

Metal-Catalyzed Acyl Transfer Reactions of Enol Esters: Role of $Y_5(O^iPr)_{13}O$ and $(thd)_2Y(O^iPr)$ as Transesterification Catalysts

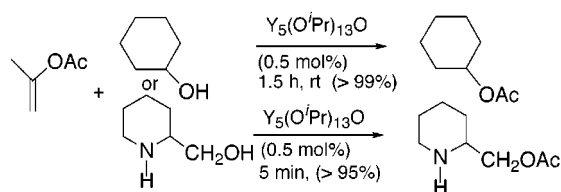
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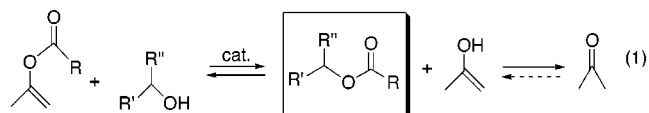
ABSTRACT



Primary and secondary alcohols react with vinyl or isopropenyl acetate at room temperature in the presence of catalytic amounts (0.05–1 mol %) of $Y_5(O^iPr)_{13}O$ to give the corresponding esters. In selected cases, the yttrium catalyst promotes the selective *O*-acylation of amino alcohols without the formation of the amide. Enol esters also react with α -amino acid esters in the absence of a catalyst, at room temperature, to give the corresponding amides.

Esters and amides occupy a central role in synthetic organic chemistry both as protecting groups and as key intermediates in functional group transformations. New, highly efficient and stereoselective methods for the synthesis of these ubiquitous functional groups continue to evolve. In this context, two of the most significant recent advances have been in the use of better acyl transfer agent/catalyst combinations¹ and the discovery of new protocols for effecting kinetic resolution of secondary alcohols.² For the synthesis of esters from alcohols and anhydrides, trimethylsilyl triflate appears to be the catalyst of choice, if no selectivity between various

kinds of alcohols (for example, primary vs secondary, or alcohol vs phenol) is the goal.^{1a} Otera^{1b} found that dioxane reagent **1** is an excellent catalyst for the synthesis of primary alcohol esters using vinyl esters as acylating agents. Acylation of alcohols and amines using enol esters can also be effected by $Cp^*_2Sm(thf)_2$,^{1c} even though the need for a catalyst for a primary amide formation from amines and vinyl esters is questionable.^{1e} Exploratory studies in search of a well-defined transition metal catalyst that could improve the efficiency and selectivity of the known transesterification processes using vinyl esters (eq 1) led us to yttrium



alkoxides³ including the pentameric yttrium aggregate $Y_5-(\mu_5-O)(\mu_3-O^iPr)_4(\mu_2-O^iPr)_4(O^iPr)_5$, generally formulated as

(1) (a) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, 63, 2342 and references therein. (b) Orita, A.; Mitsutome, A.; Otera, J. *J. Org. Chem.* **1998**, 63, 2420. (c) Ishii, Y.; Takeno, M.; Kawasaki, Y.; Muromachi, A.; Nishiyama, Y.; Sakaguchi, S. *J. Org. Chem.* **1996**, 61, 3088. (d) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, 61, 4560. (e) Kabouche, Z.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1991**, 32, 5359. (f) Degueil-Castaing, M.; De Jeso, B.; Drouillard, S.; Maillard, B. *Tetrahedron Lett.* **1987**, 28, 953. (g) See also: Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

(2) (a) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, 121, 5813 and references therein. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, 119, 1492 and references cited therein. (c) Kawabata, T.; Nagato, M.; Takasu, K.; Fujii, K. *J. Am. Chem. Soc.* **1997**, 119, 3169. (d) Yokomatsu,

T.; Arakawa, A.; Shibuya, S. *J. Org. Chem.* **1994**, 59, 3506. (e) Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, 34, 5563. (f) Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, 110, 7200.

$Y_5(O^iPr)_{13}O$.⁴ A careful examination of the literature suggests that in several structurally characterized yttrium complexes alkoxide ligands are particularly susceptible to exchange (a necessary feature if high turnovers in transacylations is the ultimate goal), while other chelating ligands such as β -diketonates are more robust.^{3d-f} The latter might provide a stereochemically well-defined coordination environment for our eventual goal of exploring stereospecific processes such kinetic resolution and desymmetrization with these catalysts.

In scouting experiments, isopropenyl acetate was treated with benzyl alcohol, 1-methylbenzyl alcohol (1-phenylethanol), and cyclohexanol in the presence catalytic amounts of $Y_5(O)(O^iPr)_{13}$ (**2**) and $(^iPrO)Y(thd)_2$ (thd = 2,2,6,6-tetramethyl-3,5-heptanedionato) (**3**).^{3d} The results are shown in

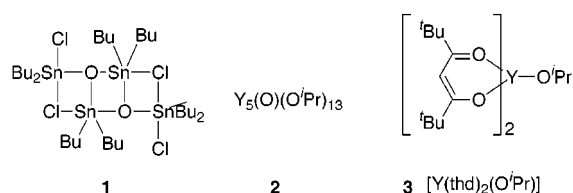


Table 1 (entries 1–5). Typically the reaction is done in neat enol ester with 0.5 mol % of the catalyst at room temperature.

Table 1. Transesterifications Catalyzed by Y Complexes^a

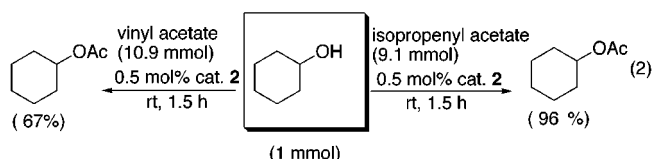
no.	alcohol	cat. S/C ^b	time (h)	convn ^c
A. Reactions with Isopropenyl Acetate				
1	benzyl alcohol	2 , 200	1	>99
2	1-phenylethanol	2 , 118	1.5	>99
3	cyclohexanol	2 , 217	1.5	>95
4	1-Ph-1,2-ethanediol	2 , 100	1.5	>99
5	<i>E</i> -cinnamyl alcohol	2 , 200	0.16	>99
Stoichiometric Reactions Using Catalyst 2				
6	benzyl alcohol	2 , 50	7	89
7	1-phenylethanol	2 , 50	27	73
8	<i>t</i> -butanol	2 , 50	96	0
Stoichiometric Reactions Using Catalyst 3				
9	benzyl alcohol	3 , 50	14	98
10	1-phenylethanol	3 , 50	20	84
11	<i>t</i> -butanol	3 , 50	96	0
B. Reactions with Vinyl Acetate				
12	<i>E</i> -cinnamyl alcohol	2 , 2000	48	72
13	benzyl alcohol	2 , 2000	24	96
14	benzyl alcohol	2 , 200	0.08	92

^a Entries 1–5 carried out in neat isopropenyl acetate (1 mL, 9.1 mmol/ mmol of substrate) at rt. Entries 12–14 carried out in neat vinyl acetate. Entries 6–11 carried out with a 1:1 molar ratio of the reagents in benzene (2 mL/mmol) at rt. ^b S/C = substrate-to-catalyst ratio. ^c Conversions were determined by GC or NMR.

Under these conditions, isopropenyl acetate gave essentially quantitative yields of the esters. The reaction can also be done with stoichiometric amounts of the reagents in a hydrocarbon solvent if higher catalyst loading and longer reaction times are employed (entries 6–11). Under these conditions, thd complex **3** is also a very effective catalyst.

Primary alcohols react faster than secondary alcohols, while tertiary alcohols are unreactive under these conditions. Vinyl acetate (Table 1, entries 12, 13, and 14 and eqs 2, 5, and 7) is an exceptionally fast acylating agent, and benzyl and cinnamyl alcohols are converted into the corresponding acetates with as little as 0.0005 equiv of complex **2** (substrate/catalyst ratio = 2000, entries 12 and 13). *Such catalytic efficiency for acyl transfer reactions is unprecedented.* With 0.005 equiv of catalyst **2**, the reaction between benzyl alcohol and vinyl acetate is virtually over in about 5 min. The recovery of the product in most cases involves evaporation of the excess enol ester and distillation or simple filtration through a column of silica gel.

In the reactions of cyclohexanol, we observed that isopropenyl acetate consistently gave cleaner reactions and better conversions and yields as compared to vinyl acetate (eq 2). This may be related to catalyst deterioration caused



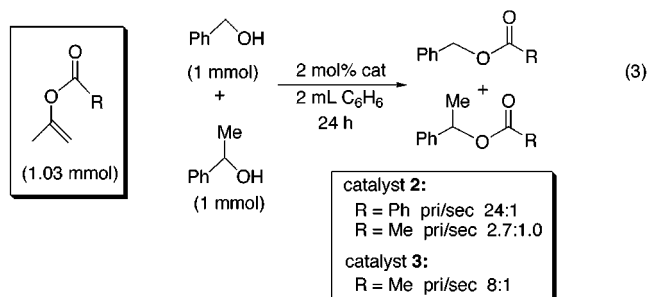
by the acetaldehyde side product in the case of vinyl acetate, especially when the acylation itself is sluggish.

When a mixture of benzyl alcohol and 1-methylbenzyl alcohol was reacted with 10.8 equiv of vinyl acetate in the presence of 0.24 mol % of **2**, in 5 min 100% of the primary alcohol and 25% of the secondary alcohol were esterified. The selectivity can be improved dramatically (>24:1) when isopropenyl benzoate (~1 equiv in benzene) is used as the acylating agent (eq 3). The catalyst also appears to have an effect on the primary vs secondary selectivity. A marked difference in acetylation of primary vs secondary hydroxyl groups was noted when isopropenyl acetate (1 equiv) was employed with catalyst **3** (selectivity 2.7:1 for **2** vs 8:1 for **3**).

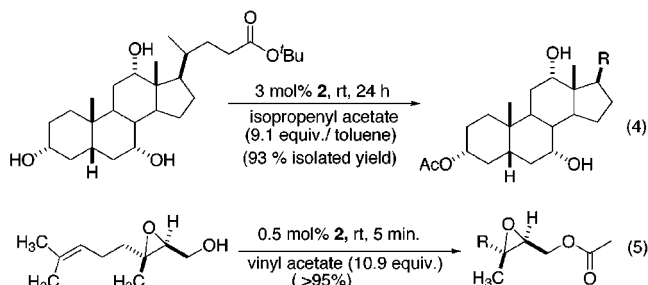
Selectivity for a primary alcohol in 1,2-diols is good to moderate. For example, in the acylation of 1-phenyl-1,2-ethanediol, the diacetate is formed in competition with the

(3) Other alkoxides investigated include $Y(OCH_2CH_2NMe_2)_3$, $SmI_2 \cdot THF$, $Ti(O^iPr)_4$, $[N[(CH_2CH(CH_3)O)_3]Ti^{IV}Cl]$, $[N[(CH_2CH(CH_3)O)_3]Zr^{IV}Cl]$, $Zr(O^iPr)_4$, $Hf(O^iPr)_4$, $Nb(OC_2H_5)_5$, $V(O)(O^iPr)_3$, $Ta(OC_2H_5)_5$, $Eu(tfc)_3$, $tfc = tris[3-(trifluoromethylhydroxymethyl)camphorato]$, $Pr(tfc)_3$, $Y(thd)_3$ (thd = tris(2,2,6,6-tetramethyl-3,5-heptanedionato), $La(thd)_3$, and $Yb(thd)_3$. The alkoxides were added at a 2 mol % loading level to a mixture (1:1) of 1-phenylethanol and isopropenyl acetate dissolved in 2 mL of benzene- d_6 , and the reaction was followed by GC and NMR. For synthetic applications of Y-alkoxides, see: (a) Anwander, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: New York, 1996; p 866. (b) Abiko, A.; Wang, G. *J. Org. Chem.* **1996**, *61*, 2264. (c) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1021. (d) McLain, S. J.; Drysdale, N. E. U.S. Patent 5028667; McLain, S. J.; Drysdale, N. E. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1992**, *33*, 463. (e) Ford, T. M.; McLain, S. J. U.S. Patent 5208297; *Chem. Abstr.* **1993**, *119*, 140012. (f) Ford, T. M.; McLain, S. J. U.S. Patent 5292859; *Chem. Abstr.* **1994**, *121*, 58221.

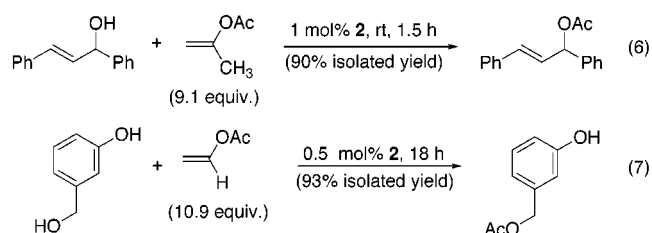
(4) (a) Mazdiyasi, K. S.; Lynch, C. T.; Smith, J. S. U.S. Patent 3278571, 1966; *Chem. Abstr.* **1966**, *65*, 20008b. (b) Poncelet, O.; Sartain, W. J.; Hubert-Pfalzgraf, L. G.; Folting, K.; Caulton, K. G. *Inorg. Chem.* **1989**, *28*, 263. (c) Coan, P. S.; Hubert-Pfalzgraf, L. G.; Caulton, K. G. *Inorg. Chem.* **1992**, *31*, 1262.



primary acetate if excess isopropenyl acetate is present (100% diacetate with 1 mol % of catalyst **2** in 1.5 h, entry 4, Table 1). With a stoichiometric amount of isopropenyl acetate and 0.5 mol % of catalyst, approximately 7:1 selectivity for the monoacetate can be achieved at 78% conversion (10 h). Exquisite selectivity for the acylation of an equatorial hydroxyl group was realized in the reaction of *tert*-butyl cholate (eq 4).

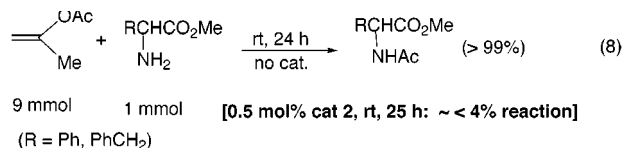


Functional group compatibility of Lewis acidic Y-alkoxides³ is a potential concern in this chemistry. However, quantitative acylation of relatively sensitive electrophilic substrates such as cinnamyl alcohol (Table 1, entry 5), 2,3-epoxygeraniol (eq 5), and 1,3-diphenylallyl alcohol (eq 6) suggests that such fears maybe unfounded. Acylation of phenols is relatively slow under these conditions. It is therefore possible to achieve excellent selectivity for the reaction at the benzyl hydroxyl group in the acylation of 3-hydroxybenzyl alcohol (eq 7) even in the presence of excess of isopropenyl acetate. This chemoselectivity is the same as that observed with Sc(OTf)₂.^{1d}

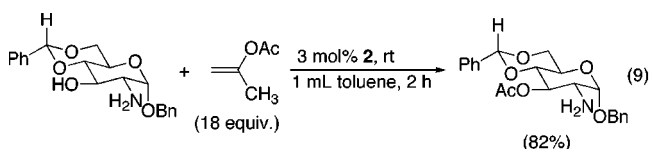


Enol esters have been reported to react with primary amines in the *absence* of catalysts.^{1e} It has also been reported that α -amino esters (and secondary amines) are unreactive without a catalyst (such as KCN) in the formation of a peptide bond. We were therefore surprised to find that phenylglycine and phenylalanine esters readily reacted with

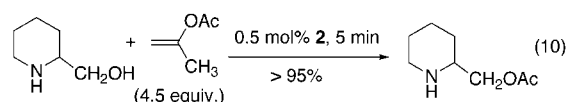
neat isopropenyl acetate (9 equiv) at room temperature, giving a quantitative yield of the expected amides (eq 8).⁵



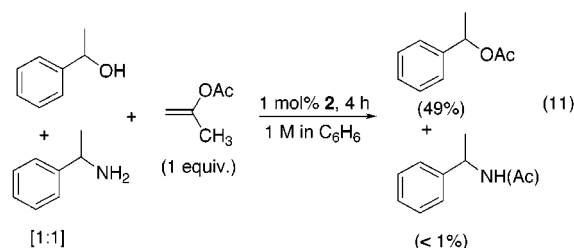
Gratifyingly, no epimerization at the α -position occurs under the reaction conditions (the ee's of products determined by chiral GC, under conditions where the limit of detection is $\pm 0.2\%$). Remarkably, there was little reaction in the *presence* of 0.5 mol % of catalyst **2**.⁶ This serendipitous observation raises the prospects of unprecedented functional group transformations, for example, *selective acylation of an alcohol in the presence of an amine*. We are just beginning to address this issue, and a few such examples are shown below. A very good yield (82%) of *O*-acylation can be realized when benzyl 2-amino-2-deoxy-4,6-di-*O*-phenylmethyl- α -D-glucopyranoside (0.5 mmol) is treated with 2 mL of isopropenyl acetate and 3 mol % of catalyst **2** at room temperature for 2 h (eq 9). The corresponding allose



derivative (-OH, axial) gave a mixture of *N*- and *O*-acyl compounds, presumably via *O* \rightarrow *N* acyl migration. Selective *O*-acylation of 2-piperidinemethanol (eq 10) is another example. Very little of the *N*-acyl derivative was formed in both reactions.



A stoichiometric mixture of 1-phenylethanol, 1-phenylethylamine, and isopropenyl acetate (1 equiv of each) in benzene quantitatively converts the alcohol (>49% of the reaction mixture) to the acetate (eq 11). Less than 0.8% (GC)



(5) Admittedly, the failed reactions were carried out with 1 M reagents in ethyl acetate with stoichiometric amount of enol ester (ref 1e). In benzene under these conditions 55% conversion was observed.

of the reaction mixture is the *N*-acyl derivative. The only amine-derived product in this mixture identified by GCMS (~19% of the reaction mixture) and NMR⁷ is the corresponding acetone imine which, upon aqueous workup, reverts back to the amine.

As we explored the scope of this reaction, some limitations have been uncovered. Tertiary alcohols are not acylated by any of the reagents discussed. Formation of side products and deterioration of primary products are observed if prolonged reaction times are needed, especially when vinyl acetate, which liberates acetaldehyde in the medium, is used as the acyl transfer agent. A number of polyhydroxylic compounds, especially carbohydrates (e.g., phenyl β -D-glucopyranoside, D-arabino-1,4-lactone, 1,2-dideoxy-4,6-*O*-benzylidene-D-arabinohexopyranose), gave a complex mixture of products with no apparent selectivity with the two vinyl esters tried. Secondary amines such as diisopropylamine and pseudoephedrine also do not react under these acylation conditions. Additional functional group compatibility of the two reagents **2** and **3** must also await further studies.

In summary, a highly efficient method for the acylation of primary and secondary alcohols using vinyl esters as acylating agents in the presence of catalytic amounts of a readily available^{4b} yttrium alkoxide is reported. In many cases

the reaction can be carried out with no solvents and the recovery of the products involves no more than a simple filtration through silica gel or direct distillation from the reaction flask. Selectivity between different kinds of hydroxyl groups can be controlled by stoichiometry, by structure of the vinyl ester, and, at least in one demonstrated case, by the nature of the yttrium catalyst. Since functionalized vinyl esters are readily available from Ru-catalyzed reactions of carboxylic acids and enol esters or acetylenes,⁸ a number of other applications of this chemistry can be envisioned. We are currently exploring the expanded scope of the metal-catalyzed transesterification reactions.

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Supporting Information Available: Experimental procedures for transformations described in Table 1 and eqs 2 and 4–11. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(6) We have no satisfactory explanation for this unusual observation, which is limited to α -amino acid esters. It is likely that the reaction of the amino group with an enol ester is catalyzed by an acid and the Y-alkoxide acts as a scavenger for acidic impurities.

(7) Identified by the following characteristic peaks: ¹H NMR 1.38 (d, *J* = 6.6 Hz, 3 H), 1.85 (s, 3H), 2.03 (s, 3 H), 4.55–4.62 (q, *J* = 6.6 Hz, 1 H), 7.1–7.4 (m, aromatic); ¹³C NMR (inter alia 18.50, 24.49, 29.37, 59.16, 165.80); GCMS *m/z* 161 (*M*⁺), 146 (*M*⁺ – CH₃), 105 (*M*⁺ – C₃H₆N).

(8) (a) Waller, F. J. Transvinilation catalysts for the production of higher vinylic esters of vinyl acetate. In *Catalysis of Organic Reactions*; Kosak, J. R., Johnson, T. A., Eds.; Marcel Dekker: New York, 1994; p 397. (b) Rupp, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1986**, 27, 6323. (c) Murray, R. E. U.S. Patent 5430179, 1995; *Chem. Abstr.* **1995**, 123, 313396. (d) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, 52, 2230. (e) Rotem, M.; Shvo, Y. *Organometallics* **1983**, 2, 1689.