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Transesterification/Acylation of Secondary Alcohols Mediated by *N*-Heterocyclic Carbene Catalysts

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Abstract: *N*-Heterocyclic carbenes (NHC) are efficient catalysts for transesterification/acylation reactions involving secondary alcohols. The catalytic transformations are carried out employing low catalyst loadings in convenient reaction times at room temperature.

The ester moiety is a common functional group in polymers, drugs, and biologically relevant compounds. In addition, the ester functionality serves as a protecting group for alcohols.[1] Preparation of esters may be achieved through reactions of alcohols with carboxylic acids or more effectively by ester interchange[2] or by transesterification,[3] where generally a methyl ester reacts with an alcohol to form a new ester and methanol.

Lewis acidic or basic catalysts have been used as either catalysts or promoters to mediate this reaction. However, Lewis acid catalysts[2] exhibit low substrate selectivity and can cleave sensitive functional groups such as acetals, dienes, and epoxides. They may also lead to formation of side products and deterioration of primary products during the prolonged reaction times.[4] Utilizing strongly basic catalysts such as sodium hydride and potassium *tert*-butoxide leads to high conversions, but the use of such species is problematic for base-sensitive substrates,[2,3] while the weaker tertiary phosphine bases are toxic and expensive. Therefore, with either acidic or basic conditions, such transesterification reactions do not prove to proceed efficiently under mild reaction conditions.[5] Organometallic catalysts such as $Cp^*_2Sm(thf)_2$[6] and distannoxanes,[7] or the basic iminophosphoranes[8] require high catalyst loadings and long reaction times to achieve this transformation. There have been continued efforts to find efficient metal-free catalysts to mediate this transformation in order to provide an environmentally friendly solution that could be carried out under mild reaction conditions.

The *N*-heterocyclic carbenes (NHC) have been shown to act as excellent phosphine mimics.[9] Not only do they possess comparable or better donating properties[9,12c] than most phosphines, but NHCs are neither toxic nor pyrophoric. NHCs were first discovered by Wanzlick[10] in the 1960s, while the isolation and utilization of stable NHCs by Arduengo occurred some 20 years later.[11] In terms of reactivity, NHCs behave as nucleophiles owing to their lone electron pair.[12] The versatility of NHCs has been established in reports demonstrating their role as efficient catalysts in the ring-opening polymerization of lactones,[13] in mediating the benzoin condensation,[14] and in multicomponent reactions.[15] Recent work has established the vast scope of NHCs and their derivatives in terms of their stabilizing effect in organometallic systems.[16]

We and the Hedrick group, simultaneously, reported the use of various alkyl- and aryl-substituted imidazol-2-ylidene carbenes as efficient transesterification/acylation reaction catalysts.[17] Here, we wish to report the use of the same imidazolium-based system for the transesterification/acylation of a variety of secondary alcohols, further establishing the versatility and utility of NHCs for such transformations.

The acylation of commercially available alcohols with varied electronic and steric properties was carried out using a simple protocol (Table 1). All entries in Table 1 reached completion in 1 h, and reported isolated yields are for reactions reaching complete conversion. The reaction of 2-propanol with methyl acetate yields the

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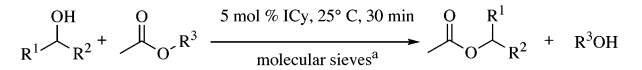
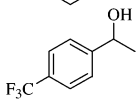
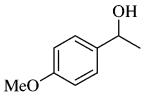
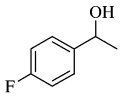
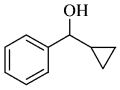
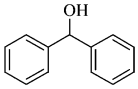
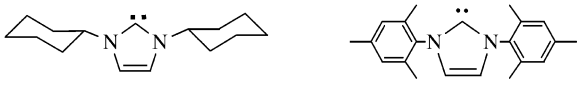
TABLE 1. ICy-Catalyzed Acylation of Secondary Alcohols[e]



entry	alcohol	% yield (MeOAc)[b]	% yield (EtOAc)[b]
1		85[d]	68[d]
2		94	87
3		93 (93)[c]	75 (76)[c]
4		75 (96)[c]	45 (93)[c]
5		85	76 (98)[c]
6		88 (88)[c]	74 (96)[c]
7		81 (96)[c]	66 (93)[c]
8		92 (86)[c]	56 (86)[c]

[a] MeOAc, 4 Å; EtOAc, 5 Å. [b] GC yields after 30 min (isolated yields in parentheses). [c] Isolated yields after 1 h, reported yields an average of two runs. [d] ICy, 10 mol %. [e] Reaction conditions: 1 mmol of alcohol, 1 mL of acetate, 0.5 g of molecular sieves.

SCHEME 1. Some NHC Transesterication Catalysts



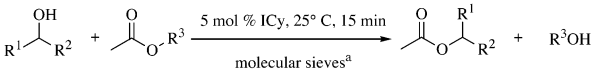
ICy **IMes**

acylated product in 85% yield after 30 min (Table 1, entry 1), with 10 mol % of ICy (ICy = 1,3-bis(cyclohexyl)-imidazol-2-ylidene) (Scheme 1). The presence of a phenyl group in the substrate improves the yield to 93% in 30 min and can be performed using only 5 mol % catalyst (Table 1 entry 3).

Variation of the para aryl substituent did not show any significant electronic effect on reaction times and yields (Table 1, entries 4−6). The presence of a cyclopropyl ring is fully compatible with the methodology (Table 1, entry 7). The presence of two aryl substituents on the alcohol (benzhydrol) does not affect the catalytic activity and lead to a 92% conversion in 30 min (entry 8).

Reactions were also carried out with ethyl acetate as the acylating agent. All reactions followed the same trends as with methyl acetate but led to slightly lower yields presumably owing to the poorer leaving group capabilities of the ethoxy group compared to the methoxy functionality.

TABLE 2. Acylation of Aliphatic Cyclic Alcohols[d]



entry	alcohol	% yield (MeOAc)[b]	% yield (EtOAc)[b]
1		96	92 (97)[c]
2		93	85 (70)[c]
3		67	47
4		10	5
5		9	5

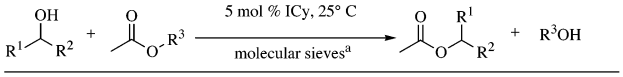
[a] MeOAc, 4 Å; EtOAc, 5 Å. [b] GC yields (isolated yields in parentheses). [c] Isolated yields after 30 min, reported yields an average of two runs. [d] Reaction conditions: 1 mmol of alcohol, 1 mL of acetate, 0.5 g of molecular sieves.

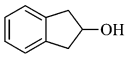
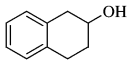
The cyclic alcohols, cyclopentanol and cyclohexanol, gave nearly quantitative yields in 15 min (Table 2 entries 1 and 2). A limited study focusing on steric effects illustrates that increasing the steric bulk at the α position to the hydroxy group greatly hinders reaction rates.

This sterically driven rate retardation is fully illustrated when examining 2- and 2,6-substituted substrates. The minimally hindered substrate, 2-methylcyclohexanol, reaches near completion in 2 h, while reactions depicted in entries 4 and 5 reach maximum conversion in *2 and 3 days, respectively!* (*rac*)2,6-Dimethylcyclohexanol and (*rac*)2-*tert*-butylcyclohexanol show conversions of only 35% and 27%, respectively, in 120 min. 2-Methylcyclohexanol shows conversion of 92% in 120 min. Again, similar sluggish conversion trends were observed for all acylations carried out with ethyl acetate as the acylating agent. The proximity effect of the hydroxyl group to an aryl group fused to a cyclic alcohol was examined (Table 3). Reaction of 1-indanol and 2-indanol with methyl acetate afforded products in 87% and 92%, respectively (Table 3, entries 1 and 2). Both substrates reach complete conversion in 15 min. The use of 1,2,3,4-tetrahydro-1-naphthol and 1,2,3,4-tetrahydro-2-naphthol as substrates afforded the desired products after 2 h in 91% and 80%, respectively (Table 3, entries 3 and 4). The two products were isolated after allowing the reaction to reach completion (3 h).

Using the described protocol, the acylation is slightly slower in the case of secondary alcohols as compared to primary alcohols. In most cases, reactions reach completion between 15 min and 3 h. The acylated products were isolated after reactions reached completion. We have reported isolated yields in parentheses, while the reported GC yields correspond to yields reached in the time given in the respective tables. This is done to allow a

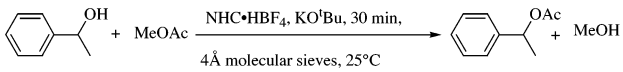
TABLE 3. Acylation of Aromatic Cyclic Alcohols[e]

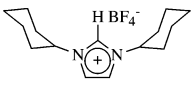
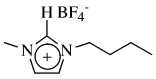


entry	alcohol	min	yield (MeOAc)[b]	yield (EtOAc)[b]
1		5	87 (91)[c]	76 (89)[c]
2		5	92 (92)[c]	82 (91)[c]
3		120	91 (89)[d]	82 (99)[d]
4		120	80 (94)[d]	92 (92)[d]

[a] MeOAc, 4 Å; EtOAc, 5 Å. [b] GC yields (isolated yields in parentheses). [c] Isolated yields after 15 min. [d] Isolated yields after 3 h, reported yields an average of two runs. [e] Reaction conditions: 1 mmol of alcohol, 1 mL of acetate, 0.5 g of molecular sieves.

TABLE 4. Acylation Utilizing NHC Generated in Situ[b]



catalyst (NHC)	catalyst loading	% yield[a]
	10 mol %	60
	5 mol %	80

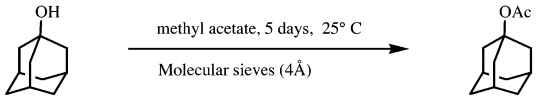
[a] GC yields. [b] Reaction conditions: 1 mmol of *sec*-phenethyl alcohol, 1 mL of methyl acetate, 0.5 g of molecular sieves, 0.9 equiv of KO^{t}Bu per NHC·HBF$_4$.

comparison between different substrates. Most reactions are however quite rapid.

The isolation of NHCs is complicated by their sensitive nature. The NHCs bearing small substituents on the nitrogens are usually prone to dimerization. Hence, we explored the reactivity of NHC generated *in situ* from the corresponding NHC·HBF$_4$ salts in the acylation of *sec*-phenethyl alcohol with methyl acetate (Table 4). The *in situ*-generated ICy was less reactive than its isolated counterpart, giving 60% conversion after 30 min using 10 mol % of the imidazolium salt precursor. The same reaction was carried out utilizing the *in situ*-generated carbene from BMIM·HBF$_4$ (BMIM = 1-butyl-3-methylimidazolium). The use of commercially available ionic liquid allows reactions to reach an 80% conversion in 30 min with 5 mol % catalyst (Table 4). This protocol using the ionic liquid and an *in situ* generation of its NHC represents a very user-friendly and convenient method for achieving transesterification. The yields of various transesterification reactions using the *in situ* route from BMIM·HBF$_4$ are in general very good to excellent.

We have carried out the *in situ* formation of carbenes with substoichiometric amounts of alkoxide since alkoxide alone could possibly mediate some of the acylation reactions investigated. This supports our claim that

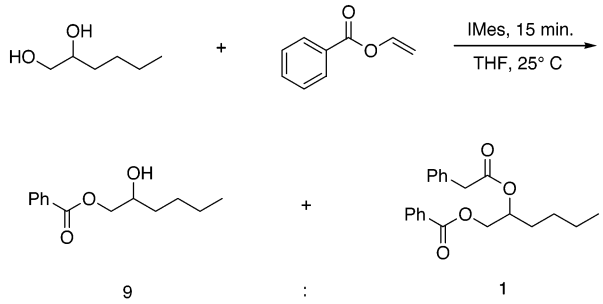
TABLE 5. Acylation of a Tertiary Alcohol[c]



Entry	Catalyst	Catalyst Loading (mol%)	% yield[a]
1	ICy	5	NR
2	ICy	10	NR
3	ICy	10	NR[b]
4	ICy	20	54
5	NaO^{t}Bu	1	10
6	NaO^{t}Bu	5	33
7	KO^{t}Bu	5	35

[a] GC yields, reported yields an average of two runs. [b] 60 °C. [c] Reaction conditions: 1 mmol of 1-adamantanol, 1 mL of MeOAc, 0.5 g of molecular sieves.

SCHEME 2. Selective Acylation of a Diol



acylation of the alcohols in our systems is indeed an effect of the free carbene, rather than of the alkoxide.

Reaction of a tertiary alcohol, 1-adamantanol, with methyl acetate required significantly higher catalyst loading to reach isolable amounts of product. The reaction does not proceed with 5−10% ICy at room temperature or at 60 °C (Table 5 entries 1−3). With 20% ICy the reaction leads to 54% conversion at room temperature in 5 days! The same reaction conducted with 1 mol % NaO^{t}Bu does not show more than 10% conversion after 5 days. Higher alkoxide loadings do not lead to more than 33% product formation in 5 days. Use of KO^{t}Bu as catalyst does not give much different results, as the reaction reaches 35% conversion in the same time period (Table 5, entry 7). The NHC is superior to the NaO^{t}Bu-catalyzed reaction, hinting at a nucleophilic rather than a basic mediated process.

Selectivity in acylation of primary alcohols over secondary alcohols is of prime concern to natural product synthesis. We were able to achieve some selectivity, under our conditions. Esterification of 1,2-hexanediol (1 mmol) was carried out with vinyl benzoate (0.9 mmol) in the presence of the less nucleophilic IMes (IMes = bis-(1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene)) (Scheme 2). Catalyst loading was reduced to 0.5 mol %. The

reaction reaches completion in 15 min with 9:1 conversionin favor of monoacylated product. The product was isolated in 86% yield.

In summary, the scope of the application of NHCs as transesterification catalysts has been expanded to now include secondary alcohols. A protocol based on the *in situ* generation of NHC has been developed and has proven very user-friendly. Selectivity of primary over secondary alcohol protection has been demonstrated. Specific issues dealing with the mechanism at play in this catalytic transformation are presently being examined.

Experimental Section

Transesterification of Esters with Alcohols. Procedure A: Esterification of Alcohols with Methyl Acetate. Under an atmosphere of argon 1 mmol of alcohol and 1 mL of methyl acetate or ethyl acetate were added sequentially to a screw cap vial loaded with 5 mol % *N*,*N*-dicyclohexylimidazole-2-ylidene (ICy) and 0.5 g of 4 Å molecular sieves (5 Å for ethyl acetate). The resulting mixture was stirred at room temperature for the indicated time; the solvent (methyl acetate) excess was evaporated, and the residue was purified by flash chromatography using ethyl acetate/hexanes mixtures.

Procedure B: Esterification of Alcohols with in Situ Generation of Catalyst. The same procedure is followed for both catalyst precursors. Under an atmosphere of argon, 1 mL of methyl acetate was added to a screw cap vial loaded with indicated amounts of imidazolium salt and base. The mixture is stirred for 15 min. Then 1 mmol of alcohol and 0.5 g of 4 Å molecular sieves were added. The resulting mixture was stirred at room temperature for the indicated time; the solvent (methyl acetate) excess was evaporated, and the residue was purified by flash chromatography using ethyl acetate/hexanes mixtures.

Procedure C: Esterification of Diol with Vinyl Benzoate. Under an atmosphere of argon 1 mmol of diol and 0.9 mmol of vinyl benzoate were added sequentially to a screw cap vial loaded with 5 mol % *N*,*N*-dicyclohexylimidazole-2-ylidene and THF. The resulting mixture was stirred at room temperature for the indicated time; the solvent (methyl acetate) excess was evaporated, and the residue was purified by flash chromatography using ethyl acetate/hexanes mixtures.

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Supporting Information Available: Experimental details and characterization data including ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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