JOC*Note*

Direct Atom-Efficient Esterification between Carboxylic Acids and Alcohols Catalyzed by Amphoteric, Water-Tolerant $TiO(acac)_2$

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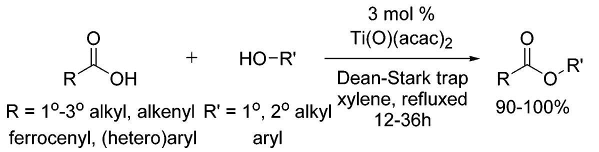

A diverse array of oxometallic species were examined as catalysts for a test direct condensation of benzoic acid and 2-phenylethanol in 1:1 stoichiometry. Besides group IVB $MOCl_2-xH_2O$ and $TiOX_2-xH_2O$, group VB $VOCl_2-x$THF and group IVB $TiO(acac)_2$ were found to be the most efficient and water-tolerant catalysts for the test reaction. The new neutral catalytic protocol with the optimal $TiO(acac)_2$ tolerates many stereo/electronic structural variations in both (di)acid (1°−3° alkyl and aryl) and (di)alcohol (1°, 2° alkyl, and aryl) components with high chemoselectivity.

The esterification of carboxylic acids with different functionalized alcohols is one of the most important and commonly used transformations in organic synthesis. Several methods have been well documented in the literature.[1] Conventionally, the direct condensation process was carried out with excess loading of limited acid-tolerant reagent classes in the presence of strong acid activators (e.g., sulfuric acid, boric acid,[2] and solid superacid).[3] In addition, several effective Lewis acid catalysts such as Ti(IV)[4] and Sn(IV)[5] salts were reported where environmental (moisture sensitive, corrosive, or toxic) concerns are waiting to be addressed. For eco-friendly chemistry, one should avoid the use of excess reagents or high catalyst loadings. Recent elegant works by Yamamoto and co-workers presented group IVB $HfCl_4$ and $ZrCl_4$ and the corresponding alkoxide species for direct esterification with equimolar amounts (i.e., atom-efficient) of both substrates.[6] For the past three years, we have identified several water-tolerant vanadyl and other oxometallic species as recoverable, amphoteric catalysts for nucleophilic acyl substitutions (NAS) of anhydrides[7a,b] and methyl esters[7c] (including transesterification) with protic nucleophiles (alcohols, amines, and thiols) with high functional group compatibility and chemoselectivity, Scheme 1. In continuation of our related works in catalysis,[8] herein we report a new air and moisture stable, environmentally benign protocol for the target atom efficient, direct esterification catalyzed by the VOX_2 and $TiOX_2$ family.

After extensive survey of various oxometallic species through the periodic table, several group IVB MOX_2 and VOX_2 species were identified to be suitable catalysts for the atom-efficient direct esterification. A model reaction between 1-phenylethanol and benzoic acid in refluxed xylene with removal of water by Dean−Stark apparatus was further chosen in view of its sensitive character to oxidation or dehydration. By varying the catalyst loadings, we found that 1−3 mol % is optimal for efficiency comparison. Among six hydrated oxometallic chlorides and triflates examined, the catalytic efficiency follows the trend of Zr > Hf > V > Ti[9] (entries 1, 2, 4, 6, 8, and 10, Table 1).[10] Notably, the ligands also play a role on the catalyst activity. Vanadyl THF complexes (entries 9 and 11) are about 1.5−2 times more reactive than the corresponding hydrate complexes (entries 8 and 10). In marked contrast, oxohafnium and oxozirconium THF complexes (entries 5 and 7) are 1.5−1.6 times less reactive than the corresponding hydrate complexes (entries 4 and 6). Overall, only $ZrOCl_2-8H_2O$, $HfOCl_2-8H_2O$, $VOCl_2-x$THF, and $TiO(acac)_2$ led to satisfactory conversions (80−97%) in 42 h. Furthermore, $TiO(acac)_2$

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(9) (a) $TiO(OTf)_2-xH_2O$ and $TiOCl_2-xH_2O$ were prepared by mixing $TiO(SO_4)-xH_2SO_4-xH_2O$ with $Ba(OTf)_2$ and $BaCl_2$, respectively, in MeOH.

(10) (a) The uses of $ZrOCl_2-8H_2O$ and $HfOCl_2-8H_2O$ for atom efficient direct esterification were reported very recently.[10b] Nevertheless, 1-phenylethanol was not studied. (b) Nakayama, M.; Sato, A.; Ishihara, K.; Yamamoto, H. *Adv. Synth.*, *Catal.* **2004**, *346*, 1275.

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SCHEME 1. Oxometallic Species-Catalyzed NAS of Methyl Esters and Anhydrides by Protic Nucleophiles

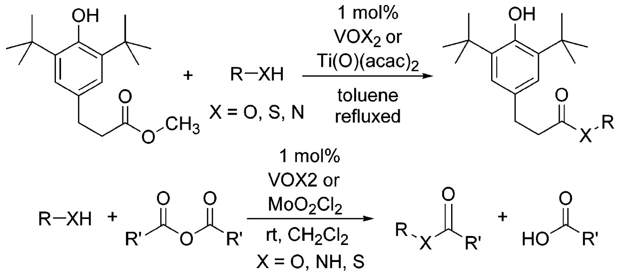
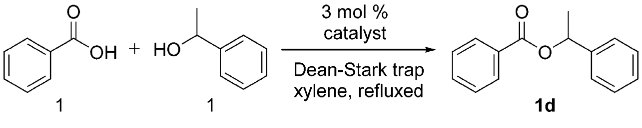


TABLE 1. Effects of Oxometallic Species and Ligands on the Direct Condensation of 1-Phenylethanol and Benzoic Acid



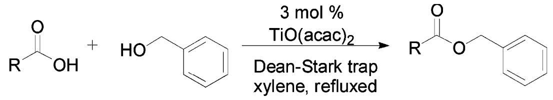
entry	MO_mX_n	time, h	yield, %
1	$TiOCl_2{-}xH_2O$	42	43
2	$TiO(OTf)_2{-}xH_2O$	42	35
3	**$TiO(acac)_2$**	**36**	**97**
4	**$ZrOCl_2{-}8H_2O$**	**42**	**90**
5	$ZrOCl_2{-}x$THF[b]	42	60
6	**$HfOCl_2{-}8H_2O$**	**42**	**85**
7	$HfOCl_2{-}x$THF[b]	42	52
8	$VO(OTf)_2{-}xH_2O$[a]	42	40
9	$VO(OTf)_2{-}x$THF[b]	42	60
10	$VOCl_2{-}xH_2O$[a]	42	40
11	**$VOCl_2{-}x$THF[b]**	**42**	**80**

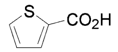
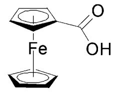
[a] These hydrate species may contain some ligated MeOH since the preparations were carried out in MeOH. [b] Prepared from the corresponding hydrate in refluxed THF.

was shown to be the most effective one, leading to complete formation of 1-phenylethyl benzoate in 97% yield in 36 h. Notably, although $TiO(acac)_2$ has been employed for catalytic oxidation, reduction, and transesterification reactions,[7c,11] there was no literature precedence regarding its catalytic use in the direct atom-efficient condensation between acids and alcohols.

The versatility of the new catalytic protocol by $TiO(acac)_2$ was illustrated by its application to a wide range of carboxylic acids. In all cases, the atom-efficient direct esterification of six representative carboxylic acids with a given 1° benzyl alcohol (Table 2) proceeded smoothly in excellent yields (92−100%) in 12−36 h. The current protocol is suitable to acid substrates such as ferrocene carboxylic acid (quasiaromatic), benzoic acid (aromatic), thiophene-2-carboxylic acid (heteroaromatic), cinnamic acid and crotonic acid (α,β-unsaturated), and 2-bromophenylacetic acid (aliphatic). The acid substrate activity follows the order of β-aryl-α,β-unsaturated acid (entry 4) > 1°, 2°-aliphatic (entry 6 in Table 2 and entry 9 in Table 4) ≥ aryl (entries 1, 2) > quasiaromatic (entry 3) > $R_2C{=}CH$ (entry 5) and 3° aliphatic (entry 11 in Table 4). The steric hindrance of the carboxylic acid slows down the reaction.

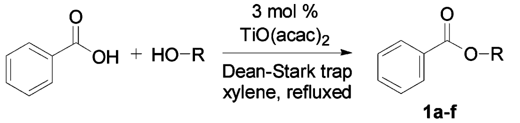
TABLE 2. The Effects of Acid Substrates on the Direct Condensation with Benzyl Alcohol Catalyzed by $TiO(acac)_2$

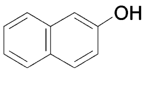


entry	$R{-}CO_2H$[a]	time, h	yield,[b] %
1	$PhCO_2H$	15	100 (**1a**)
2		24	96 (**2**)
3		24	92 (**3**)
4	$PhCH{=}CHCO_2H$	12	95 (**4**)
5	$(CH_3)_2C{=}CHCO_2H$	36	93 (**5**)
6	$2{-}BrC_6H_4CH_2CO_2H$	15	95 (**6**)

[a] One equivalent of acid was used unless otherwise stated. [b] Isolated yields after column chromatography.

TABLE 3. The Effects of Alcohols on the Direct Condensation with Benzoic Acid Catalyzed by $TiO(acac)_2$



entry	R-OH[a]	time, h	yield,[b] %
1	$PhCH_2OH$	15	100 (**1a**)
2	$Ph(CH_2)_2OH$	15	100 (**1b**)
3	$HO(CH_2)_3OH$	15	92 (**1c**)
4	$PhCH(CH_3)OH$	36	97 (**1d**)
5	$4{-}MeOC_6H_4OH$	18	85 (**1e**)
6		36	100 (**1f**)

[a] One equivalent of alcohol was used unless otherwise stated. [b] Isolated yields after column chromatography.

To explore the generality and scope of the direct condensation, the reaction was further studied with various primary, secondary, and aromatic alcohols under the optimal conditions (Table 3). The reactions proceed cleanly and the resultant esters **1a**−**f** were obtained in high yields (85−100%). In general, the reaction rates follow the trend of primary alcohols (entries 1−3) > phenol (entry 5) > 2° (entry 4) ~ 2-naphthol (entry 6). The reactions with 2° alcohols (e.g., 36 h in entry 4) are about 2.5 times slower than those with primary alcohols (15 h, entries 1−3). 4-Methoxyphenol (entry 5, 18 h) reacts 2 times faster than 2-naphthol (entry 6, 36 h) presumably due to inductive activation exerted by the 4-methoxy group.

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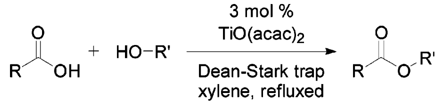
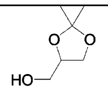
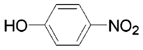
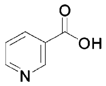
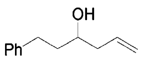
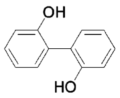
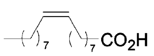
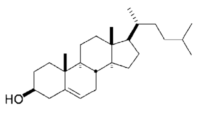
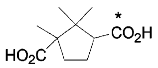
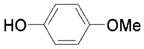
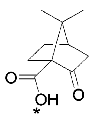
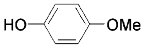
TABLE 4. Direct Esterification and Chemoselective Esterification with Functionalized Substrates Catalyzed by TiO(acac)$_2$



entry	R-CO$_2$H^a	HO-R'^{a}	time, h	yield,^{b} %
1	PhCO$_2$H		16	95 (**7**)
2	4-MeOC$_6$H$_4$CO$_2$H		34	90 (**8**)
3		HO(CH$_2$)$_4$OTHP	12	95 (**9**)
4	Ph(CH$_2$)$_2$CO$_2$H	HO(CH$_2$)$_4$OTBS	12	95 (**10**)
5	Ph(CH$_2$)$_2$CO$_2$H	HOCHPh$_2$	30	90 (**11**)
6	Ph(CH$_2$)$_2$CO$_2$H		38	91 (**12**)
7	CH$_3$(CH$_2$)$_4$CO$_2$H		100	91 (**13**)
8			36	100 (**14**)
9	PhCH(OH)CO$_2$H	HOCH$_2$Ph^c	18	75 (**15**)
10^d			30	91 (**16**)
11^d			36	93 (**17**)
12	HO$_2$C(CH$_2$)$_4$CO$_2$H	HO(CH$_2$)$_2$O(CH$_2$)$_2$OH	23	95 (**18**)

[a] One equivalent of alcohol was used unless otherwise stated. [b] Isolated yields after column chromatography. [c] 1.1 equiv of alcohol was used. [d] The asterisk signifies the reactive site.

To gain insight into functional group compatibility, a variety of substituted alcohols, phenols, and different acids were further applied, Table 4. The new direct condensation protocol tolerates acid-sensitive acetonide (entry 1), tetrahydropyrenyl (THP) ether (entry 3), *tert*-butyldimethylsilyl (TBS) ether (entry 4), and nitro (entry 2), pyridine (entry 3), alkene (entries 6 and 8), and ketone (entry 11) functionalities. Phenols with electron-donating groups (entry 5, Table 3) react faster than those bearing electron-withdrawing groups (e.g., entry 2, Table 4). Primary alcohol (entry 4) reacts 2.5–3 times faster than secondary alcohols (entries 5 and 6) with 3-phenylpropionic acid. Surprisingly, 2,2′-biphenol (a aromatic diol) also reacts smoothly with hexanoic acid to give ester-**13** in 91% yield albeit with prolonged reaction time (4 days, entry 7).

By taking advantage of the significant rate differences among 1° and 2° alcohols, direct esterification works chemoselectively for the hydroxyl-containing mandelic acid (entry 9) with 1° benzyl alcohol (1.1 equiv) along with about 6% of self-polymerization byproduct. The steric hindrance of a carboxylic acid also plays a crucial role in the chemoselective esterification of camphoric acid with 4-methoxyphenol (entry 10). The reaction occurs exclusively at the acid site bearing a 2° alkyl group. To our surprise, ketopinic acid bearing a 3° alkyl group next to the acid unit and a ketone group reacts smoothly with 4-methoxyphenol to provide ester-**17** in 93% yield (entry 11). Direct esterification of aromatic 1,4-dicarboxylic acid with a diol was sluggish due to its poor solubility even in hot xylene. Nevertheless, polycondensation between the aliphatic adipic acid and the aliphatic diethylene glycol was achieved in essentially quantitative yield (entry 12).

In conclusion, we have documented a new catalytic protocol by using an oxometallic type TiO(acac)$_2$ as an efficient and chemoselective catalyst for the direct esterification between an equimolar amount of carboxylic acids and alcohols of varying steric and electronic demands in refluxed xylene. The details of the catalytic pathway and applications to products of industrial interest are currently under investigation.

Experimental Section

General Procedure for the Direct Condensation between Acids and Alcohols. In a dry 25-mL, two-necked, round-bottomed flask equipped with a Dean–Stark trap topped with a reflux condenser was added acid (1.0 mmol), alcohol (1.0 mmol), and TiO(acac)$_2$ (3 mmol %) in anhydrous xylene (10 mL). The reaction mixture was heated until completion of the reaction as monitored by TLC analysis. The reaction mixture was then gradually cooled to room temperature and quenched with saturated aqueous NaHCO$_3$ solution (5 mL) then extracted with CH$_2$Cl$_2$ (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (anhydrous MgSO$_4$), filtered, and evaporated to give a crude product that was purified by column chromatography on silica gel.

Acknowledgment. We thank the National Science Council of Taiwan for generous financial support of this research.

Supporting Information Available: Spectral data for all end products and ^{1}H and ^{13}C NMR spectra for all the products **1a**–**f** and **2**–**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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