JOC*Article*

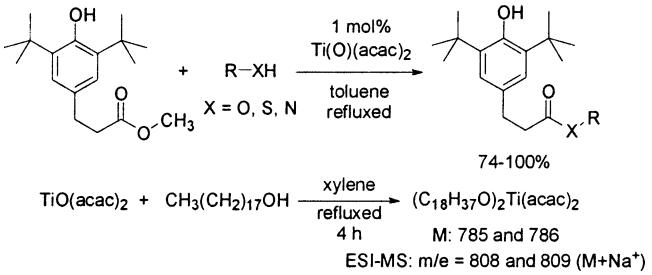
# Nucleophilic Acyl Substitutions of Esters with Protic Nucleophiles Mediated by Amphoteric, Oxotitanium, and Vanadyl Species

Chien-Tien Chen,* Jen-Huang Kuo, Cheng-Hsiu Ku, Shiue-Shien Weng, and Cheng-Yuan Liu

*Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan 11650*

*chefv043@scc.ntnu.edu.tw*

*Received August 30, 2004*




A diverse array of oxometallic species were examined as catalysts in nucleophilic acyl substitution (NAS) reactions of methyl (or ethyl) esters with protic nucleophiles. Among them, oxotitanium acetylacetonate ($TiO(acac)_2$) and vanadyl chloride ($VOCl_2-(THF)_x$) served as the most efficient and water-tolerant catalysts. Transesterifications of methyl and/or ethyl esters with functionalized (including acid- or base-sensitive) 1° and 2° alcohols can be carried out chemoselectively in refluxed toluene or xylene in a 1:1 substrate stoichiometry using 1 mol % catalyst loading. The resultant products were furnished in 85−100% yields by simple aqueous workup to remove water-soluble catalysts. The new NAS protocol is also amenable to amines and thiols in 74−91% yields, albeit with higher loading (2.5 equiv) of protic nucleophiles. Representative examples of commercial interests such as Padimate O and antioxidant additives for plastics were also examined to demonstrate their practical applications. A 1:1 adduct between $TiO(acac)_2$ and a given 1-octadecanol was identified as $(C_{18}H_{37}O)_2Ti(acac)_2$ and was responsible for its subsequent NAS of methyl esters.

## Introduction

Nucleophilic acyl substitutions of methyl and/or ethyl esters with functionalized alcohols represent one of the most important transformations in organic synthesis in view of their diverse and practical utilities in functional molecules and polyesters of industrial interest.[1] A general protocol to effect such transformation often requires a readily removable stoichiometric or catalytic promoter. The currently available catalysts to promote the NAS of esters by alcohols are diverse and are mainly based on (1) Brønsted mineral acids ($H_3PO_4$, $H_2SO_4$, HCl)[2] and organic (*p*-TSA[3]) acids, (2) alkali (NaOR[4] and KOR[5]) or alkaline earth (ROMgBr[6]) metal alkoxides, (3) Lewis bases (DMAP,[7] DBU,[8] and imidazolinium carbenes[9]), (4) Lewis acids ($BX_3$,[10] $AlCl_3$,[11] and $Al(OR)_3$[12]), and (5) tin ($Bu_3BuOR$[13,14], palladium,[15] and titanium alkoxides/chloride).[16,17] Despite the fact that these existing catalytic systems can effect such a transformation with high conversion, long-lasting issues such as (1) use of a large

(1) (a) Otera, J. *Chem. Rev.* **1993**, *93*, 1449. (b) Otera, J. *Esterification: Methods, Reactions, and Applications*; Wiley Europe: 2003.

(2) (a) Rehberg, C. E.; Fisher, C. H. *J. Am. Chem. Soc.* **1944**, *66*, 1203. (b) Rehberg, C. E.; Faucette, W. A.; Fisher, C. H. *J. Am. Chem. Soc.* **1944**, *66*, 1723. (c) Rehberg, C. E. *Org. Synth.* **1955**, *3*, 146. (d) Hagenmeyer, H. J., Jr.; Hull, D. C. *Ind. Eng. Chem.* **1949**, *41*, 2920. (e) DeWolfe, R. H. *Synthesis* **1974**, 153.

(3) Rothman, E. S.; Hecht, S. S.; Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1972**, *37*, 3551.

(4) (a) Taft, R. W., Jr.; Newman, M. S.; Verhoek, F. H. *J. Am. Chem. Soc.* **1950**, *72*, 4511. (b) Billman, J. H.; Smith, W. T., Jr.; Rendall, J. L. *J. Am. Chem. Soc.* **1947**, *69*, 2058.

(5) (a) Reimer, M.; Downes, H. R. *J. Am. Chem. Soc.* **1921**, *43*, 945. (b) Rossi, R. A.; de Rossi, R. H. *J. Org. Chem.* **1974**, *39*, 855.

(6) Frank, R. L.; Davis, H. R., Jr.; Drake, S. S.; McPherson, J. B., Jr. *J. Am. Chem. Soc.* **1944**, *66*, 1509.

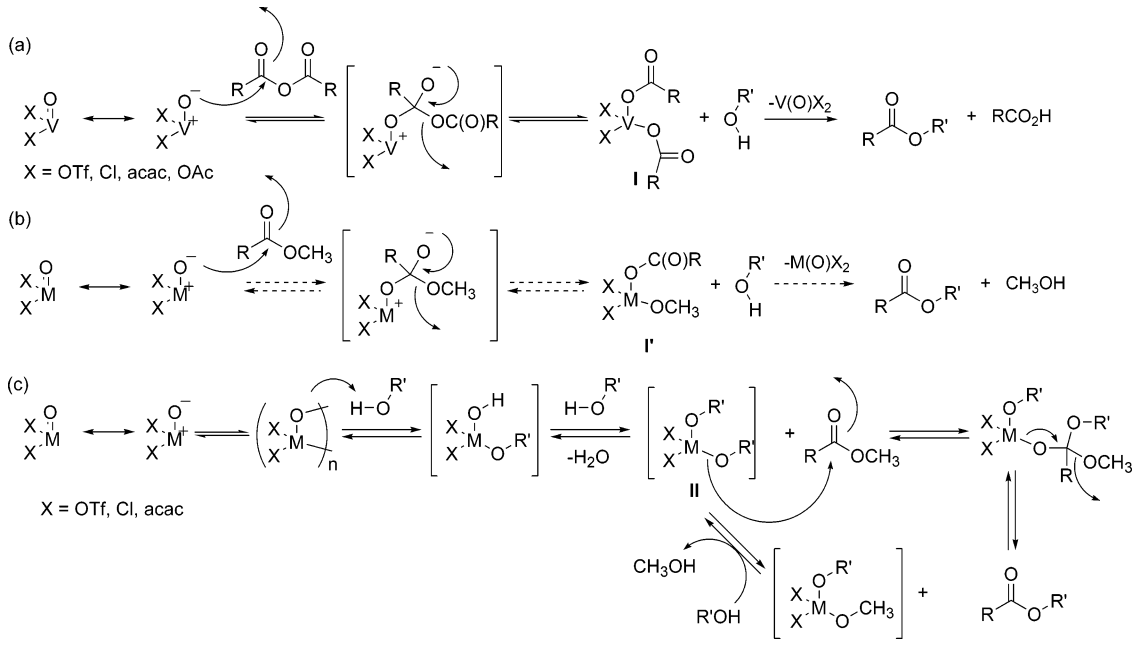
(7) (a) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618. (b) Mottet, C.; Hamelin, O.; Garavel, G.; Deprés, J.-P.; Greene A. E. *J. Org. Chem.* **1999**, *64*, 1380.

(8) Seebach, D.; Thaler, A.; Blaser, D.; Ko. S. Y. *Helv. Chim. Acta* **1991**, *74*, 1102.

(9) For N-heterocyclic carbenes, see: (a) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583. (b) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587. (c) Grasa, G. A.; Güveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *68*, 2812. (d) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209.

10.1021/jo0484878 CCC: $30.25 
Published on Web 01/22/2005

**SCHEME 1**[a]




[a] Reaction a: Equilibrium between an amphoteric vanadyl species and an anhydride in catalytic acylation with an alcohol. Reaction b: Putative equilibrium between an oxometallic species and a methyl ester in catalytic transesterification with an alcohol. Reaction c: Proposed equilibrium between a polymeric oxometallic species and an alcohol in catalytic transesterification with a methyl ester.

excess of alcohols or esters, (2) employment of higher catalyst loadings, and (3) environmental issues associated with the organotin compounds remain to be fully solved. Therefore, the requests for designing a new, ideal, amphoteric catalyst that meets the criteria of (1) atom economy (1:1 substrate stoichiometry), (2) easy recovery of catalyst, (3) environmental benignity (air and moisture stable, neutral, and water soluble), (4) and broad functional group compatibility and high chemoselectivity (substrate scope) remain a challenge.

**Background.** Previously, we have discovered that various neutral and water-soluble vanadyl species can serve as efficient catalysts to promote the NAS of anhydrides with various functional, protic nucleophiles at ambient temperature.[18] We have also determined that the V=O unit in vanadyl species is amphoteric in nature and serves to activate an anhydride to form a vanadyl dialkanoate intermediate, responsible for the subsequent NAS event with a protic nucleophile, Scheme 1a. As part of our ongoing program toward the uses of vanadyl and oxometallic species in new catalytic reactions,[19] we thought to explore their catalytic profiles in the NAS of methyl or ethyl esters with alcohols and other protic nucleophiles. So far, di-*n*-butyltin oxide was the only documented oxometallic species examined as the catalyst (10 mol %) to trigger the NAS of functionalized esters with alcohols (e.g., MeOH, EtOH, and *i*-PrOH) as solvents.[20] In addition, vanadyl(IV) acetate was also found to catalyze (13.5 mol %) the NAS of methyl acetoacetate with alcohols in refluxed toluene in 45−98% yields.[21] One can envision that the direct NAS-like activation of methyl esters by oxometallic species is unlikely even at elevated temperatures due to the direct involvement of a methoxy anion migration in a neutral or even acidic medium, Scheme 1b. On the other hand, oxometallic species may condense with 2 equiv of an alcohol with extrusion of $H_2O$ to generate dialkoxide **II**, which would further react with a methyl ester in NAS fashion leading to the transesterification product, Scheme 1c. A brief mechanistic study to support the latter scenario for $TiO(acac)_2$-mediated catalysis was also carried out.

## Results and Discussion

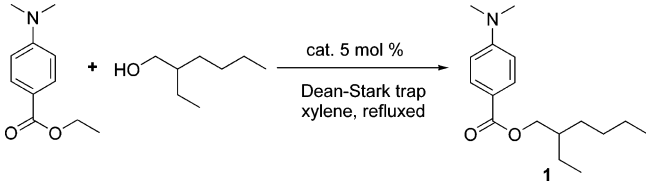
**Screening of Oxometallic Species.** NAS (i.e., transesterification) of ethyl 4-dimethylaminobenzoate by 2-eth-

(10) Yazawa, H.; Tanaka, K.; Kariyone, K. *Tetrahedron Lett*. **1974**, 3995.
(11) Blossey, E. C.; Turner, L. M.; Neckers, D. C. *Tetrahedron Lett*. **1973**, 1823.
(12) (a) Kunz, H.; Waldmann, H. *Angew. Chem., Int. Ed. Engl*. **1983**, *22*, 62. (b)Waldmann, H.; Kunz, H. *J. Org. Chem*. **1988**, *53*, 4172.
(13) (a) Pereyre, M.; Colin, G.; Delvigne, J.-P. *Bull. Soc. Chim. Fr*. **1969**, 262. (b) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett*. **1986**, *27*, 2383. (c) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem*. **1991**, *56*, 5307. (d) Otera, J.; Ioka, S.; Nozaki, H. *J. Org. Chem,* **1989**, *54*, 4013.
(14) For perfluoro-tin oxides, see: Xiang, J.; Toyoshima, S.; Orita, A.; Otera, J. *Angew. Chem., Int. Ed. Engl*. **2001**, *40*, 3670.
(15) (a) Kubota, M.; Yamamoto, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 146. (b) Kim, Y.-J.; Osakada, K.; Takenaka, A.; Yamamoto, A. *J. Am. Chem. Soc*. **1990**, *112*, 1096.
(16) (a) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, D.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138. (b) Imwinkelreid, R.; Schiess, M.; Seebach, D. *Org. Synth*. **1987**, *65*, 230.
(17) For Group IV B, see: Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140.
(18) (a) Chen, C.-T.; Kuo, J.-H.; Li, C.-H.; Barhate, N. B.; Hon, S.-W.; Li, T.-W.; Chao, S.-D.; Liu, C.-C.; Li, Y.-C.; Chang, I.-H.; Lin, J.-S.; Liu, C.-J.; Chou, Y.-C. *Org. Lett*. **2001**, *3*, 3729. (b) Chen, C.-T. US patent #: 6541659 B1, 2003. (c) Chen, C.-T.; Lin, J.-S.; Kuo, J.-H.; Weng, S.-S.; Cuo, T.-S.; Lin, Y.-W.; Cheng, C.-C.; Huang, Y.-C.; Yu, J.-K.; Chou, P.-T. *Org. Lett*. **2004**, *6*, 4471.
(19) (a) Hon, S.-W.; Li, C.-H.; Kuo, J.-H.; Barhate, N. B.; Liu, Y.-H.; Wang, Y.; Chen, C.-T. *Org. Lett*. **2001**, *3*, 869. (b) Barhate, N. B.; Chen, C.-T. *Org. Lett*. **2002**, *4*, 2529.
(20) Giannis, A. *Angew. Chem., Int. Ed*. **2001**, *40*, 3672.

yl-1-hexanol was first examined with a series of Group IVb and Group VIb oxometallic species (5 mol %) since the test ester substrate is less reactive and more challenging due to the electron-donating nature of the 4-amino unit. In addition, several oxometallic species in their highest oxidation states exhibit strong oxidizing character toward alcohols (e.g., $VO(OR)_3$[22] or $CrO_2Cl_2$[23]) or to polymerize aniline derivatives.[24] Furthermore, it tends to be demethylated by Lewis/Brønsted acid catalysts and the targeted product, Padimate O, is useful as a major commercial UV absorber for sunblocks.[25] It was found that only Group IVb oxotitanium species, including chloride, triflate, and acetylacetonate (i.e., $TiOCl_2$,[26] $TiO(OTf)_2$, and $TiO(acac)_2$[27]), were able to achieve clean conversions (entries 1−3, 18−70 h, 95−98% yields) and were far more efficient than the Group VIb ones (entries 16−21, 96 h, 10−59% yields) when the test reactions were carried out in refluxed xylene, Table 1. In addition, the fourth period $TiOCl_2$ and $CrO_2Cl_2$ are 6 times and 2 times more effective, respectively, than the corresponding sixth period $HfOCl_2$ and $WO_2Cl_2$ (compare entries 1 and 18 with entries 5 and 21).[28] In turn, both sixth period $HfOCl_2$ and $WO_2Cl_2$ are about 2−4 times more effective than the fifth period $ZrOCl_2$ and $MoO_2Cl_2$ (compare entries 5, 17, and 21 with entries 4, 16, and 19). Notably, the trend is somewhat similar to the one obtained by using Group IVb $MCl_4$ (i.e., Ti > Hf) as the catalyst for NAS of esters by alcohols as demonstrated by Yamamoto and co-workers.[29] The effect of counteranion on the catalyst efficiency follows the trend of basicity (i.e., triflate < Cl < acac, entries 1−3 and 19−20). Dioxometallic chlorides and the corresponding oxometallic ones are not suitable for the test reactions (entries 16, 17, 19, and 21) due to their high oxidation powers. Therefore, the best NAS reaction protocol comes ultimately to the use of $TiO(acac)_2$ as the catalyst (18 h, 98%).

Since both the freshly made ($TiOCl_2$ and $TiO(OTf)_2$) and commercial group IVb ($ZrOCl_2$, $HfOCl_2$) species are either ligated by MeOH and/or by $H_2O$ (hydrated), the extent of ligation greatly alters their structures. However, the majority of these compounds are polymeric in nature (particularly in $ZrOCl_2$ species) and bear only M−O single bonds. The great difference of reactivity of Ti species could be the result of differing mechanisms. However, in the case with $TiO(acac)_2$, the mechanism proposed in Scheme 1c is the most probable on the basis of the preference of Ti to form polymeric single Ti−O and on the very low acidity of the compound.

**TABLE 1. Effects of Oxometallic Species and Ligands on the NAS of Ethyl 4-Dimethylaminobenzoate by 2-Ethyl-1-hexanol**




| entry | $MO_mX_n$ | time, h | yield, % |
|---|---|---|---|
| 1 | **IVb**: $TiOCl_2-(H_2O)_x$[a] | 50 (24) | 95 (50) |
| 2 | $TiO(OTf)_2-(H_2O)_x$[a] | 70 (24) | 97 (37) |
| 3 | $TiO(acac)_2$ | 18 | 98 |
| 4 | $ZrOCl_2-(H_2O)_x$ | 96 | 21 |
| 5 | $HfOCl_2-(H_2O)_x$ | 96 | 34 |
| 6 | **Vb**: $VO(OTf)_2-(H_2O)_x$[a] | 77 (24) | 96 (30) |
| 7 | $VO(OTf)_2-(THF)_x$[b] | 30 (24) | 94 (81) |
| 8 | $VOCl_2-(H_2O)_x$[a] | 78 (24) | 97 (33) |
| 9 | $VOCl_2-(THF)_x$[b] | 24 | 98 |
| 10 | $VO(OAc)_2-(H_2O)_x$[a] | 56 (24) | 97 (42) |
| 11 | $VO(acac)_2$ | 96 | 43 |
| 12 | $VO(OEt)_2$ | 96 | 11 |
| 13 | $NbOCl_2-(THF)_2$[c] | 96 | 22 |
| 14 | $VOCl_3/VCl_3$ | 96/96 | 43/28 |
| 15 | $VO(O\text{-}iPr)_3$ | 96 | 54 |
| 16 | **VIb**: $MoOCl_4/MoCl_5$ | 96/96 | 10/24 |
| 17 | $WOCl_4/WCl_6$ | 96/96 | 43/37 |
| 18 | $CrO_2Cl_2$ | 96 | 59 |
| 19 | $MoO_2Cl_2$ | 96 | 15 |
| 20 | $MoO_2(acac)_2$ | 96 | 42 |
| 21 | $WO_2Cl_2$ | 96 | 32 |
| 22 | $Re(O)_3CH_3$ | 96 | 5 |
| 23 | $Bu_2Sn(O)$ | 18 | 98 |
| 24 | | 96 | 0 |

[a] These hydrate species may contain some ligated MeOH since the preparations were carried out in MeOH. [b] Prepared form the corresponding hydrate in refluxed THF. [c] Prepared from $NbCl_4-(THF)_2$.

To our expectation, we have also discovered that the test reaction can be effected by the use of water-tolerant and -soluble vanadyl(IV) species.[30,31] In all cases except $VO(acac)_2$ and $VO(OEt)_2$, the NAS reactions were effective and clean in a reasonable period of time (24−78 h) and in 94−98% yields (entries 6−12). The effect of counteranion on the catalyst efficiency follows the trend of basicity only for OAc > Cl > OTf (entries 7 and 9; entries 6, 8, and 10). The conversion efficiency is reversed in the cases of $VO(acac)_2$ and $VO(OEt)_2$ (acac > OEt, entries 11 and 12). There also exists a significant ligand effect on the catalytic efficacy. In general, the THF-coordinated vanadyl species are at least two times more reactive than the corresponding hydrated species (entries 6−9). In marked contrast, the corresponding strongly oxidizing oxovanadium(V) and moisture-sensitive vanadium(III) species are far less effective (entries 14 and 15) as catalysts. The results indicate the participating roles of the amphoteric V=O and Ti=O units in our studies. Similar to the group IVb and VIb family, the fourth period $VOCl_2-(THF)_x$ is 18 times more efficient than the

(21) (a) Kantam, M. L.; Neeraja, V.; Bharathi, B.; Reddy, C. V. *Catal. Lett.* **1999**, *62*, 67. (b) See also: Chairgulprasert, V.; Drew, M. G. B.; Jahans, A.; Harwood, L. M. *Arkivoc* **2002**, *11*, 37.

(22) (a) Mota, S.; Abon, M.; Volta, J. C.; Dalmon, J. A. *J. Catal.* **2000**, *193*, 308. (b) Mota, S.; Volta, J. C.; Vorbeck, G.; Dalmon, J. A. *J. Catal.* **2000**, *193*, 319.

(23) San Filippo, J., Jr.; Chern, C.-I. *J. Org. Chem.* **1977**, *42*, 2182.

(24) Huguenin, F.; Torresi, R. M.; Buttry, D. A. *J. Electro. Soc.* **2002**, *149*, A546.

(25) (a) Reisch, M. S. *Chem. Eng. News* **2001**, *79* (49), 25. (b) Reisch, M. S. *Chem. Eng. News* **2002**, *80* (25), 38.

(26) (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.

(27) Grobe, J.; Zimmermann, H. *Z. Naturforsch. B: Anorg. Chem. Org. Chem.* **1984**, *39*, 808.

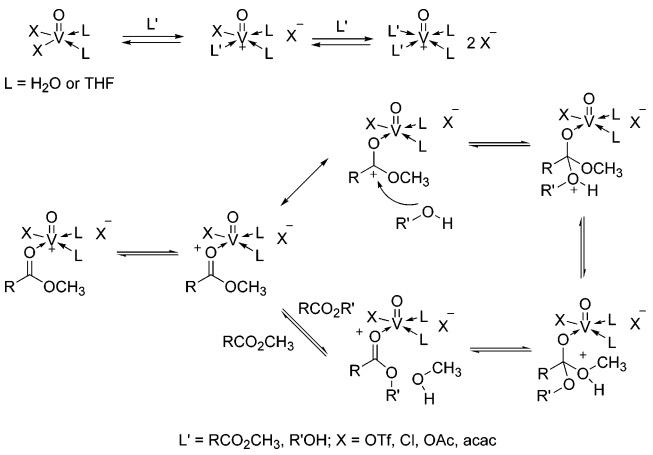
(28) (a) It has been noted that $TiCl_4$ is a more efficient catalyst than $ZrCl_4$ and $HfCl_4$ in mediating NAS of a methyl ester with a 1° alcohol: ref 17. (b) Significantly larger catalyst loadings (35−60%) were necessary for similar reactions catalyzed by $Ti(OR)_4$.

(29) (a) Ishihara, K.; Nakayama, M.; Ohara, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8179. (b) Ref 17.

(30) They are now commercially available from the institute.

(31) Vanadyl alcoholate, organic titanate, and polyhydric alcohol compositions have been patented as potential catalysts for NAS of methyl esters: Vogt, H. C.; Parekh, M.; Cenker, M.; Patton, J. T., Jr. U.S. Patent 4072631, 1978.

**SCHEME 2**




fifth period $NbOCl_2$−$(THF)_2$ (entries 9 and 13).[32] Therefore, $VOCl_2$−$(THF)_x$ is the most effective catalyst among all the Group Vb oxometallic species examined. Finally, methyltrioxorhenium (MTR), an excellent oxidation catalyst for olefins and sulfides,[33] was found not suitable for the NAS of ethyl esters.

On the basis of the results in the vanadyl series, the catalyst efficiency increases with increasing acidity only for the $VOX_2$ bearing the counteranion from a mild conjugate acid (HOAc > Hacac > HOEt). However, the trend is reversed with $VO(OTf)_2 \leq VOCl_2 < VO(OAc)_2$ (acidity: HTf > HCl > HOAc). Namely, the catalyst efficiency decreases with increasing acidity of the strong conjugate acid in the three cases. Besides the amphoteric reactivity proposal in Scheme 1c, the results indicate that the vanadyl species may also partially ionize during the reaction. The extent of ionization highly hinges on the propensity of the counterion. In this way, an ionized vanadyl species ($VOX^+$) may be coordinated better by a nucleophile, like the carbonyl oxygen in the ester, determining its polarized activation necessary for the subsequent addition of an alcohol molecule in a NAS event, Scheme 2. In addition, it is also known in the literature that the ionization of $VOX_2$ can be facilitated in the presence of alcohols.[34] For example, $VOCl_2$ attracts alcohols to form complex combinations such as $VOCl_2$−$(ROH)_3$ or $VOCl_2$−$(ROH)_4$ (some of the alcohol molecules can be replaced by THF). Due to an increased electron density on the vanadium center, the latter combination can easily lose chloride anion to form the corresponding vanadyl salt, even isolable as a crystal in the case of $[VOCl(i\text{-}PrOH)_4]^+Cl^-$. Although the ionization process is retrograded under the reaction conditions (i.e., in nonpolar solvents such as toluene or xylene), it could take place to a minor extent sufficient for catalysis.

The esters, which bear an $sp^2$ carbonyl oxygen, remain more basic than the alcohols due to the resonance effect of the *p*-amino group. Therefore, the esters tend to coordinate to the vanadyl species ($VOL_2X^+X^-$) faster than the alcohols. On the other hand, the species with straight coordinated alcohols are not productive even though there exists a possible equilibrium for ligand L′ exchange. In the case of $VO(acac)_2$ complex, the nucleophilic leaving group acac tends to return back to a stable five-membered chelate through its carbonyl recoordination. Therefore, the replacement of the carbonyl group from acac with that of an ester becomes more endothermic in nature and retarded. As a consequence, the NAS catalytic efficiency decreases significantly. Therefore, the amphoteric mechanism (Scheme 1c) does not seem to operate in the $VO(acac)_2$ case. If the amphoteric mechanism were involved, the more electron-rich acac complex would have been more reactive than the triflate complexes as in the Ti series.

The mechanism changes for diethylvanadite ($VO(OEt)_2$), in which no ionization is possible. The increased electron density on V=O would favor the mechanism in Scheme 1c, but the yield is the lowest presumably due to its poorer thermal stability. Another piece of evidence against the mechanism in Scheme 1c is that $V(OR)_4$ tends to get hydrolyzed to $VO(OR)_2$ irreversibly.[35]

Notably, the efficiency trend in the fourth period Group IVb−VIb oxometallic species follows the order of decreasing oxidizing power: Cr < V < Ti. Nevertheless, one major advantage of $VOCl_2$−$(THF)_x$ over the corresponding oxotitanium species is that they can be readily removed by a simple aqueous wash. The Padimate O can be furnished by direct distillation under reduced pressure, and the catalysts may be either reused from the distillation residue or recovered from the aqueous layer after concentration and reused for at least four consecutive runs with intact catalytic efficiency (90−95% product yields) after reactivation in refluxed THF. Notably, both $Ti(O)(acac)_2$ and vanadyl(IV) species have been widely employed as precatalysts for the epoxidation of allylic alcohols[36] and oxidative coupling of 2-naphthols[37] in the presence of peroxide and/or oxygen co-oxidants.[38] However, there is no literature precedence regarding the uses of $TiO(acac)_2$ and $VOCl_2$−$(THF)_x$ toward the NAS reactions of esters by alcohols. In comparison, they are slightly less reactive than di-*n*-butyltin oxide (18 h, 98% yield in entry 23). Nevertheless, they may be considered as excellent substitutes for $Bu_2Sn(O)$ if environmental protection turns out to be the major concern.[39]

**Effects of Additives.** A lot of metal and oxometallic chlorides are sensitive to alcohols upon heating, leading

(32) (a) By following the procedure for making $VOCl_2$ and $NbOCl_3$ from $VCl_4$ and $NbCl_5$, respectively, we have synthesized the corresponding $NbOCl_2$ from $NbCl_4$ and $((CH_3)_3Si)_2O$, see: (b) Herrmann, W. A.; Thiel, W. R.; Herdtweck, E. *Chem. Ber.* **1990**, *123*, 271.

(33) For reviews, see: (a) Herrmann, W. A.; Kühn, F. E. *Acc. Chem. Res.* **1997**, *30*, 169. (b) Romão, C. C.; Kühn, F. E.; Herrmann, W. A. *Chem. Rev.* **1997**, *97*, 3197. (c) See also: Adam, W.; Mitchell, C. M.; Saha-Moller, C. R.; Weichold, O. J. *Am. Chem. Soc.* **1999**, *121*, 2097. For its recent uses in epoxidations, see: (d) Adam, W.; Mitchell, C. M.; Saha-Möller, C. R. *J. Org. Chem.* **1999**, *64*, 3699.

(34) (a) Belyaeva, V. K.; Filippova, I. S.; Turevskaya, E. P.; Turova, N. Y.; Marov, I. N. *Zh. Neorg. Khim.* **1989**, *34*, 830. (b) Turevskaya, E. P.; Turova, N. Y. *Koord. Khim.* **1989**, *15*, 373. (c) Turevskaya, E. P.; Yanovskii, A. I.; Turova, N. Y.; Struchkov, Y. T. *Koord. Khim.* **1989**, *15*, 191.

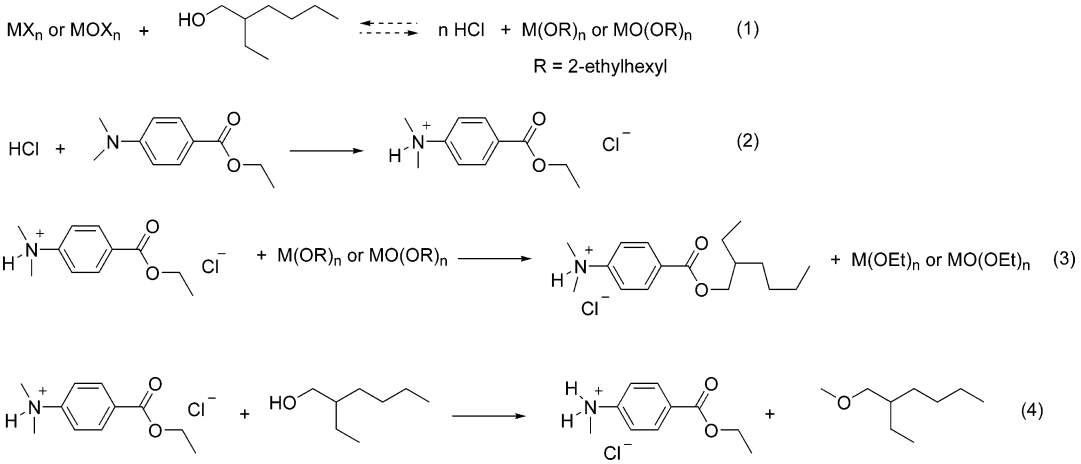
(35) Turevskaya, E. P.; Turova, N. Y. *Zh. Obsch. Khim.* **1988**, *58*, 1441.

(36) (a) Bortolini, O.; Furia, F. D.; Modena, G. *J. Mol. Catal.* **1985**, *33*, 241. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica* **1970**, *12*, 63. (c) For allylic alcohol oxidation, see: Kaneda, K.; Jitsukawa, K.; Imanishi, K.; Imanaka, T. *J. Mol. Catal.* **1989**, *57*, 201. (d) $TiO(acac)_2$/$NaBH_4$ in carbonyl reductions, see: Zeynizadeh, B. *Z. Naturforsch., B: Chem. Sci.* **2003**, *58*, 1220.

(37) Hwang, D. R.; Chen, C. P.; Uang, B. J. *J. Chem. Soc., Chem. Commun*. **1999**, 1207.

(38) For the only example on the use of oxotitanium(IV) binolate in catalyzing asymmetric Mukaiyama aldol additions, see: Mukaiyama, T.; Inubushi, A.; Suda, S.; Hara, R.; Kobayashi, S. *Chem. Lett*. **1990**, 1015.

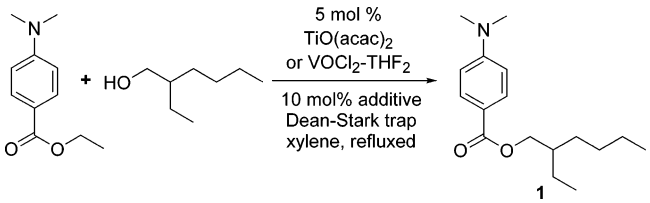
**SCHEME 3**




to HCl gas and the corresponding alkoxides (eq 1, Scheme 3). As mentioned above, the current test ester substrate possessing a dimethylamino unit tends to facilitate this process for certain alcohol-sensitive catalysts by scavenging HCl, eq 2. The observed NAS transformations for these cases may have to do with metal- or oxometallic alkoxide-mediated catalyses, eq 3. The intervening demethylation (eq 4) along with two possible side reactions (oxidation and polymerization), particularly for strongly oxidizing metal or oxometallic species, are responsible for the significant reduction of the NAS conversion yields. The current test substrate system indeed serves as a suitable indicator to identify several alcohol-tolerant oxometallic chlorides such as $TiOCl_2{-}xH_2O$, $VOCl_2{-}xH_2O$, and $VOCl_2{-}(THF)_x$ (entries 1, 8, and 9 in Table 1). Among them, $VOCl_2{-}(THF)_x$ was thus selected as the most efficient and suitable oxometallic chloride-type catalyst for subsequent studies.

Attempts to further improve the conversion performance of $TiO(acac)_2$ or $VOCl_2{-}(THF)_x$-mediated catalysis by some mild acid scavengers (e.g., $K_2CO_3$ and 2,6-di-*tert*-butyl-4-methylpyridine) and a buffer (e.g., NaOAc) were not successful, Table 2. In both $TiO(acac)_2$ and $VOCl_2{-}(THF)_x$, the NAS performance was retained with the addition of 10 mol % 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). In the case of $TiO(acac)_2$, the addition of $K_2CO_3$ tends to slow the reaction by a factor of 2. The addition of NaOAc was even worse (37% yield, 48 h), presumably due to the nucleophilic nature of the acetate that may replace the acetylacetonate ligand in $TiO(acac)_2$ upon vigorous heating. Even worse results were observed for the case of $VOCl_2{-}(THF)_x$. Very low product yields (30−43%) were attained when the test NAS reaction was carried out with the addition of $K_2CO_3$ or NaOAc. The catalyst, $VOCl_2{-}(THF)_x$, may be converted to the corresponding less efficient $VOCO_3{-}(THF)_x$ or $VO(OAc)_2{-}(THF)_x$ with precipitation of KCl or NaCl under the reaction conditions. Notably, very low conversions (0−10%) were observed when other metal and oxometallic chlorides (entries 4, 5, 13, 14, 16−19, and 21) were used as catalysts in the presence of 10 mol % DTBMP under the same reaction conditions, supporting the operating role of these two optimal catalysts.

**TABLE 2. Effects of Additives on the NAS of Ethyl 4-Dimethylaminobenzoate by 2-Ethyl-1-hexanol Catalyzed by $VOCl_2{-}(THF)_x$ and $TiO(acac)_2$**




| catalyst | additive | reaction time | yield,[a] % |
|---|---|---|---|
| $TiO(acac)_2$ | $K_2CO_3$ | 48 | 90 |
| $TiO(acac)_2$ | DTBMP[b] | 21 | 92 |
| $TiO(acac)_2$ | NaOAc | 48 | 37 |
| $VOCl_2{-}(THF)_x$ | $K_2CO_3$ | 48 | 43 |
| $VOCl_2{-}(THF)_x$ | DTBMP | 26 | 93 |
| $VOCl_2{-}(THF)_x$ | NaOAc | 48 | 30 |

[a] Isolated yield. [b] DTBMP: 2,6-di-*tert*-butyl-4-methylpyridine.

The base-dependent effect for $VOCl_2{-}(THF)_x$ again does not fit into the mechanistic scenario in Scheme 1c. Nevertheless, the effect strongly indicates that the mechanism as shown in Scheme 2 is somewhat operable particularly for vanadyl species. The retrogradation of ionization by adding bases (except by DTBMP, which may act as a cocatalyst in NAS) thus induces a sharp decrease in the transesterification yields.

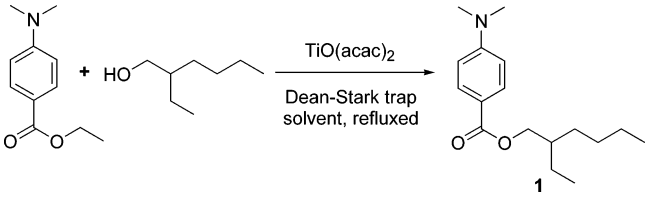
**Effects of Solvents and Catalyst Loadings.** The test reaction was further optimized with $TiO(acac)_2$ by reducing the catalyst loading to 1 mol % without any discernible rate and conversion changes, Table 3. In addition, toluene and xylene were found to be the solvents of choice among six different aprotic solvents examined. Moderate conversions were observed in $CCl_4$ (48 h, 74% yield) and in $CH_3CH_2CN$ (48 h, 53% yield). No reaction occurred at all when the NAS was performed in $C_2H_5NO_2$ and 1,4-dioxane.

**Effects of Ester Substrates.** With the optimal NAS protocol in hand (1 mol % $TiO(acac)_2$,[40] refluxed xylene or toluene), we further examined the ester substrate

(39) Some vanadium-containing species, particularly vanadates, are toxic. However, the so-called vanadium tablet is composed of vanadyl(IV) sulfate ($VOSO_4$) and is used as a vitamin supplement. In addition, several vanadyl(IV) chelates are potentially useful for treating diabetes: McNeil, J. H.; Orvig, C. U.S. Patent 5,888,993, 1999.

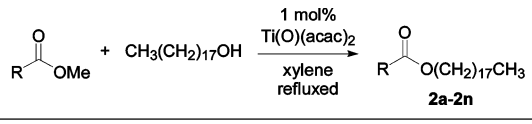
(40) Application of $VOCl_2{-}(THF)_x$ was somewhat limited only to 1° alcohols and was therefore not chosen for subsequent extensive substrate scope studies.

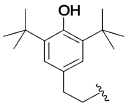
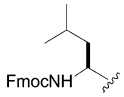
**TABLE 3. Effects of Solvents and TiO(acac)$_2$ Loadings on the NAS of Ethyl 4-Dimethylaminobenzoate by 2-Ethyl-1-hexanol**




| entry | solvent | catalyst, mol % | time, h | yield, % |
|---|---|---|---|---|
| 1 | $CH_3CH_2CN$ | 5 | 48 | 53 |
| 2 | $CCl_4$ | 5 | 48 | 74 |
| 3 | $CH_3CH_2NO_2$ | 5 | 48 | 0 |
| 4 | 1,4-dioxane | 5 | 48 | 0 |
| 5 | toluene | 5 | 40 | 94 |
| 6 | xylene | 5 | 18 | 98 |
| 7 | xylene | 0.05 | 30 | 98 |
| 8 | xylene | 1 | 21 | 98 |
| 9 | xylene | 3 | 19 | 97 |
| 10 | xylene | 10 | 14 | 98 |

**TABLE 4. Effects of Ester Substrates on the NAS with 1-Octadecanol Catalyzed by Ti(O)(acac)$_2$**

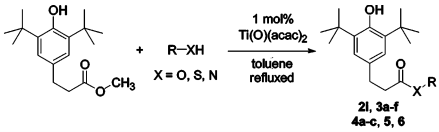


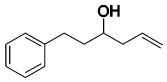
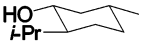
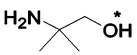

| entry | ester (R) | time, h | yield,[a] % |
|---|---|---|---|
| 1 | Ph | 7 | 95 (**2a**) |
| 2 | 2-(HO)$C_6H_4$ | 10 | 100 (**2b**) |
| 3 | 4-$Me_2NC_6H_4$[b] | 24 | 96 (**2c**) |
| 4 | 4-$BrC_6H_4$ | 5 | 99 (**2d**) |
| 5 | 4-$NO_2C_6H_4$ | 4.5 | 99 (**2e**) |
| 6 | 4-$CH_3OC(O)C_6H_4$ | 15 | 100 (**2f**) |
| 7 | *trans*-PhCH=CH | 14 | 100 (**2g**) |
| 8 | PhCH(OH) | 10 | 91 (**2h**) |
| 9 |  | 11 (12[c]) | 100 (97[c]/**2i**) |
| 10 |  | 120[d] | 86 (**2j**) |
| 11 | $CH_3C(O)CH_2$ | 8 | 95 (**2k**) |
| 12 |  | 13 | 93 (**2l**) |
| 13 |  | 13 | 99 (**2m**) |
| 14 |  | 13 | 95 (**2n**) |

[a] Isolated yields after purification. [b] Ethyl ester was used. [c] Data in parentheses correspond to the catalysis mediated by $VOCl_2$–$(THF)_x$. [d] Toluene was used as a solvent.

scope with a given 1-octadecanol, Table 4. In all cases, the NAS reactions were complete in 7−24 h and the products were provided in 86−100% yields. The substrate activity order follows the trend of A−$C_6H_4$ > $C_6H_5$ ∼ aliphatic > RCH=CH > D−$C_6H_4$ (A = electron-withdrawing group; D = electron-donating group). It was found that the current recipe is amenable to various electron-rich (2-hydroxy and 4-amino) and -deficient (4-Br, 4-$CO_2$Me, and 4-$NO_2$) aromatic esters (entries 2−6) and an α,β-unsaturated ester (entry 7). In addition, selective monoNAS by 1 equiv of 1-octadecanol is attainable with dimethyl 1,4-dibenzoate (entry 6). The electronic effect of the longer alkyl ester at the para position of **2f** instead of carbomethoxy group may prevent its further substitution by 1-octadecanol. A competition experiment by treating a 1:1 mixture of dimethyl 1,4-dibenzoate and **2f** with 1 equiv of 1-octadecanol under the same reaction conditions led again to **2f** only, indicating the weaker electron-withdrawing nature of the $CO_2C_{18}H_{37}$ group. By taking advantage of the significant rate differences among 1°, 2°, and aromatic alcohols (vide infra), the NAS protocol works chemoselectively for the unmasked 2-hydroxybenzoate (entry 2) and mandelate (entry 8) without any self-polymerization or deoxygenation byproducts. Functionalities such as base-sensitive Fmoc, carbamate (entry 10), β-keto esters (entry 11), and heteroaromatic esters of bidentate nature (entries 12−14) are also completely tolerant under the optimal reaction conditions. Finally, 3-(4-hydroxy-3,5-di-*tert*-butyl)phenylpropanoate, a BHT-like antioxidant for plastics, was also readily synthesized in quantitative yield in 11 h by the current catalytic system (entry 9).

**TABLE 5. Effects of Protic Nucleophiles on the NAS of 3-Arylpropanoate Catalyzed by Ti(O)(acac)$_2$**




| entry | R'-XH[a] | Time, h | Yield,[b] % |
|---|---|---|---|
| 1 | $CH_3(CH_2)_{17}OH$ | 11 | 100 (**2i**) |
| 2 | 4-THPO$(CH_2)_4$OH | 9 | 95 (**3a**) |
| 3 | 4-TBSO$(CH_2)_4$OH | 10 | 93 (**3b**) |
| 4 | 2-ethylhexanol | 20 | 95 (**3c**) |
| 5 | *trans*-PhCH=$CHCH_2OH$ | 57 | 89 (**3d**) |
| 6 |  | 75 | 85 (**3e**) |
| 7 |  | 80 | 85 (**3f**) |
| 8 | $PhCH_2NH_2$ | 16 (24[c]) | 65 (91[c]/**4a**) |
| 9 | $Ph_2CHNH_2$ | 62 (96[c]) | 70 (83[c]/**4b**) |
| 10 |  | 50 (72[c])[d] | 70 (83[c]/**4c**)[d] |
| 11 | $PhCH_2SH$ | 62 (96[c]) | 52 (74[c]/**5**) |
| 12 |  | 48 | 28 (**6**) |

[a] Performed with 1 equiv of protic nucleophile unless otherwise stated. [b] Isolated yields after column chromatography. [c] Performed with 2.5 equiv. [d] Asterisk signifies the reactive site.

**Protic Nucleophile Scopes.** To gain insight into the scope of functional group compatibility under the optimal catalytic protocol, a diverse array of protic nucleophiles were further explored by using the antioxidant methyl 3-arylpropanoate as the test substrate (Table 5). Its NAS reactions by alcohols highly depend on their steric

attributes proximal to the nucleophilic hydroxyl site. In general, the reaction rates follow the trend of 1° (entries 1−3) > β-branched 1° (entries 4 and 5) > 2° (entries 6 and 7) ≫ 3° alcohols. The reactions with 2° (75−80 h) alcohols are about 8 times slower than those with linear 1° alcohols (9−11 h). Less efficient conversions (96 h, 73−75% yields) were observed for 2° alcohols catalyzed by $VOCl_2$−$(THF)_x$. The catalytic protocol is amenable to substrates bearing acid-sensitive (e.g., THP ether, 95%, entry 2) or base-sensitive (e.g., TBS ether, 93%, entry 3) groups. No rearrangement product was observed with *trans*-cinnamyl alcohol (89%, entry 5). The NAS reactions did not proceed with 3° alcohols (e.g., *tert*-BuOH) and aromatic alcohols (e.g., phenol) even for prolonged reaction time (>96 h) presumably due to increased steric hindrance or reduced nucleophilicity.

NAS reactions of methyl esters with 1° amines commonly require a stoichiometric Lewis acid catalyst like $InI_3$, methylalumoxane, and $Sb(OEt)_3$.[41] Similar to the NAS with alcohols, the reaction rates for amines were governed by steric effects, i.e., 1° (entry 8) > α-branched 1° (entries 9 and 10) ≫ 2° amines. For the NAS reactions with α-branched 1 amines (e.g., benzyl and diphenylmethylamines) performed under standard catalytic conditions, the resultant amides were furnished in only 65−70% yields (entries 8−10). Nevertheless, the chemical conversions may be improved to 83−91% by using 2.5 equiv of the amine substrates. To our surprise, the transesterification proceeds exclusively over the competitive amidation with a 2-amino-ethanol substrate (entry 10). The sterically encumbered dimethyl substitution next to the amino group may play a role.[42] The result is complementary to the exclusive amidation of the same substrate with an acid chloride under basic media. To further expand the catalytic utility, the NAS with an alkanethiol was also tested.[43] Preliminary results for benzylmercaptan indicate that it is a reasonably facile process that affords moderate yields (up to 74% yield, entry 11). The NAS with other less nucleophilic agents such as oxazolidin-2-one (entry 12) was unsatisfactory. The resultant *N*-acyl-oxazolidin-2-one was isolated in merely 28% after 48 h.

**Mechanistic Study.** On the basis of the counteranion effect observed in the $TiOX_2$ series, $TiO(acac)_2$ tends to fit into the mechanistic proposal in Scheme 1c. Initial nucleophilic attack of a protic nucleophile (R′XH) to the Ti=O unit in monomeric form or Ti−O in polymeric form followed by displacement of the hydroxyl group in the incipient $(HO)(R'X)Ti(acac)_2$ with a second equivalent of R′XH and with concomitant extrusion of $H_2O$ would lead to $(R'X)_2Ti(acac)_2$ **II**, Scheme 4. Activation of the ester C=O unit by **II** followed by intramolecular nucleophilic delivery of either R′X group in **II** (NAS) to the C=O unit would provide a tetrahedral carbonyl addition intermediate **III** (TCAI). The TCAI **III** would restore the C=O unit

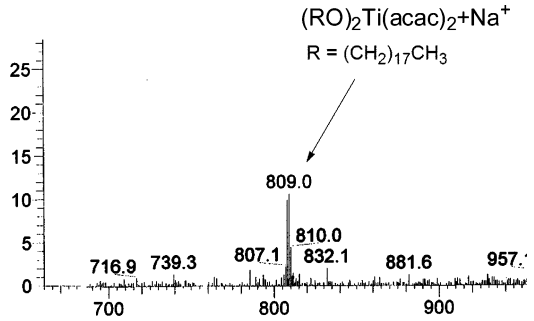
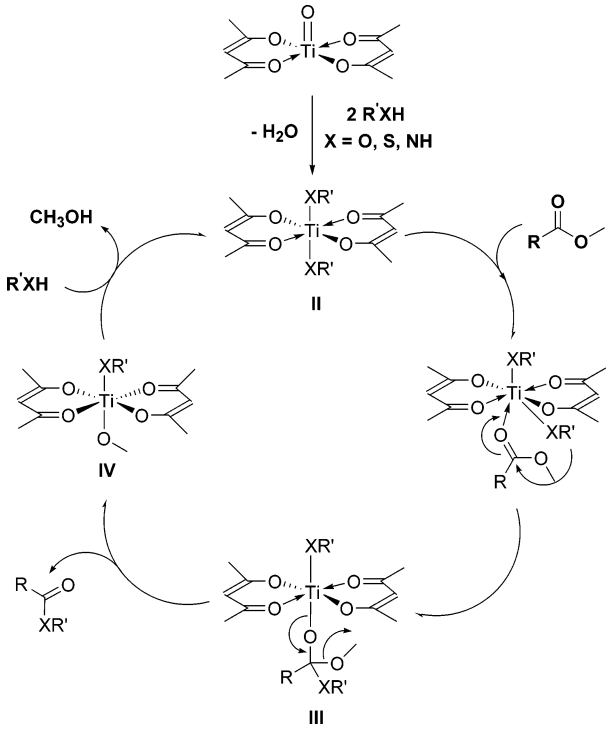



**FIGURE 1.** ESI-MS analysis of a mixture of $Ti(O)(acac)_2$ and 2 equiv of 1-octadecanol refluxed in xylene for 4 h.

**SCHEME 4**




with extrusion of methoxide leading to the NAS end product along with $(MeO)(R'X)Ti(acac)_2$ **IV**. Subsequent exchange of the methoxide in **IV** by another protic nucleophile substrate with removal of MeOH by Dean−Stark trap would regenerate the turnover catalyst **II**, thus completing the catalytic cycle.

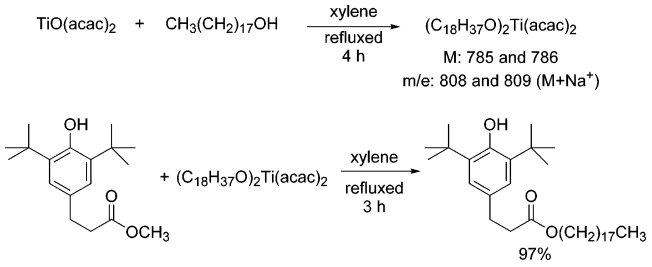
To support the mechanistic hypothesis, we have treated $Ti(O)(acac)_2$ with 2 equiv of 1-octadecanol in refluxed xylene for 4 h. Besides the unreacted $TiO(acac)_2$, the resultant concentrate contained about 15−20% $(C_{18}H_{37}O)_2$-$Ti(acac)_2$ **II**, as evidenced by ESI-MS analysis (Figure 1), and was subjected to the NAS reaction of methyl 3-(4-hydroxy-3,5-di-*tert*-butyl)phenylpropanoate under similar reaction conditions (refluxed xylene, 3 h). The desired 1-octadecyl 3-arylpropanoate was isolated in 97%, Scheme 5. No species related to $TiO(OC_{18}H_{37})_2$ or $Ti(OC_{18}H_{37})_4$ was observed by ESI-MS analysis, thus excluding their potential involvement as incipient catalysts. On the other hand, by first treating $Ti(O)(acac)_2$ with 1 equiv of methyl 3-(4-hydroxy-3,5-di-*tert*-butyl)phenylpropanoate in refluxed xylene for 24 h, the individual components remain

(41) (a) $InI_3$: Ranu, B. C.; Dutta, P. *Synth. Commun.* **2003**, *33*, 297. (b) Methylalumoxane: Akakura, M.; Yamamoto, H. *Synlett* **1997**, *3*, 277. (c) $Sb(OEt)_3$: Ishihara, K.; Kuroki, Y.; Hanaki, N.; Ohara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 1569. (d) For transamidation by $AlCl_3$, see: Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 4035.

(42) Same chemoselectivity was observed when the reaction was carried out in the presence of 10 mol % DTBMP.

(43) Ponde, D. E.; Deshpande, V. H.; Bulbule, V. J.; Sudalai, A.; Gajare, A. S. *J. Org Chem.* **1998**, *63*, 1058.

**SCHEME 5**




intact and no addition product similar to **I′**, shown in Scheme 1b, was observed.

In conclusion, we have documented a new NAS protocol with various functionalized protic nucleophiles catalyzed by $Ti(O)(acac)_2$ (or by $V(O)Cl_2$ for 1° alcohols). The neutral and water-compatible catalyst of $TiO(acac)_2$ was found to be amphoteric in nature and to tolerate 1° and 2° alcohols, amines, and thiols bearing acid- and base-sensitive groups. We have also demonstrated their synthetic feasibility to access several commercial products such as Padimate O and antioxidants for plastics. ESI-MS analysis of the 1:2 adduct between $TiO(acac)_2$ and 1-octadecanol supports its double nucleophilic additions to $TiO(acac)_2$ with extrusion of $H_2O$ leading to an incipient $(R'X)_2Ti(acac)_2$ turnover catalyst responsible for subsequent NAS of a given methyl ester. The mechanistic proposal similar to the NAS of anhydrides by protic nucleophiles as shown in Scheme 1b or to the preionization of $VOX_2$ as in Scheme 2 was thus excluded. Research toward the applications of the new catalytic methodology on the synthesis of polypeptides, polyesters, and the dendritic analogues is underway.

## Experimental Section

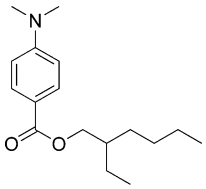
**General Procedure for NAS of Methyl/Ethyl Esters by Protic Nucleophiles.** To a dry 50 mL, two-necked, round-bottomed flask equipped with a Dean−Stark trap topped with a reflux condenser was added a solution of ester (5.0 mmol) and nucleophile (5.0 mmol) in xylene (10 mL). The mixture was heated to reflux for 30 min and then cooled to room temperature. About 1 mL of $H_2O$ was added to the Dean−Stark trap, which contained xylene in order to remove MeOH or EtOH generated during the reaction. A solution of $TiO(acac)_2$ (13−65 mg, 0.05−0.25 mmol) in xylene (2 mL) was slowly added to the above solution, and the reaction mixture was refluxed for the indicated time periods. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature and quenched with cold, saturated aqueous $NaHCO_3$ solution (25 mL). From the above solution, the separated organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by column chromatography on silica gel. The product obtained was characterized by routine spectroscopic methods.

**Preparation of $TiO(OTf)_2$−$xH_2O$ and $TiOCl_2$−$xH_2O$ (May Contain Some Ligated MeOH).** $TiO(SO_4)$−$xH_2SO_4$−$xH_2O$ was washed with anhydrous acetone and dried before use. $TiO(OTf)_2$−$xH_2O$ and $TiOCl_2$−$xH_2O$ were prepared by mixing $TiO(SO_4)$−$xH_2SO_4$−$xH_2O$ (1 mmol) with 1 equiv of $Ba(OTf)_2$ and $BaCl_2$, respectively, in anhydrous MeOH (15 mL) for 3 h. A copious amount of $BaSO_4$ precipitated out. The resultant mixture was filtered, and the collected filtrate was concentrated to give $TiO(OTf)_2$−$xH_2O$ and $TiOCl_2$−$xH_2O$, respectively, which were used directly without further purification.

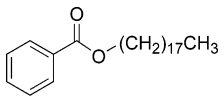
**Preparation of $VOCl_2$−$(THF)_x$ and $VO(OTf)_2$−$(THF)_x$.** The THF complexes were prepared by dissolving the corresponding hydrates (i.e., $VOCl_2$−$(H_2O)_x$ and $VO(OTf)_2$−$(H_2O)_x$) in THF and refluxed for 12 h. The resultant solutions were concentrated and dried in vacuo at 40 °C for 2 h, affording a brownish solid that was used directly without further purification.

**General Procedure for the Recovery of $VOCl_2$−$(THF)_x$.** After completion of the reaction as monitored by TLC, the reaction mixture was quenched with ice-cold water (25 mL). The separated aqueous layer was concentrated by rotary evaporation at 40 °C. Subsequently, the recovered catalyst was refluxed in THF for 12 h and dried in vacuo at 40 °C for 2 h, affording a brownish solid in essentially quantitative recovery.

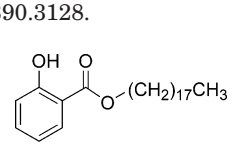
**2-Ethylhexyl 4-Dimethylaminobenzoate, 1.** Data: IR ($CH_2Cl_2$) 3064 (s), 2964 (s), 1695 (s), 1607 (s), 1528 (s), 1427 (s), 1288 (s), 1245 (s), 1185 (s), 1113 (s); $^1$H NMR (400 MHz, $CDCl_3$) 7.92 (d, $J$ = 9.0, 2H), 6.65 (d, $J$ = 9.1, 2H), 4.24−4.15 (m, 2H), 3.19 (s, 6H), 1.73−1.65 (m, 1H), 1.53−1.26 (m, 8H), 0.95 (t, $J$ = 7.5, 3H), 0.93 (t, $J$ = 7.8, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 167.0, 153.1, 131.0, 117.3, 111.6, 66.4, 39.8, 38.9, 30.6, 28.9, 24.0, 22.9, 13.9, 11.0; MS (70 eV) 277 ($M^+$, 100), 165 (66), 148 (70); TLC $R_f$ 0.4 (EtOAc/hexane, 1/8); HR-MS calcd for $C_{17}H_{27}NO_2$: 277.2042, found: 277.2042.




**Octadecyl Benzoate, 2a.**[44] Data: mp 42−44 °C; IR ($CH_2Cl_2$) 3049 (s), 2987 (s), 1700 (m), 1422 (s), 1280 (s), 1251 (s), 896 (s), 778(s); $^1$H NMR (400 MHz, $CDCl_3$) 8.04 (d, $J$ = 6.8, 2H), 7.57−7.53 (m, 1H), 7.45−7.42 (m, 2H), 4.32 (t, $J$ = 6.6, 2H), 1.80−1.74 (m, 2H), 1.46−1.43 (m, 2H), 1.35−1.26 (bs, 28H), 0.89−0.86 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 166.7, 132.7, 130.6, 129.5, 128.3, 65.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.8, 26.1, 22.7, 14.1; MS (70 eV) 374 ($M^+$, 3), 252 (10), 122 (100), 104 (38), 83 (13), 57 (12); TLC $R_f$ 0.35 (EtOAc/hexane, 1/9); HR-MS calcd for $C_{25}H_{42}O_2$: 374.3185, found: 374.3179.



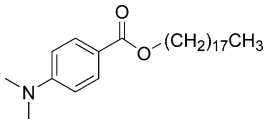

**Octadecyl 2-Hydroxybenzoate, 2b.** Data: mp 52−54 °C; IR ($CH_2Cl_2$) 3693 (w), 3063 (s), 2987 (s), 1551 (w), 1422 (s), 1280 (s), 1251 (s); $^1$H NMR (400 MHz, $CDCl_3$) 10.86 (s, 1H), 7.85 (dd, $J$ = 7.9, 1.5, 1H), 7.45 (dt, $J$ = 7.8, 1.5, 1H), 6.98 (d, $J$ = 8.4, 1H), 6.88 (t, $J$ = 7.8, 1H,), 4.34 (t, $J$ = 6.8, 2H), 1.78 (quint, $J$ = 7.0, 2H), 1.48−1.41 (m, 2H), 1.26 (bs, 28H), 0.89 (t, $J$ = 6.8, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 170.2, 161.7, 135.5, 129.8, 119.0, 117.5, 112.7, 65.5, 31.9, 29.7 29.63, 29.56, 29.5, 29.4, 29.2, 28.6, 26.0, 22.7, 14.1; MS (70 eV) 391 (M + $H^+$, 50), 390 ($M^+$, 100), 372 (5), 240 (7), 138 (90), 120 (52); TLC $R_f$ 0.4 (EtOAc/hexane, 1/10); HR-MS calcd for $C_{25}H_{42}O_3$: 390.3134, found: 390.3128.



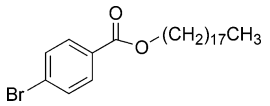

**Octadecyl 4-Dimethylaminobenzoate, 2c.** Data: mp 70−72 °C; IR ($CH_2Cl_2$) 3060 (s), 3041 (s), 2987 (s), 1696 (s), 1608 (w), 1422 (s), 1280 (s), 1251 (s); $^1$H NMR (400 MHz, $CDCl_3$) 7.92 (d, $J$ = 9.0, 2H), 6.67 (d, $J$ = 9.0, 2H), 4.2 (t, $J$ =

(44) (a) Goedl, S.; Trathnigg, B.; Junek, H. *Monatsh. Chem.* **1984**, *115*, 1185. (b) Cussans, N. J.; Ley, S. V.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1650.

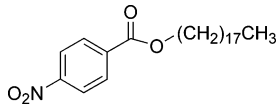
6.7, 2H), 3.04 (s, 6H), 1.75−1.72 (m, 2H), 1.44−1.35 (m, 2H), 1.26 (bs, 28H), 0.88 (t, $J$ = 7.2, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 167.1, 153.3, 131.2, 117.5, 110.7, 64.3, 40.0, 31.9, 29.68, 29.64, 29.58, 29.55, 29.34, 29.31, 28.9, 25.9, 22.7, 14.1; MS (70 eV) 418 (M + H$^+$, 39), 417 (100), 165 (57), 148 (60); TLC $R_f$ 0.5 (EtOAc/hexane, 1/10); HR-MS calcd for $C_{27}H_{47}NO_2$: 417.3607, found: 417.3599. Anal. Calcd for $C_{27}H_{47}NO_2$: C, 77.64; H, 11.34; N, 3.35. Found: C, 77.56; H, 11.74; N, 3.07.



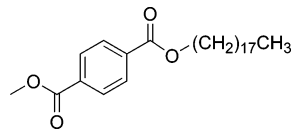
**Octadecyl 4-Bromo-benzoate, 2d.**[45] Data: mp 53−55 °C; IR (KBr) 2959 (m), 2922 (s), 2856 (s), 1716 (s), 1590 (m), 1472 (s), 1402 (m), 1310 (m), 1288 (s), 1174 (w), 1126 (m), 1107 (m), 1067 (m), 1012 (m), 957 (w); $^1$H NMR (400 MHz, $CDCl_3$) 7.91−7.88 (m, 2H), 7.59−7.56 (m, 2H), 4.30 (t, $J$ = 6.8, 2H), 1.76 (quint, $J$ = 6.8, 2H), 1.44−1.21 (m, 30H), 0.88 (t, $J$ = 6.8, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 165.9, 131.7, 131.1, 129.5, 127.9, 65.4, 31.9, 29.7, 29.5, 29.4, 29.3, 28.7, 26.0, 22.7, 14.1; TLC $R_f$ 0.32 (EtOAc/hexane, 1/10); HR-MS (FAB+) calcd for $C_{25}H_{41}BrO_2$ + H: 453.2368, found: 453.2357. Anal. Calcd for $C_{25}H_{41}BrO_2$: C, 66.21; H, 9.11. Found: C, 66.54; H, 9.21.



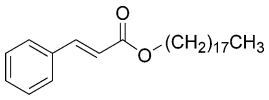
**Octadecyl 4-Nitro-benzoate, 2e.**[46] Data: mp 63−65 °C; IR (KBr) 3122 (w), 2967 (m), 2923 (s), 2856 (s), 1719 (s), 1606 (w), 1528 (s), 1473 (m), 1351 (m), 1292 (s), 1126 (m), 1108 (m), 876 (m); $^1$H NMR (400 MHz, $CDCl_3$) 8.28−8.27 (m, 2H), 8.21−8.19 (m, 2H), 4.36 (t, $J$ = 6.8, 2H), 1.78 (quint, $J$ = 6.8, 2H), 1.46−1.25 (m, 30H), 0.87 (t, $J$ = 6.4, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 164.7, 150.5, 135.9, 130.6, 123.5, 66.1, 31.9, 29.7, 29.6, 29.54, 29.48, 29.3, 29.2, 28.6, 26.0, 22.7, 14.1; TLC $R_f$ 0.31 (EtOAc/hexane, 1/10); HR-MS (FAB+) calcd for $C_{25}H_{41}NO_4$ + H: 420.3114, found: 420.3104. Anal. Calcd for $C_{25}H_{41}NO_4$: C, 71.56; H, 9.85; N, 3.34. Found: C, 71.65; H, 9.67; N, 3.11.



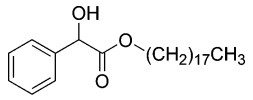
**1-Methyl-4-Octadecyl Terephthalate, 2f.** Data: mp 55−56 °C; IR ($CH_2Cl_2$) 3070 (s), 3041 (s), 2979 (s), 2305 (s), 1719 (s), 1551 (w), 1436 (s), 1290 (s), 1241 (s); $^1$H NMR (400 MHz, $CDCl_3$) 8.10 (s, 4H), 4.34 (t, $J$ = 6.8, 2H), 3.95 (s, 3H), 1.78 (quint, $J$ = 6.8, 2H), 1.48−1.41 (m, 2H), 1.36−1.26 (m, 28H), 0.88 (t, $J$ = 7.0, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 166.2, 165.8, 134.3, 133.8, 129.5, 129.5, 65.5, 52.3, 31.9, 29.7, 29.54, 29.48, 29.3, 29.2, 28.6, 26.0, 22.7, 14.1; MS (70 eV) 432 (M$^+$, 8), 181 (100), 163 (33), 97 (13), 57 (10); TLC $R_f$ 0.5 (EtOAc/hexane, 1/15). Anal. Calcd for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 74.93; H, 10.70.



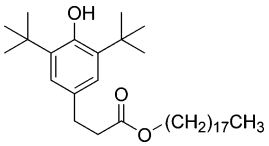
**Octadecyl 3-Phenylacrylate, 2g.**[47] Data: mp 48−49 °C; IR ($CH_2Cl_2$) 3053 (s), 2986 (s), 1707 (w), 1551 (w), 1422 (s), 1278 (s), 1253 (s); $^1$H NMR (400 MHz, $CDCl_3$) 7.69 (d, $J$ = 16.0, 1H), 7.53−7.51 (m, 2H), 7.38−7.37 (m, 3H), 6.44 (d, $J$ = 16.0, 1H), 4.21 (t, $J$ = 6.8, 2H), 1.71 (quint, $J$ = 7.4, 2H), 1.40−1.32 (m, 2H), 1.27 (bs, 28H), 0.89 (t, $J$ = 6.8, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 167.0, 144.5, 134.5, 130.1, 128.8, 128.0, 118.3, 64.7, 31.9, 29.7, 29.6, 29.6, 29.5, 29.33, 29.26, 28.7, 26.0, 22.7, 14.1; MS (70 eV) 401 (M + H$^+$, 20), 250 (9), 189 (13), 148 (100), 131 (78), 103 (32), 57 (15); TLC $R_f$ 0.45 (EtOAc/hexane, 1/10); HR-MS calcd for $C_{27}H_{44}O_2$: 400.3341, found: 400.3335. Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.82; H, 11.11.



**Octadecyl Mandelate, 2h.** Data: mp 47−48 °C; IR (KBr) 3450 (s), 3395 (s), 2922 (s), 2851 (s), 1735 (s), 1695 (s), 1602 (m), 1472 (s), 1455 (s), 1398 (m), 1373 (m), 1344 (m), 1303 (s), 1271 (s), 1202 (s), 1174 (s), 1101 (s), 1070 (m), 991 (m); $^1$H NMR (400 MHz, $CDCl_3$) 7.44−7.31 (m, 5H), 5.16 (d, $J$ = 5.7, 1H), 4.17−4.14 (m, 2H), 3.46 (d, $J$ = 6.2, 1H), 1.57 (quint, $J$ = 6.8, 2H), 1.30−1.20 (m, 30H), 0.88 (t, $J$ = 7.0, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 173.8, 138.5, 128.5, 128.4, 126.5, 72.8, 66.3, 31.9, 29.69, 29.65, 29.61, 29.5, 29.42, 29.35, 29.0, 28.4, 25.6, 22.7, 14.1; TLC $R_f$ 0.26 (EtOAc/hexane, 1/10); HR-MS (FAB+) calcd for $C_{26}H_{44}O_3$ + Na: 427.3188, found: 427.3191. Anal. Calcd for $C_{26}H_{44}O_3$: C, 77.18; H, 10.96. Found: C, 77.03; H, 11.15.



**Octadecyl 3-(3,5-Di-*tert*-butyl-4-hydroxy)phenylpropanoate, 2i.**[48] Data: mp 49−51 °C; IR ($CH_2Cl_2$) 3637 (w), 3050 (s), 2928 (s), 2855 (s), 1726 (m), 1422 (s), 1280 (s), 1249 (s), 1163 (m); $^1$H NMR (400 MHz, $CDCl_3$) 7.00 (s, 2H), 5.07 (s, 1H), 4.08 (t, $J$ = 6.8, 2H), 2.88 (t, $J$ = 7.6, 2H), 2.60 (t, $J$ = 7.5, 2H), 1.64−1.59 (m, 2H), 1.44 (s, 18H), 1.37−1.27 (bs, 30H), 0.89 (t, $J$ = 6.9, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 173.3, 152.1, 125.9, 131.2, 124.8, 64.6, 36.5, 34.3, 32.0, 31.1, 30.3, 29.71, 29.68, 29.6, 29.5, 29.4, 29.3, 28.7, 22.7, 14.1; MS (70 eV) 530 (M$^+$, 100), 516 (59), 277 (16), 219 (58), 203 (18), 147 (15); TLC $R_f$ 0.4 (EtOAc/hexane, 1/7); HR-MS calcd for $C_{35}H_{62}O_3$: 530.4699, found: 530.4697.



**Octadecyl 2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4-methyl-pentanoate, 2j.** Data: mp 39−41 °C; IR (KBr) 2959 (s), 2915 (s), 2849 (s), 1746 (s), 1716 (s), 1661 (w), 1469 (m), 1418 (m), 1373 (m), 1362 (m), 1322 (m), 1259 (m), 1182 (m), 1159 (m), 1097 (m), 1078 (m), 1041 (m); $^1$H NMR (400 MHz, $CDCl_3$) 7.76 (d, $J$ = 7.5, 2H), 7.62 (t, $J$ = 7.5, 2H), 7.40 (t, $J$ = 7.4, 2H), 7.31 (t, $J$ = 7.4, 2H), 5.39 (bd, $J$ = 8.8, 1H), 4.45−4.41 (m, 4H), 4.24 (t, $J$ = 7.0, 1H), 4.16 (t, $J$ = 5.4, 1H), 1.71−1.64 (m, 5H), 1.35−1.25 (bs, 30H), 1.00−0.98 (m, 6H), 0.92 (t, $J$ = 7.0, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 173.2, 155.9, 143.8,

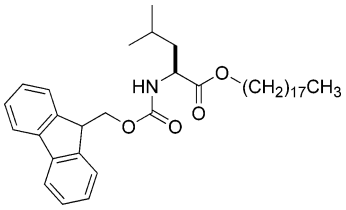
(45) Mueller, D.; Frank, B.; Beckert, R.; Goerls, H. *Naturforsch. B* **2002**, *57*, 471.

(46) Matsunaga, Y.; Sakamoto S.; Togashi, A.; Tsujimoto, M. *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A* **1994**, *250*, 161.

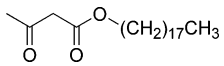
(47) (a) Ramesh, V.; Weiss, R. G. *J. Org. Chem.* **1986**, *51*, 2535. (b) Bolt, R. *Tetrahedron Lett.* **1976**, 2595.

(48) (a) Pastor, S. D.; Hessell, E. T. *J. Organomet. Chem.* **1987**, *328*, 263. (b) Roginskii, V. A. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1985**, *34*, 1833.

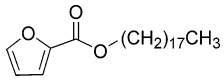
141.3, 127.6, 127.0, 125.1, 119.9, 66.9, 65.5, 65.4, 52.6, 47.2, 41.9, 31.9, 29.7, 29.3, 29.2, 29.0, 28.5, 25.8, 24.8, 22.8, 22.7, 21.9; TLC $R_f$ 0.30 (EtOAc/hexane, 1/9); HR-MS (FAB+) calcd for $C_{39}H_{59}NO_4$ + H: 606.4522, found: 606.4524. Anal. Calcd for $C_{39}H_{59}NO_4$: C, 77.31; H, 9.82; N, 2.31. Found: C, 77.55; H, 9.63; N, 2.18.



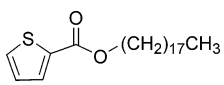
**Octadecyl Acetoacetate, 2k (Including Enol Isomer).**[49] Data: mp 39−40 °C; IR (KBr) 2959 (m), 2915 (s), 2849 (s), 1746 (s), 1709 (m), 1465 (w), 1414 (w), 1370 (w), 1322 (m), 1263 (m), 1159 (m), 1053 (w), 1038 (w); $^1$H NMR (400 MHz, $CDCl_3$) 12.08 (s, 1H, enol), 4.94 (s, 1H, enol), 4.09 (t, $J$ = 6.8, 2H), 4.07 (t, $J$ = 6.9, 2H, enol), 3.40 (s, 2H), 2.22 (s, 3H), 1.60 (quint, $J$ = 7.1, 2H), 1.22 (bs, 30 H), 0.84 (t, $J$ = 6.6, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 200.3, 175.2, 172.6, 167.0, 89.6, 65.4, 63.9, 50.0, 31.8, 29.9, 29.61, 29.58, 29.55, 29.5, 29.4, 29.3, 29.2, 29.1, 28.4, 25.8, 25.7, 25.6, 14.0; TLC $R_f$ 0.38 (EtOAc/hexane, 1/9); HR-MS (FAB+) calcd for $C_{22}H_{42}O_3$ + H: 355.3212, found: 355.3219.



**Octadecyl Furan-2-carboxylate, 2l.**[50] Data: mp 47−48 °C; IR (KBr) 3151 (m), 3122 (m), 2967 (m), 2923 (s), 2841 (s), 1709 (s), 1639 (m), 1580 (m), 1484 (s), 1469 (s), 1381 (m), 1296 (s), 1233 (m), 1174 (s), 1126 (s), 1078 (m), 1012 (m), 957 (m), 920 (m); $^1$H NMR (400 MHz, $CDCl_3$) 7.57−7.56 (m, 1H), 7.16−7.15 (m, 1H), 6.50−6.49 (m, 1H), 4.29 (t, $J$ = 6.8, 2H), 1.74 (quint, $J$ = 6.8, 2H), 1.42−1.25 (m, 30H), 0.87 (t, $J$ = 6.7, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 158.9, 146.1, 145.0, 117.6, 111.7, 65.1, 31.9, 29.7, 29.64, 29.57, 29.5, 29.4, 29.3, 28.7, 25.9, 22.7, 14.1; MS (70 eV) 364 ($M^+$, 5), 113 (100), 95 (84), 67 (36), 57 (58); TLC $R_f$ 0.38 (EtOAc/hexane, 1/10); HR-MS (FAB+) calcd for $C_{23}H_{40}O_3$ + H: 365.3056, found: 365.3050.



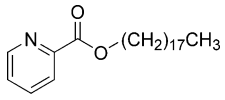
**Octadecyl Thiophene-2-carboxylate, 2m.** Data: mp 38−39 °C; IR (KBr) 3107 (m), 2959 (s), 2923 (s), 2849 (s), 2686 (m), 1716 (s), 1701 (s), 1524 (m), 1476 (m), 1421 (m), 1384 (m), 1359 (m), 1259 (s), 1229 (m), 1100 (m), 1078 (m), 957 (w), 861 (w); $^1$H NMR (400 MHz, $CDCl_3$) 7.81−7.80 (m, 1H), 7.55−7.54 (m, 1H), 7.12−7.09 (m, 1H), 4.30 (t, $J$ = 6.7, 2H), 1.75 (quint, $J$ = 6.9, 2H), 1.43−1.24 (m, 30H), 0.89 (t, $J$ = 6.8, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 162.3, 134.2, 133.2, 132.1, 127.7, 65.3, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 28.7, 26.0, 23.0, 22.7, 14.1; MS (20 eV) 381 ($M^+$, 39), 111 (100), 55 (58); TLC $R_f$ 0.40 (EtOAc/hexane, 1/10); HR-MS (FAB+) calcd for $C_{23}H_{40}O_2S$ + H: 381.2827, found: 381.2830. Anal. Calcd for $C_{23}H_{40}O_2S$: C, 72.58; H, 10.59. Found: C, 72.51; H, 10.65.



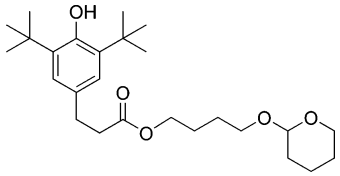
(49) (a) Mauz, O. *Justus Liebigs Ann. Chem.* **1974**, 345. (b) Baindur, N.; Rutledge, A.; Triggle, D. J. *J. Med. Chem.* **1993**, *36*, 3743.

(50) Castells, J.; Pujol, F.; Llitjos, H.; Moreno-Manas, M. *Tetrahedron* **1982**, *38*, 337.

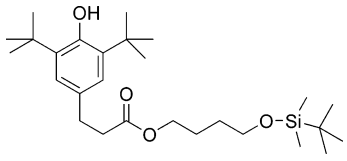
**Octadecyl Pyridine-2-carboxylate, 2n.**[51] Data: mp 49−52 °; IR (KBr) 2959 (m), 2915 (s), 2849 (s), 1720 (s), 1594 (w), 1473 (m), 1425 (w), 1300 (m), 1237 (w), 1189 (w), 1134 (m), 1093 (w), 1030 (w), 957 (w); $^1$H NMR (400 MHz, $CDCl_3$) 9.21 (d, $J$ = 1.3, 1H), 8.75−8.73 (m, 1H), 8.29−8.26 (m, 1H), 7.37−7.34 (m, 1H), 4.33 (t, $J$ = 6.7, 2H), 1.76 (quint, $J$ = 7.0, 2H), 1.44−1.23 (m, 30H), 0.83 (t, $J$ = 6.8, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 165.3, 153.3, 150.9, 137.0, 126.4, 123.2, 65.6, 31.9, 29.7, 29.64, 29.55, 29.5, 29.3, 29.2, 28.6, 26.0, 22.7, 14.1; MS (20 eV) 376 (M + $1^+$, 5), 124 (100), 106 (56), 78 (40); TLC $R_f$ 0.35 (EtOAc/hexane, 1/10); HR-MS (FAB+) calcd for $C_{24}H_{41}NO_2$ + H: 376.3216, found: 376.3214.



**4-(Tetrahydropyran-2-yloxy)butyl 3-(3,5-Di-*tert*-butyl-4-hydroxy)phenylpropanoate, 3a.** Data: IR ($CH_2Cl_2$) 3635 (s), 3005 (w), 2921 (s), 1727 (s), 1605 (w), 1469 (m), 1361 (m), 1318 (m), 1265 (m), 1250 (s), 1122 (s), 1075 (s), 1033 (s); $^1$H NMR (400 MHz, $CDCl_3$) 7.00 (s, 2H), 5.09 (s, 1H), 4.59 (dd, $J$ = 4.3, 2.5, 1H), 4.13 (t, $J$ = 6.3, 2H), 3.85 (dt, $J$ = 6.4, 2.5, 1H), 3.80−3.74 (m, 1H), 3.53−3.49 (m, 1H), 3.44−3.38 (m, 1H), 2.88 (t, $J$ = 7.6, 2H), 2.61 (t, $J$ = 7.5, 2H), 1.84−1.51 (m, 10H), 1.44 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) 173.1, 152.1, 135.9, 131.1, 124.7, 98.7, 66.8, 64.2, 62.1, 36.4, 34.2, 30.9, 30.6, 30.2, 26.2, 25.6, 25.4, 19.5; MS (20 eV) 435 (M + $H^+$, 5), 352 (10), 350 (57), 295 (30), 219 (22), 147 (16), 85 (100); TLC $R_f$ 0.52 (EtOAc/hexane, 1/10); HR-MS calcd for $C_{26}H_{42}O_5$: 434.3032, found: 434.3021. Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.99; H, 9.52.



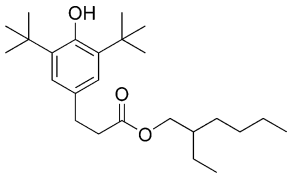
**4-(*tert*-Butyldimethylsilanyloxy)butyl 3-(3,5-Di-*tert*-butyl-4-hydroxy)phenylpropanoate, 3b.** Data: IR (Nujol) 3638 (s), 3065 (w), 2949 (s), 2881 (s), 1732 (s), 1602 (w), 1436 (s), 1388 (s), 1358 (s), 1307 (m), 1249 (s), 1232 (s), 1198 (s), 1151 (s), 1123 (s), 1076 (s), 1028 (s), 987 (m), 974 (m), 902 (m); $^1$H NMR (400 MHz, $CDCl_3$) 7.05 (s, 2H), 5.14 (s, 1H), 4.17 (t, $J$ = 6.4, 2H), 3.69 (t, $J$ = 6.4, 2H), 2.94 (t, $J$ = 7.5, 2H), 2.66 (t, $J$ = 7.5, 2H), 1.79−1.72 (m, 2H), 1.65−1.58 (m, 2H), 1.49 (s, 18H), 0.96 (s, 9H) 0.12 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) 173.1, 152.1, 135.9, 131.1, 124.7, 64.2, 62.5, 36.4, 34.2, 31.0, 30.3, 29.1, 25.9, 25.2, 18.2, −5.4; MS (70 eV) 465 (M + $H^+$, 5), 407 (10), 220 (26), 219 (100), 187 (58); TLC $R_f$ 0.3 (EtOAc/hexane, 1/5); HR-MS calcd for $C_{27}H_{48}SiO_4$: 464.3322, found: 464.3325.



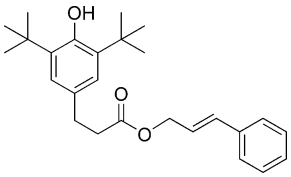
**2-Ethylhexyl 3-(3,5-Di-*tert*-butyl-4-hydroxy)phenylpropanoate, 3c.** Data: IR ($CH_2Cl_2$) 3636 (w), 3061 (s), 2986 (s), 1725 (s), 1425 (s), 1280 (s), 1251 (s); $^1$H NMR (400 MHz, $CDCl_3$) 7.06 (s, 2H), 5.13 (s, 1H), 4.10−4.02 (m, 2H), 2.94 (t, $J$ = 7.5, 2H), 2.67 (t, $J$ = 7.4, 2H), 1.65−1.58 (m, 1H), 1.49 (s, 18H), 1.44−1.34 (m, 8H), 0.95 (t, $J$ = 7.5, 3H), 0.93 (t, $J$ = 7.5, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 173.4, 152.1, 135.9, 131.2,

(51) Carey E. *J. Econ. Entomol.* **1949**, *42*, 798.

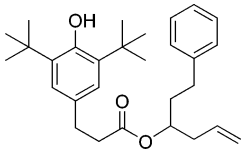
124.7, 66.8, 38.8, 36.5, 34.3, 31.0, 30.4, 30.3, 28.9, 23.8, 22.9, 14.0, 10.8; MS (70 eV) 391 (M + $H^+$, 22), 390 (100), 375 (80), 335 (13), 263 (12), 219 (52); TLC $R_f$ 0.5 (EtOAc/hexane, 1/4); HR-MS calcd for $C_{25}H_{42}O_3$: 390.3134, found: 390.3131. Anal. Calcd for $C_{25}H_{42}O_3$: C, 76.87, H, 10.84. Found: C, 76.99, H, 10.90.



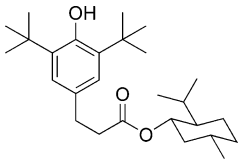
**3-Phenylallyl 3-(3,5-Di-*tert*-butyl-4-hydroxy)phenylpropanoate, 3d.** Data: 59−61 °C; IR ($CH_2Cl_2$) 3657 (w), 3054 (s), 2986 (s), 1731 (w), 1422 (s), 1278 (s), 1259 (s), 1158 (m); $^1$H NMR (400 MHz, $CDCl_3$) 7.40 (d, $J$ = 7. 8, 2H), 7.35 (t, $J$ = 7.6, 2H), 7.28 (t, $J$ = 7.7, 1H), 7.03 (s, 2H), 6.67 (d, $J$ = 15.8, 1H), 6.31 (dt, $J$ = 15.9, 6.4, 1H), 5.09 (s, 1H), 4.78 (dd, $J$ = 6.5, 1.0, 2H), 2.94 (t, $J$ = 7.5, 2H), 2.69 (t, $J$ = 7.5, 2H), 1.46 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) 172.9, 152.2, 136.2, 135.9, 134.2, 131.0, 128.6, 128.0, 126.6, 124.8, 123.2, 65.0, 36.5, 34.3, 31.0, 30.3; MS (70 eV) 394 ($M^+$, 8), 292 (32), 277 (100), 235 (27), 219 (29), 203 (13), 147 (21), 117 (50); TLC $R_f$ 0.4 (EtOAc/hexane, 1/4); HR-MS calcd for $C_{26}H_{34}O_3$: 394.2508, found: 394.2505. Anal. Calcd for $C_{26}H_{34}O_3$: C, 77.15, H, 8.69. Found: C, 77.59, H, 8.74.



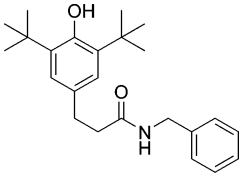
**1-Phenethyl-but-3-enyl 3-(3,5-Di-*tert*-butyl-4-hydroxy)-phenylpropanoate, 3e.** Data: IR ($CH_2Cl_2$) 3657 (w), 3054 (s), 2986 (s), 1725 (m), 1551 (w), 1422 (s), 1279 (s), 1253 (s), 1160 (m); $^1$H NMR (400 MHz, $CDCl_3$) 7.38−7.34 (m, 2H), 7.26 (t, $J$ = 7.3, 1H), 7.26−7.22 (m, 2H), 7.12 (s, 2H), 5.85−5.74 (m, 1H), 5.14 (d, $J$ = 18.8, 1H), 5.17−5.06 (m, 3H), 2.98 (t, $J$ = 7.6, 2H), 2.75−2.61 (m, 2H), 2.70 (t, $J$ = 7.6, 2H), 2.42 (t, $J$ = 6.8, 2H), 2.03−1.90 (m, 2H), 1.53 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) 172.7, 152.1, 141.4, 135.8, 133.4, 131.0, 128.30, 128.25, 125.8, 124.7, 117.7, 72.6, 38.6, 36.4, 35.2, 34.2, 31.7, 31.0, 30.3; MS (70 eV) 436 ($M^+$, 100), 421 (23), 277 (74), 263 (64), 235 (24), 219 (80), 203 (23), 117 (20), 91 (20); TLC $R_f$ 0.5 (EtOAc/hexane, 1/5); HR-MS calcd for $C_{29}H_{40}O_3$: 436.2977, found: 436.2985. Anal. Calcd for $C_{29}H_{40}O_3$: C, 79.77, H, 9.23. Found: C, 80.00, H, 9.53.



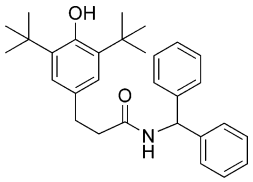
**(1′*R**,2′*S**,5′*R**)-2′-Isopropyl-5′-methyl-cyclohexyl 3-(3,5-Di-*tert*-butyl-4-hydroxyl)phenylpropanoate, 3f.** Data: IR ($CH_2Cl_2$) 3009 (w), 2871 (s), 1721 (s), 1481 (w), 1367 (m), 1265 (m), 1179 (m); $^1$H NMR (400 MHz, $CDCl_3$) 6.99 (s, 2H), 5.05 (s, 1H), 4.68 (dt, $J$ = 10.8, 4.3, 1H), 2.86 (t, $J$ = 7.6, 2H), 2.58 (t, $J$ = 7.6, 2H), 1.96−1.94 (m, 1H), 1.86−1.78 (m, 1H), 1.68−1.64 (m, 2H), 1.53−1.33 (m, 5H), 1.43 (s, 18H), 0.89 (d, $J$ = 6.6, 3H), 0.87 (d, $J$ = 7.0, 3H), 0.73 (d, $J$ = 7.0, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 172.8, 152.1, 135.9, 131.2, 124.8, 74.1, 47.0, 41.0, 36.7, 34.3, 31.4, 31.1, 30.5, 30.3, 26.3, 23.5, 22.0, 20.7, 16.4; MS (70 eV) 417 (M + $H^+$, 20), 416 ($M^+$, 100), 401 (10), 279 (20), 277 (84), 263 (70), 223 (21), 219 (39); TLC $R_f$ 0.5 (EtOAc/hexane, 1/5); HR-MS calcd for $C_{27}H_{44}O_3$: 412.3290, found: 416.3279. Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83, H, 10.64. Found: C, 77.80; H, 10.98.



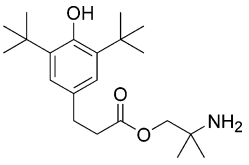
***N*-Benzyl-3-(3,5-di-*tert*-butyl-4-hydroxy)phenylpropanamide, 4a.** Data: mp 63−66 °C; IR ($CH_2Cl_2$) 3657 (w), 3057 (s), 2986 (s), 1733 (w), 1551 (w), 1422 (s), 1278 (s), 1259 (s), 1158 (m); $^1$H NMR (400 MHz, $CDCl_3$) 7.31−7.24 (m, 3H), 7.15 (d, $J$ = 7.4, 2H), 7.00 (s, 2H), 5.67 (bs, 1H), 5.08 (s, 1H), 4.40 (d, $J$ = 5.6, 2H), 2.91 (t, $J$ = 7.4, 2H), 2.50 (t, $J$ = 7.5, 2H), 1.41 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) 172.3, 152.2, 138.2, 136.1, 131.3, 128.7, 127.7, 127.4, 124.8, 43.6, 39.0, 34.3, 31.8, 30.3; MS (70 eV) 368 (M + $H^+$, 100), 367 ($M^+$, 51), 352 (22), 312 (40), 296 (31), 232 (12), 219 (18), 148 (16), 108 (18), 106 (44), 91 (70), 57 (22); TLC $R_f$ 0.4 (EtOAc/hexane, 1/4); HR-MS calcd for $C_{24}H_{33}NO_2$:367.2511, found: 367.2518.



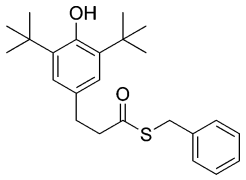
***N*-Diphenylmethyl-3-(3,5-di-*tert*-butyl-4-hydroxy)phenylpropanamide, 4b.** Data: mp 65−67 °C; IR ($CH_2Cl_2$) 3657 (w), 3054 (s), 2986 (s), 1551 (w), 1422 (s), 1278 (s), 1259 (s), 1156 (w); $^1$H NMR (400 MHz, $CDCl_3$) 7.31−7.22 (m, 6H), 7.10 (d, $J$ = 7.1, 4H), 7.02 (s, 2H), 6.23 (d, $J$ = 8.0, 1H), 5.95 (bd, $J$ = 7.8, 1H), 5.10 (s, 1H), 2.93 (t, $J$ = 7.8, 2H), 2.59 (t, $J$ = 7.6, 3H), 1.41 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) 171.3, 152.3, 141.6, 136.2, 131.1, 128.6, 127.4, 127.3, 124.8, 56.8, 38.6, 34.3, 31.5, 30.3; MS (70 eV) 444 (M + $H^+$, 31), 443 ($M^+$, 44), 276 (37), 182 (37), 167 (100), 165 (21), 152 (12), 57 (18); TLC $R_f$ 0.4 (EtOAc/hexane, 1/4); HR-MS calcd for $C_{30}H_{37}NO_2$: 443.2824, found: 443.2831.



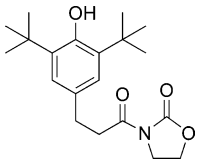
**2-Amino-2-methylpropyl 3-(3,5-Di-*tert*-butyl-4-hydroxy)-phenylpropanoate, 4c.** Data: mp 102−105 °C; IR ($CH_2Cl_2$) 3636 (w), 3054 (s), 2986 (s), 1667 (w), 1650 (w), 1551 (w), 1422 (s), 1265 (s); $^1$H NMR (400 MHz, $CDCl_3$) 7.02 (s, 2H), 5.07 (s, 1H), 3.92 (s, 2H), 2.86 (t, $J$ = 7.9, 2H), 2.54 (t, $J$ = 7.9, 2H), 1.43 (s, 24H), 1.26 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) 165.5, 152.1, 135.8, 131.3, 124.9, 78.9, 66.9, 34.26, 34.25, 30.5, 30.3, 28.4; MS (70 eV) 350 (M + $H^+$, 18), 332 (39), 331 (50), 294 (17), 259 (18), 232 (27), 219 (100), 203 (55), 161 (20), 147 (29), 113 (15), 72 (25), 57 (63); TLC $R_f$ 0.5 (EtOAc/hexane, 1/2); HR-MS calcd for $C_{21}H_{35}NO_3$: 349.2617, found: 349.2615.



***S*-Benzyl 3-(3,5-Di-*tert*-butyl-4-hydroxy)phenylthiopropanoate, 5.** Data: mp 71−75 °C; IR ($CH_2Cl_2$) 3657 (w), 3081 (s), 3000 (s), 2972 (s), 1452 (s), 1408 (s), 1300 (s), 1232 (s); $^1$H NMR (400 MHz, $CDCl_3$) 7.34−7.25 (m, 5H), 7.01 (s, 2H), 5.1 (s, 1H), 4.17 (s, 2H), 2.98−2.93 (m, 2H), 2.9−2.87 (m, 2H), 1.45 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) 198.1, 152.2, 137.6, 136.0, 130.5, 128.8, 128.6, 127.2, 124.8, 45.8, 34.3, 33.1, 31.4, 30.3; MS (70 eV) 385 (M + $H^+$, 21), 384 ($M^+$, 100), 369 (28), 329 (10), 232 (39), 219 (95), 203 (37), 91 (22); TLC $R_f$ 0.7 (EtOAc/hexane, 1/10); HR-MS calcd for $C_{24}H_{32}SO_2$: 384.2123, found: 384.2121. Anal. Calcd for $C_{24}H_{32}SO_2$: C, 74.95; H, 8.39; S, 8.34. Found: C, 74.93; H, 8.00; S, 8.60.




**3-[3-(3,5-Di-*tert*-butyl-4-hydroxy)phenylpropanoyl]-oxazolidin-2-one, 6.** Data: IR ($CH_2Cl_2$) 3692 (w), 3057 (s), 2986 (s), 1725 (m), 1551 (w), 1422 (s), 1278 (s), 1253 (s); $^1$H NMR (400 MHz, $CDCl_3$) 7.06 (s, 2H), 5.10 (s, 1H), 4.38 (t, $J$ = 7.8, 2H), 4.03 (t, $J$ = 7.8, 2H), 3.24 (t, $J$ = 7.8, 2H), 2.91 (t, $J$ = 7.8, 2H), 1.45 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) 172.8, 153.4, 152.1, 135.8, 130.9, 125.0, 61.9, 42.5, 37.3, 34.2, 30.4, 30.2; MS (70 eV) 347 ($M^+$, 77), 277 (13), 276 (100), 236 (17), 203 (42), 161 (18), 147 (48), 91 (20); TLC $R_f$ 0.3 (EtOAc/hexane, 1/5); HR-MS calcd for $C_{20}H_{29}NO_4$: 347.2097, found: 347.2091.




**Acknowledgment.** We thank the National Science Council of Taiwan for a generous financial support of this research. We are indebted for the partial grant support from a special research-promoting program (ORD 92-3) from the National Taiwan Normal University. We thank Professor Liviu Birzan at Institute of Organic Chemistry, Bucharest, Romania, for his enlightening suggestions and his kindness in allowing us to quote his insightful explanation and discussion regarding the mechanistic aspects of the vanadyl and oxotitanium species-mediated catalysis.

**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0484878