate.

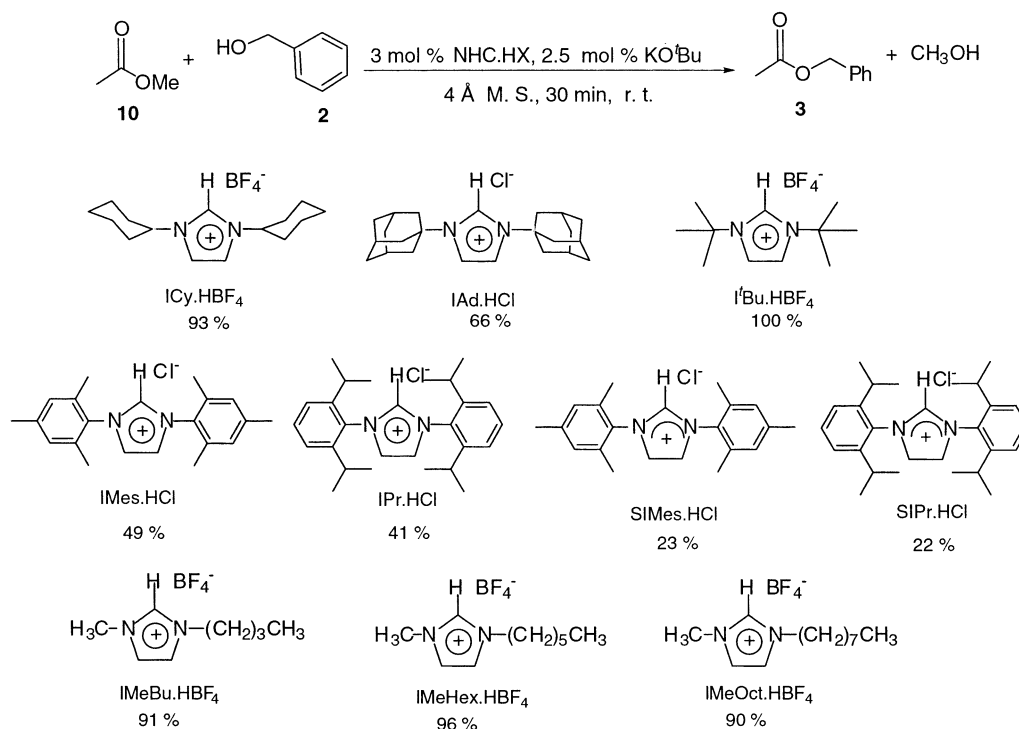**Transesterification with Imidazolium Salts as Catalyst Precursors.** Imidazol-2-ylidene carbenes are considerably less stable to air and moisture than their corresponding imidazolium salts. Although NHC bearing less bulky alkyl substituents on the nitrogen atoms are more active for transesterification reaction of less active esters, they are more difficult to isolate since they can easily dimerize.[37] To circumvent the preparation and isolation of the carbene, we used our previously developed protocol in which the carbene ligand can be generated in situ from the imidazolium salt for Pd/imidazolium salt system-catalyzed cross-coupling reactions.[38]

With use of a similar procedure, catalytic amounts of imidazolium salt and base stirred at room temperature for 15 min in THF, followed by substrates addition leads to comparable activity/yields as when isolated NHCs (Scheme 6) were used. Notably, commercially available alkyl-substituted imidazolium salts, used as ionic liquid solvents,[39] IMeBu·HBF$_4$, IMeHex·HBF$_4$, and IMeOct·HBF$_4$, are also efficient catalyst precursors for this transformation (Scheme 6).

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SCHEME 6. Reaction of Methyl Acetate with Benzyl Alcohol Catalyzed by Various Nucleophiles[a]

[a] Reaction conditions: 1 mmol of benzyl alcohol, 1 mL of methyl acetate, 3 mol % of imidazolium salt, 2.5 mol % of KO^{t}Bu, 0.5 g of 4 Å molecular sieves, room temperature, 30 min.

SCHEME 7. Synthesis of Nicotinate Esters
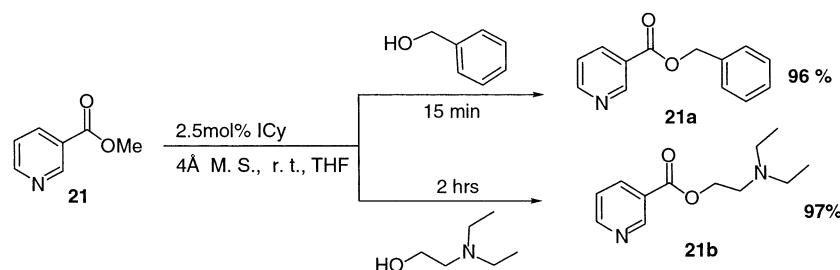
Application of NCH-Catalyzed Transesterification toward Drug Synthesis. We previously reported the synthesis of a haloalkyl methacrylate monomer (**19**), which serves as a building block for the synthesis of anticholesteremic haloalkyl methacrylate polymer, using metal-free ICy-catalyzed transesterification.[25a,40]
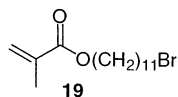
With aim at broadening the scope of this catalytic transformation, we were interested in esters bearing the nicotinate moiety, which have important applications in cosmetics and pharmaceutical industry.[41] With use of our general protocol (2.5 mol % of ICy, 4 Å molecular sieves, room temperature), benzyl nicotinate **21a**, which is an active component in cosmetics and drugs,[42] displayed high compatibility with the catalyst, being obtained in high yield (Scheme 7). Moreover, ICy catalyst presents high tolerance with respect not only to heterocyclic esters, but also to amino alcohols. Nicametate **21b**, used as a vasodilator,[43a,b] and usually obtained from the corresponding acid and diethylaminoethyl chloride,[42c,d] was obtained in high isolated yield by acylation of *N,N*-diethylethanol amine with methyl-2-nicotinate (Scheme 7).

Conclusions

NHCs are excellent catalysts for the transesterification reaction. Unsaturated NHCs are very efficient organic catalysts for the transesterification of various enol esters with primary alcohols. Since selective protection of primary alcohols versus secondary alcohols is very important in organic synthesis, selectivity experiments revealed that by using enol esters as substrates, primary alcohols can be acylated efficiently over secondary alcohols in the presence of the IMes catalyst. Moreover, challenging substrates such as methyl and ethyl esters

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can be activated for the transesterification of various primary alcohols with the aid of more nucleophilic alkyl-substituted carbenes. Secondary alcohols were also effectively acylated with use of methyl or ethyl esters particularly. The scope and application of this catalyst/transformation was broadened to the in situ generation of NHC catalysts. The NHC family displays significant functional group tolerance, being compatible with amine, olefin, nitro, ether, and thioether functions. Work focusing on a number of catalytic transformations involving NHC as well as a complete mechanistic investigation of the role of NHC in transesterification is ongoing.

Experimental Section

Transesterification of Esters with Alcohols: Procedure A. Transesterification of Vinyl Acetate with Alcohols. Under an atmosphere of argon, 1 mL of THF, 1 mmol of alcohol, and 1.2 mmol of vinyl acetate were added sequentially to a screw cap vial loaded with 0.5 mol % of catalyst. The resulting mixture was stirred at room temperature for the indicated time; the solvent and ester excess were evaporated and the residue was purified by flash chromatography, using 10% of ethyl acetate/hexanes.

Procedure B. Transesterification of Methyl Acetate with Alcohols. Under an atmosphere of argon, 1 mL of methyl acetate and 1 mmol of alcohol were added sequentially to a screw cap vial loaded with 2.5 mol % of catalyst and 0.5 g of molecular sieves. The resulting mixture was stirred at room temperature for the indicated time; methyl acetate was evaporated and the residue was purified by flash chromatography, using 10% of ethyl acetate/hexanes.

Procedure C. Transesterification of Methyl Esters with Benzyl Alcohol. Under an atmosphere of argon, 1 mL of THF, 1 mmol of methyl ester, and 2 mmol of benzyl alcohol were added sequentially to a screw cap vial loaded with 2.5 mol % of catalyst and 0.5 g of molecular sieves. The resulting mixture was stirred at room temperature for the indicated time; the solvent was evaporated and the residue was purified by flash chromatography, using 10% ethyl acetate/hexanes.

Supporting Information Available: Experimental procedures, characterization of new compounds, and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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