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N-Heterocyclic Carbenes as Versatile Nucleophilic Catalysts for Transesterification/Acylation Reactions

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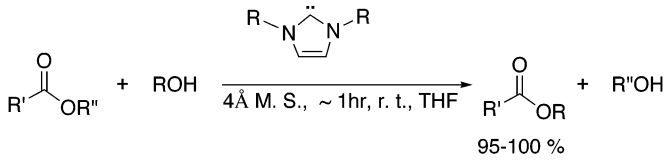
ABSTRACT



Imidazol-2-ylidenes, a family of N-heterocyclic carbenes (NHC), are efficient catalysts in the transesterification between esters and alcohols. Low catalyst loadings of aryl- or alkyl-substituted NHC catalysts mediate the acylation of alcohols with vinyl acetate in convenient reaction times at room temperature. Commercially available and more difficult to cleave methyl esters react with numerous alcohols in the presence of alkyl-substituted NHC to form efficiently the corresponding esters in very short reaction times.

The ester moiety represents one of the most ubiquitous functional groups in chemistry, playing a paramount role in biology and serving either as key intermediate or protecting group in organic transformations.[1] As a consequence, highly efficient methods for the synthesis of different esters are potentially very useful. In this context, base-[2] or Lewis acid-catalyzed[3] acylation of alcohols by acetic anhydride can suffer from poor selectivity between primary and secondary alcohols or cleavage of acid-sensitive functional groups. Transesterification by exchange of an alkoxy moiety has been efficiently achieved using enol esters as acylating agents.[1] Although organometallic catalysts such as $Cp^*_2Sm(thf)_2$[4] and distannoxanes[5] or the very basic iminophosphoranes[6] have been employed to this end, they are either limited to non-acid-sensitive substrates[5] or require high catalyst loading and long reaction times.[4−6] On the other hand, readily available methyl esters require fairly harsh conditions to enable alcohol deprotection and, at the same time, do not easily undergo transesterification to higher homologues due to the reversibility of the reaction.[1,7] Herein, we disclose the first versatile catalytic method leading to the synthesis of various esters using N-heterocyclic carbenes (NHC, imidazol-2-ylidenes) (Scheme 1) as nucleophilic catalysts in transesterification reactions.[8]

Scheme 1. Various *N*-Heterocyclic Carbenes

R		R'	
2,4,6-trimethylphenyl	IMes	2,4,6-trimethylphenyl	SIMes
2,6-di-*iso*-propylphenyl	IPr	2,6-di-*iso*-propylphenyl	SIPr
tert-butyl	I^{t}Bu		
adamantyl	IAd		
cyclohexyl	ICy		

We have reported that NHC represent a class of ligands with a considerable stabilizing effect in organometallic systems[9] as compared to the widely utilized tertiary phos-

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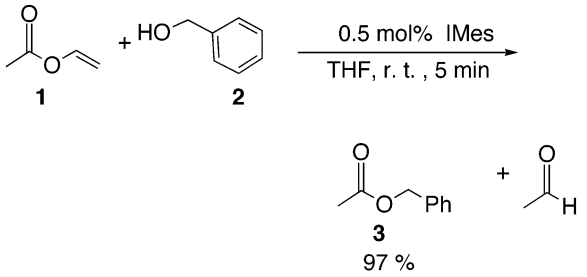
phines. Our expertise with NHC and the fact that transesterification of enol esters can be effected by basic tertiary phosphines such as PBu_3[2d] or iminophosphoranes[6] led us to attempt transesterification utilizing NHC. Indeed, as little as 0.5 mol % of the NHC IMes catalyzes the reaction of benzyl alcohol with vinyl acetate in THF, with almost quantitative conversion to benzyl acetate in 5 min at room temperature (Scheme 2).

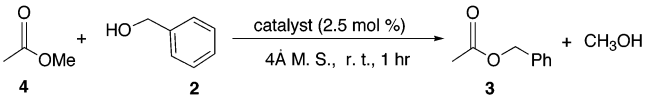
Scheme 2. IMes-Catalyzed Acylation of Benzyl Alcohol with Vinyl Acetate



On the basis of this promising result, the acylation of a commercially available and more challenging substrate, methyl acetate, was tested with different nucleophiles. To the best of our knowledge, this is the first report on the use of methyl acetate as an acylating agent. Two main factors were identified for biasing the reaction in the desired direction. First, 4 Å molecular sieves are required to absorb the liberated methanol. This use leads to quantitative conversion of benzyl alcohol to benzyl acetate in 1 h with 2.5 mol % of ICy (Table 1, entries 5 and 6). Second, the nature of the nucleophile also influences the efficacy of transesterification. Under similar conditions (2.5 mol % catalyst, 1 mL of methyl acetate, 1 h, molecular sieves), IMes afforded the product in 93% conversion, while IPr led to only a moderate conversion (possibly due to its steric bulk) (Table 1, entries 1 and 2). The corresponding aryl-substituted imidazolin-2-ylidenes, SIMes and SIPr, afforded the products in low conversion (Table 1, entries 3 and 4).[10] The alkyl-substituted ICy, I^{t}Bu, and IAd performed much better in the model reaction affording the product quantitatively (Table 1, entries 5, 7, and 8) presumably due to their higher nucleophilicity.[9a,11]

Strongly basic species such as DMAP,[2] DABCO,[12] and DBU[13] are not effective catalysts for the transesterification

Table 1. Transesterification of Methyl Acetate with Benzyl Alcohol Catalyzed by Various Nucleophiles



entry	catalyst	yield[a] (%)
1	IMes	93
2	IPr	45
3	SIMes	21
4	SIPr	21
5	ICy	100
6	ICy	84[b]
7	IAd	100
8	I^{t}Bu	100
9	DMAP	15
10	DABCO	45
11	DBU	24
12	NaH	95
13	KO^{t}Bu	95

[a] GC yield, average of two runs. [b] Molecular sieves were not used.

of methyl acetate with benzyl alcohol (Table 1, entries 9−11). 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.[1,14]

Once having established that the NHC represent excellent catalysts for the transesterification reaction of vinyl acetate/methyl acetate with benzyl alcohol, we investigated various substrates (Table 2). Geraniol **5** and cinnamyl alcohol **7** react rapidly with vinyl acetate in the presence of 1 mol % IMes to form the desired products quantitatively (Table 2, entries 1 and 2). Alcohols bearing acid-sensitive functional groups such as **9**[5] led to the corresponding acetate in very short reaction times and in the presence of only 0.5 mol % catalyst (Table 2, entry 3). Acrylic esters can be problematic substrates for the transesterification reaction due to undesirable side reactions such as isomerization or polymerization. Vinyl acrylate effectively acylated benzyl alcohol, albeit using a higher loading of the more active catalyst ICy (Table 2, entry 12).

The scope and generality of this method was also expanded to the readily available methyl esters. The use of methyl acetate effected not only the transesterification of benzyl alcohol in excellent yield (Table 2, entry 4), but also performed well in the reaction with the acid-labile alcohol **9**, affording the product **10** in 90% isolated yield (Table 2, entry 5). Ethyl acetate, used commonly as solvent, also underwent efficient transesterification with benzyl alcohol. The ethyl alcohol generated in the course of the reaction was removed from the equilibrium using 5 Å molecular sieves (Table 2, entry 11).

The deprotection of methyl esters usually requires severe reaction conditions; therefore, their conversion to benzyl

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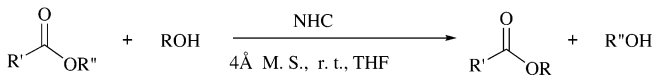
Table 2. ICy-Catalyzed Transesterification of Various Esters and Alcohols



entry	ester	aclohol	product	cat/mol%	time(min)	yield(%)[e]
1	**1**	**5**	**6**	IMes/1.0	60	99[a]
2	**1**	**7**	**8**	IMes/1.0	15	96[a]
3	**1**	**9**	**10**	IMes/0.5	15	100[a]
4	**4**	**2**	**3**	ICy/2.5	60	95[b]
5	**4**	**9**	**10**	ICy/2.5	30	90[b]
6	**11**	**2**	**12**	ICy/2.5	30	95[c]
7	**13**	**2**	**14**	ICy/2.5	15	96[c]
8	**15**	**2**	**16**	ICy/2.5	180	97[c]
9	**17**	**2**	**18**	ICy/2.5	30	99[c]
10	**19**	**2**	**3**	ICy/2.5	30	94[d]
11	**19**	**7**	**8**	ICy/2.5	60	93[c]
12	**20**	**2**	**21**	ICy/5	15	95[a]

[a] 1 mmol of alcohol, 1.2 mmol of vinyl acetate, 0.5−1 mol % of IMes, 1 mL of THF, room temperature. [b] 1 mmol of alcohol, 1 mL of methyl acetate, 2.5 mol % of ICy, 0.5 g of 4 Å molecular sieves, room temperature. [c] 1 mmol of methyl ester, 2 mmol of benzyl alcohol, 1 mL of THF, 2.5 mol % of ICy, 0.5 g of 4 Å molecular sieves, room temperature. [d] 1 mmol of alcohol, 1 mL of ethyl acetate, 2.5 mol % of ICy, 0.5 g of 5 Å molecular sieves, room temperature. [e] Isolated yield, average of two runs.

esters, which are easily cleaved under mild conditions, is desirable.[15] To prove the efficacy of the present system in performing such a transformation, various alkyl and aryl methyl esters were converted in high yield and short reaction time to their benzyl homologues (Table 2, entries 6−9).

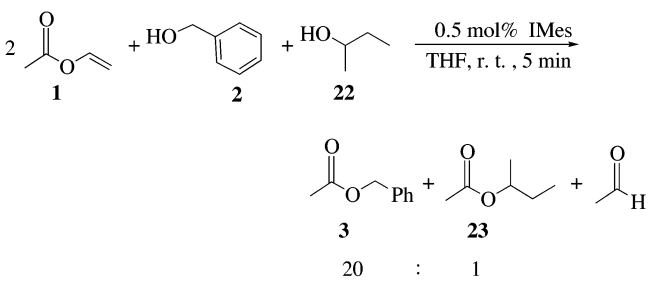
Activated substrates such as *p*-nitro-substituted compounds can be problematic due to the involvement of this functionality in side reactions.[13] Nonetheless, methyl *p*-nitrobenzoate **13** was converted to the corresponding benzyl ester **14** in excellent yield in only 15 min in the presence of 2.5 mol % ICy (Table 2, entry 7). Sterically hindered, acidic, and α,*β*-unsaturated methyl esters underwent clean reaction with benzyl alcohol under our standard conditions (Table 2, entries 6, 8, and 9).

Efficient selectivity of primary over secondary alcohols is important for an acylation catalyst to be useful in organic synthesis. Selective protection of primary alcohols has been achieved using organometallic systems such as distannoxane/enol ester[5] or $Sc(OTf)_3/Ac_2O$.[16] Transesterification selectivity under our standard reaction conditions with respect to primary alcohols was confirmed by the substantially lower activity 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 (Scheme 3).

We were able to expand the scope and applicability of this method by synthesizing the haloalkyl methacrylate monomer **26**, which serves as a building block for the synthesis of anticholesteremic haloalkyl methacrylate polymer. The synthesis of monomer **26** was originally achieved by the transesterification of methyl acrylate with bromoundecanol using $Ti(O^iPr)_4$ as catalyst.[17] However, this metal-catalyzed reaction, performed neat, requires an oxygen atmosphere and refluxing temperature. When ICy was used as catalyst and vinyl methacrylate as acylating agent, the target monomer **26** was obtained in 90% isolated yield at room temperature after a reaction time of 15 min (Scheme 4). This metal-free catalyzed process represents a clear advantage over $Ti(O^iPr)_4$-catalyzed reaction in terms of reaction rate, reaction conditions, and workup procedure.

In conclusion, NHC are excellent nucleophilic catalysts for transesterification/acylation reactions. Unsaturated NHC are very efficient organic catalysts for the transesterification of various enol esters with primary alcohols. Selectivity experiments reveal that when enol esters are used as

Scheme 3. IMes-Catalyzed Selective Acylation of Benzyl Alcohol



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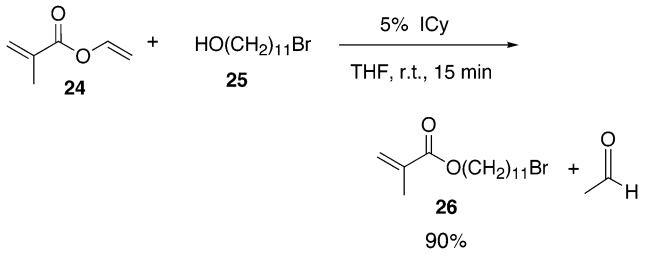
Scheme 4. Synthesis of Haloalkylmethacrylate Monomer



substrates, primary alcohols can be acylated efficiently over secondary alcohols in the presence of the IMes catalyst. Moreover, methyl and ethyl esters can be activated for the transesterification of various primary alcohols with the aid of the more nucleophilic alkyl-substituted NHC. The generality of this transformation and the tolerance of this catalyst family were tested in the synthesis of a haloalkyl methacrylate monomer, the building block for the anticholesteremic haloalkyl methacrylate polymer. Further explorations into the uses of this NHC catalyst family in organic transformations as well as mechanistic investigations focusing of the mode of action of the NHC catalyst in transesterification and related reactions are ongoing.

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

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