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Nucleophilic Acyl Substitutions of Anhydrides with Protic Nucleophiles Catalyzed by Amphoteric, Oxomolybdenum Species

Chien-Tien Chen,* Jen-Huang Kuo, Vijay D. Pawar, Yogesh S. Munot, Shieu-Shien Weng, Cheng-Hsiu Ku, and Cheng-Yuan Liu

Department of Chemistry, National Taiwan Normal University, #88, Sec. 4, Ding-jou Road, Taipei 11650, Taiwan

chefv043@scc.ntnu.edu.tw

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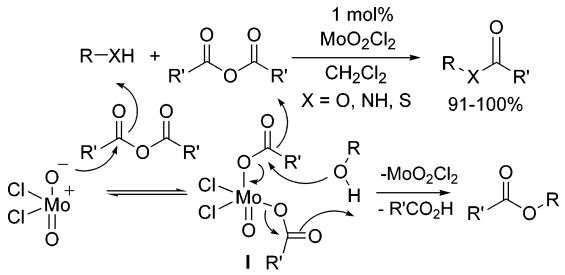

M: 386 (R' = *tert*-Bu), ESI-MS: m/e = 450 ($M+CH_3CN+Na^+$)

Among six different group VIb oxometallic species examined, dioxomolybdenum dichloride and oxomolybdenum tetrachloride were the most efficient catalysts to facilitate nucleophilic acyl substitution (NAS) of anhydrides with a myriad array of alcohols, amines, and thiols in high yields and high chemoselectivity. In contrast to the well-recognized redox chemical behaviors associated with oxomolybdenum(VI) species, the catalytic NAS was unprecedented and tolerates virtually all kinds of functional groups. By using benzoic anhydride as a mediator for in situ generation of an incipient mixed anhydride−MoO_2Cl_2 adduct with a given functional alkanoic acid, one can achieve oleate, dipeptide, diphenylmethyl, *N*-Fmoc-α-amino, pyruvic, and *tert*-butylthio ester, *N*-*tert*-butylamide, and trityl methacrylate syntheses with appropriate protic nucleophiles. The amphoteric character of the Mo=O unit in oxomolybdenum chlorides was found to be responsible for the catalytic NAS profile as supported by a control NAS reaction of using an authentic adduct−$MoOCl_2(O_2CBu^t)_2$ between pivalic anhydride and MoO_2Cl_2 as the catalyst.

Introduction

The acylations of protic nucleophiles including alcohols, amines, and thiols are important and commonly used transformations in organic synthesis.[1] The resultant esters, amides, and thioesters constitute three major classes of carboxylic acid derivatives, serving as important functional components and/or intermediates in synthetic chemistry and biological systems.[2] In these reactions, acid halides or anhydrides are often employed as the acyl source in basic media[3] or in the presence of Lewis base (e.g., DMAP, phosphines, and proazaphosphatrane),[4] Brønsted acid[5] or Lewis acid (e.g., $AlCl_3$, $TiCl_4$,[6] La(O-*i*-Pr)$_3$,[7] and $CoCl_2$[8]) catalysts. For the past 10 years, trimethylsilyl (TMS) triflate[9] and metal salts derived from triflates and perchlorates such as lithium,[10] magnesium,[11] indium,[12] tin,[13] bismuth,[14] titanium,[15] copper,[16] zinc,[17] and scandium[18] have been found to be effective in catalyzing the acetylation of alcohols with anhydrides.

Although these metal triflates and perchlorates along with other Lewis acid catalysts are available for the acetylation reactions, few of them have been studied for the similar pivalation, benzoylation, or with more ex-

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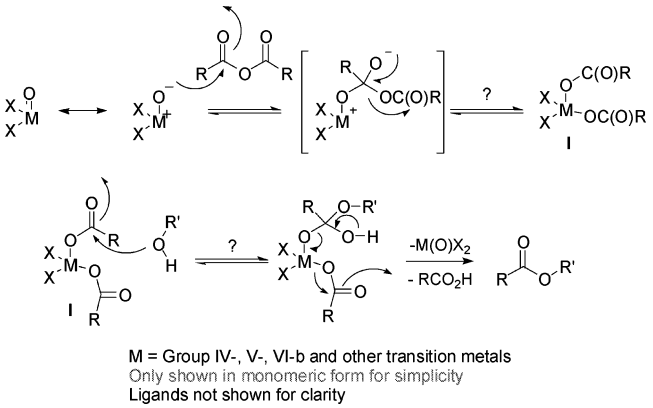
tended anhydride scope.[9a,14,18a] In addition, substrates bearing acid-sensitive groups such as acetonide, THP ether, allylic, and stilbene-type diol might not be fully compatible. For instance, in scandium triflate catalyzed acetylations of allylic alcohols, rearranged products have been observed.[19] And, TMS triflate was found to be too reactive and moisture sensitive.[9] As a result, its mediated reactions often need to be performed at or below 0 °C to minimize the decomposition of other existing functional groups. More importantly, the actual catalytic roles of these metal salt species remain elusive in view of the facile intervention of acid[5,20] or acyl triflate[21] catalysis. In these contexts, searches for achieving general nucleophilic acyl substitutions (NAS) of anhydrides and other acyl sources with protic functionalized nucleophiles in a catalytic, mild, and handy fashion with integrity of existing acid- and/or base-sensitive functionalities remain in great demand.

Background, Significance, and Aims

Amphoteric Characters of Oxovanadium Species. Recently, we have demonstrated for the first time that various vanadyl species can react with an anhydride (a carbonyl-centered electrophile) to establish a fast equilibrium with a putative anhydride adduct (Scheme 1).[22] Under such circumstances, a protic nucleophile (e.g., an alcohol) may add to one of the two alkanoates in the adduct **I** and with a concomitant elimination of an alkanoic acid to regenerate the vanadyl species (i.e., a catalytic nucleophilic acyl substitution (NAS) of an anhydride). We have thus unraveled a mild, chemoselective, catalytic profile of amphoteric vanadyl species for the construction of C−O, C−N, and C−S bond by NAS of anhydrides with various functionalized protic nucleophiles. To gain some insight into the mechanistic proposal, an incipient putative adduct **I** was isolated by heating vanadyl triflate in trifluoroacetic anhydride and found to be responsible for the subsequent substitution by a protic nucleophile (e.g., 2-phenylethanol) in an intra- or intermolecular fashion.[22a]

SCHEME 1. Proposed Equilibrium between an Amphoteric Vanadyl or Other Oxometallic Species and an Anhydride in Catalytic Acylation with an Alcohol



Other Oxometallic Species. Conventionally, the transition-metal complexes of groups IV−VIb are well-known to form bridged compounds[23] and for their abilities toward catalytic oxygen-transfer reactions to sulfides and olefins.[24] In particular, dioxomolybdenum complexes bearing oxygen,[25] nitrogen,[26] and/or sulfur[27] donor ligands

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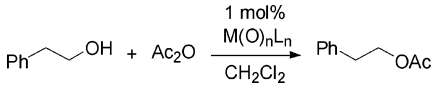
TABLE 1. Acetylation of 2-Phenylethanol Catalyzed by Group VIb Oxometallic Species



entry	MO_nL_n[a]	time (h)	$t_{1/2}$[b]	yield,[c] %
1	$MoOCl_4$	0.08	40 s	97
2	$WOCl_4$	28	6.8 h	96
3	CrO_2Cl_2	7	2.1 h	100
4	MoO_2Cl_2	0.05	7 s	100
5	$MoO_2(acac)_2$	10	2.5 h	98
6	WO_2Cl_2	47	16.8 h	100

[a] Hydrate ligands were omitted unless otherwise stated. [b] The reaction time at 50% conversion. [c] Isolated yields.

have been examined extensively to serve as model systems for the active site in oxo-transfer molybdato enzymes.[23,28] However, the acyl-transfer profiles mediated by these and other oxometallic species[29] have never been explored. To probe if the amphoteric character associated with the V=O unit also exists in group VIb oxo-metallic species toward anhydride, we have carried out an in-depth study as to their catalytic effects on the NAS of anhydrides. In addition, we would like to independently verify the involvement of adduct **I** in its subsequent reaction with a protic nucleophile. We herein describe our findings toward these aspects.

Results and Discussions

Screening of Group VIb Oxometallic Species. Six different commercial group VIb oxometallic species were examined for mediating the test acetylation of 2-phenylethanol, Table 1. Their kinetic trace experiments determined by HPLC analyses of the reaction mixture with reaction time are shown in Figure 1. It was found that the catalytic activity of an oxometallic species highly depends on the metal attributes, the number of oxo ligand(s), and the ligand's electronic (accepting or donating) attribute. The fifth-period oxomolybdenum species are 189−1080 times more reactive than the forth-period oxochromium one (compare $t_{1/2}$ in entries 1, 3, and 4)![30] The sixth-period oxotungsten species ($WOCl_4$ and WO_2Cl_2) are the least reactive (entries 2 and 6). The acetylations went to completion in 28 and 47 h, respectively.

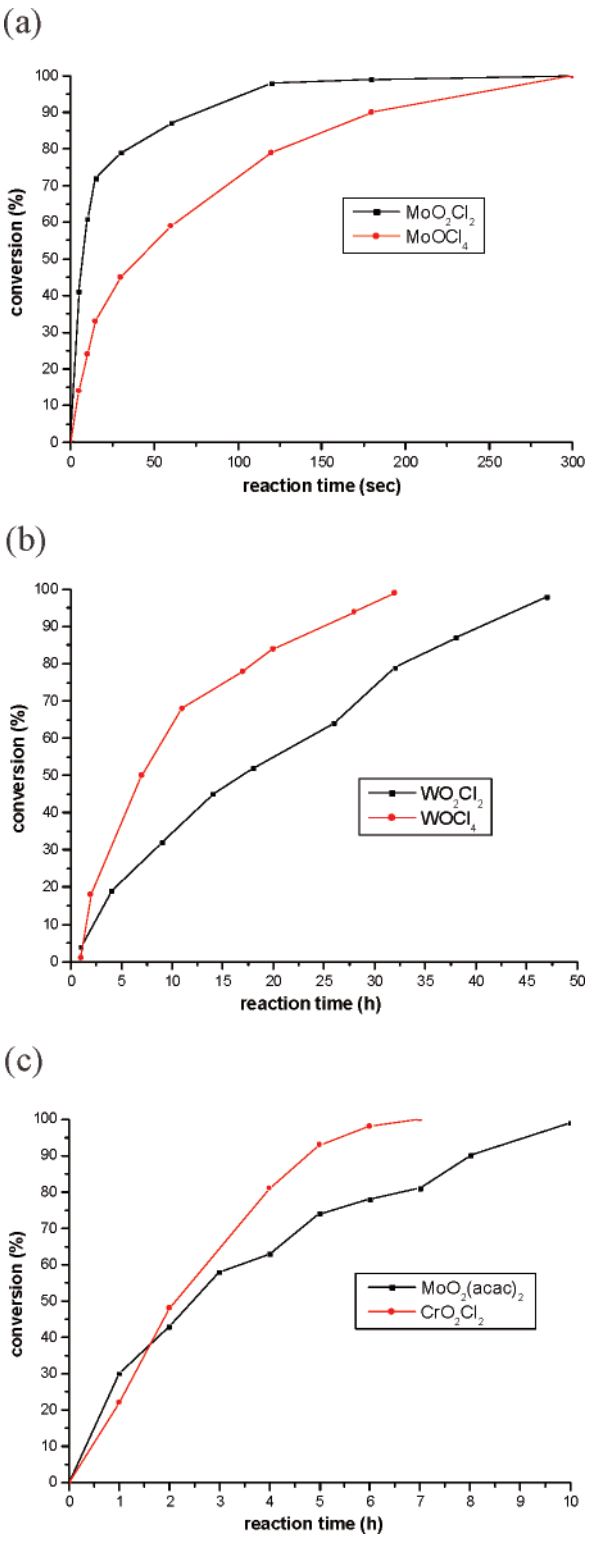


FIGURE 1. (a) Stacked kinetic plots for MoO_2Cl_2- and $MoOCl_4$-catalyzed acetylation. (b) Stacked kinetic plots for WO_2Cl_2- and $WOCl_4$-catalyzed acetylation. (c) Stacked kinetic plots for $MoO_2(acac)_2$- and CrO_2Cl_2-catalyzed acetylation.

Notably, the number of oxo ligand(s) does not play a constant role in the catalytic activity of oxometallic species. For example, MoO_2Cl_2 ($t_{1/2}$, 7 s, entry 4) is slightly more reactive (by 6 times) than $MoOCl_4$ ($t_{1/2}$, 40 s, entry 1). On the other hand, the trend is reversed in the WO_nL_n

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(30) $CrOCl_4$ is not available. Therefore, its catalytic behavior could not be evaluated.

family where WO_2Cl_2 ($t_{1/2}$, 16.8 h, entry 6) is less reactive by 2.5 times than $WOCl_4$ ($t_{1/2}$, 6.8 h, entry 2).

As illustrated above, the amphoteric character of the M = O unit is highly metal dependent. The MoO_2Cl_2 and WO_2Cl_2 exhibit extremely different catalytic activities ($t_{1/2}$: 7 s vs 16.8 h, entries 4 and 6) in the model reaction despite the fact that W and Mo bear very similar atomic and covalent radii.[31] In addition, even though Mo=O and Cr=O derivatives show stretching vibrations similar to those of vanadyl (V=O) species,[32] they display very different catalytic profiles from that of $VOCl_2$ (7.5 h, 94% yield). *The higher catalytic reactivity of MoO_2Cl_2 may have to do with the weaker Mo=O double-bond character relative to that of WO_2Cl_2 as reflected in the larger M=O stretching vibration frequency (higher bond order) for WO_2Cl_2.*[31b,c] *Therefore, the smaller π-electron density in Mo=O results in higher electron density and more nucleophilic nature on its oxygen lone pairs.* As mentioned in Scheme 1, the esterification is a two-step reaction. It is initiated with nucleophilic attack of the lone pair on the oxygen of MO_2Cl_2 to the acid anhydride, followed by nucleophilic attack of the alcohol to the resulting metalate−carboxylic acid mixed anhydride. On the basis of the frontier molecular orbital (FMO) theory, the energy level of the oxygen lone pair on MO_2Cl_2 (M = Cr, Mo, W) should be essential for the initial step (Scheme 1) and the σ^* M−O energy of the incipient meatallocarboxylate must be important for the latter step, respectively. Presumably, the molybdenum catalyst is more suitable for both steps. Consistent with the observed higher reactivity for the oxygenation of $MoOCl_4$ toward $(Me_3Si)_2O$ to form MoO_2Cl_2 among the group VIb species,[33] the uniquely higher catalytic activity of MoO_2Cl_2 (as compared to those of CrO_2Cl_2 and WO_2Cl_2) toward NAS of anhydrides strongly indicates that the amphoteric character of Mo=O plays the dominant role in activating $SOCl_2$,[34] $(Me_3Si)_2O$,[35] $(Bu_3Sn)_2O$,[36] and currently the unprecedented carbonyl-centered electrophiles (i.e., $(RC(O))_2O$). Similar to vanadyl species-mediated catalysis, the counteranion effect on the catalyst activity follows the trend of electronegativity (i.e., Cl > acac).

The Effects of Solvents. The test acetylation was further examined with 1 mol % of MoO_2Cl_2 in eight different solvents at ambient temperature. It was found that the acetylations proceed much faster (all in less than 20 min) in haloalkane (e.g., CH_2Cl_2, $CHCl_3$, and CCl_4) and aromatic (e.g., toluene and benzene) solvents than those in polar coordinating solvents such as ether (42 min), THF (18 h), and CH_3CN (6 h). The results suggest that polar coordinating solvents suppress the activation of acetic anhydride by MoO_2Cl_2 due to reduced nucleophilicity of Mo=O units. In addition, pre-coordination of a protic nucleophile (e.g., 2-phenylethanol) to adduct **I** (Scheme 1) might be involved in the second NAS step. Polar coordinating solvents tend to retard this event due to competing coordination, thus slowing down the acetylations.

Best Water-Tolerant Candidates. Besides the VOX_2 family, water-tolerant MoO_2Cl_2 and $MoOCl_4$ were found to be the most reactive and are superior to both $V(O)Cl_2$ and $V(O)(OTf)_2$. Acetylations were complete in 6 and 12 min, respectively, leading to phenethyl acetate in ≥97% yields. It should be noted that the corresponding moisture-sensitive $MoCl_5$ and WCl_6 are also catalytically active but with significantly different reaction times (2 and 3 h, respectively), supporting the mechanistic role of the M=O unit in the group VIb oxometallic catalysts. In addition, there is no need for chromatographic purification with the new catalytic acetylation protocol (i.e., with MoO_2Cl_2) since the remaining acetic anhydride can be readily quenched by aqueous workup. More importantly, similar to the VOX_2 family, MoO_2Cl_2 can be recovered in >95% yield by the usual aqueous workup and reused with intact catalytic activity for at least five consecutive runs. The use of water-tolerant oxometallic chlorides with substantiated catalytic roles in acylation chemistry is a significant breakthrough since triflic acid[20] and acyl triflate[21] have been found to operate in the metal triflate-mediated catalyses as pointed out previously.

Anhydride Scopes. Besides acetic anhydride, the catalytic system is amenable to a diverse array of acyclic and cyclic, aliphatic and aromatic anhydrides, Table 2. In general, the more hindered the anhydride, the slower the acylation rate (i.e., $CH_3 \sim CF_3 \sim ClCH_2 >$ Pr ~ *i*-Pr > *t*-Bu, entries 1−6). Notably, the use of chloroacetic anhydride allows for subsequent functional manipulation at the chloro moiety by S_N2 reactions, e.g., replaced by an azido group.[37] Acylation with an aromatic anhydride (e.g., R = Ph, entry 8) is up to 270 times slower than those with aliphatic anhydrides (entries 1−3). Acylation with di-*tert*-butyl dicarbonate, a common protective agent for alcohols and amines,[38] also proceeds well and with a faster rate by a factor of 3 than that of benzoylation (entries 7 and 8). Cyclic anhydrides such as succinic, tetrahydrophthalic (THphthalic), diglycolic, and phthalic anhydride are the least reactive. Acylations generally took 2−2.5 days (entries 9−10, 12−13). The anhydride in entry 11, a Diels−Alder adduct between furan and maleic anhydride and a commonly used substrate in ring-opening metatheses[39] and in asymmetric acylation,[40] condenses smoothly with 2-phenylethanol at 4 °C in 4.5 days, leading to the corresponding ester in 92% yield

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(32) Matsuda, Y.; Yamada, S.; Murakami, Y. *Inorg. Chim. Acta* **1980**, *44*, L309.

(33) The oxygenation of $MoOCl_4$ occurs at ambient temperature. However, the similar reaction for $WOCl_4$ proceeds at 100−120 °C; see: Gibson, V. C.; Kee, T. P.; Shaw, A. *Polyhedron* **1988**, *7*, 579.

(34) For the preparation of $MoOCl_4$ from MoO_3 in refluxing $SOCl_2$, see: (a) Taylor, J. C.; Waugh, A. B. *J. Chem. Soc., Dalton Trans.* **1980**, 2006. (b) Diversi, P.; Ingrosso, G. I.; Lucherini, A.; Landucci, M. *Polyhedron* **1987**, *6*, 281.

(35) (a) For Lewis base character of Mo=O toward Brønsted acids, see: Gibson, V.; Graham, A. J.; Ormsby, D. L.; Ward, B. P.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **2002**, 2597. (b) For Lewis acid character of Mo=O toward organosilanes, see: Kim, G.-S.; Huffman, D.; Dekock, C. W. *Inorg. Chem.* **1989**, *28*, 1279.

(36) For the activation of molybdenum blue or $MoO_2(acac)_2$ by $(Bu_3Sn)_2O$ to form $(Bu_3SnO)_2MoO_2$, see: Kamiyama, T.; Inoue, M.; Enomoto, S. *Chem. Lett.* **1989**, 1129.

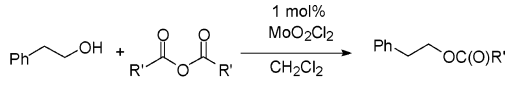
(37) For the practical use of azido esters in click chemistry, see: Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2596.

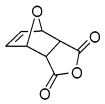
(38) Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368.

(39) For one leading application, see: Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zecri, F. J. *Org. Lett.* **2000**, *2*, 261.

(40) For leading applications, see: (a) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542. (b) Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190. (c) Bolm, C.; Schiffers, I.; Dinter, C. I.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984.

TABLE 2. Catalytic Acylations of 2-Phenylethanol with Various Anhydrides in the Presence of MoO_2Cl_2



entry	Anhydride/R'	time (h)	yield,[a] %
1	CH_3	0.1	100
2	CF_3	0.1	98
3	$ClCH_2$	0.1	98
4	$CH_2CH_2CH_3$	0.15	100
5	*i*-Pr	0.15	99
6	*tert*-Bu	12	99
7	*tert*-BuO	9	96
8	Ph	27	99
9	succinic	48	98
10		60	98
11		108[b]	92
12	CH_2-O-CH_2	56	91
13	phthalic	78	92
14		4[c]	95

[a] Isolated yields by column chromatography. [b] Performed at 0 °C. [c] Performed in toluene at 50 °C.

(entry 11).[41] Finally, a malonic acid−acetonide adduct (Meldrum's acid, entry 14) was tested for the catalytic acylation.[42] The MoO_2Cl_2-mediated NAS process proceeds in warm toluene at 50 °C in 4 h, leading to mono-2-phenethyl malonate in 95% yield. In comparison, no desired product was observed when the reaction was carried out in toluene at 50 °C for 24 h in the absence of MoO_2Cl_2. Conventionally, the reaction was effected in only 34−73% yields in refluxed benzene or toluene.[43] To achieve even more complete conversion, the reactions need to be carried out in neat Meldrum's acid at 110−120 °C.[44]

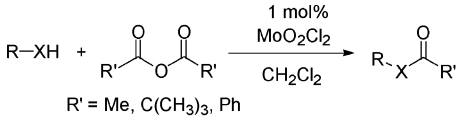
(41) A retro-Diels−Alder process was dominant when the reaction was performed at ambient temperature.

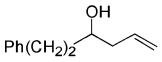
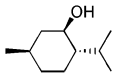
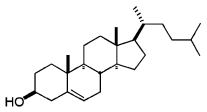
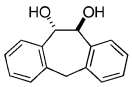
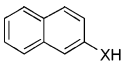
(42) For enzymatic processes in warm media, see: de Gonzalo, G.; Brieva, R.; Sánchez, V. M.; Bayod, M.; Gotor, V. *J. Org. Chem.* **2003**, *68*, 3333.

(43) (a) Costa, M.; Dalcanale, E.; Dias, F. S.; Graiff, C.; Tiripicchio, A.; Bigliardi, L. *J. Organomet. Chem.* **2001**, *619*, 2179. (b) Stauber, M. J.; Debiak-Krook, T.; Miller, M. J. *Heterocycles* **1993**, *35*, 1205. (c) Callahan, J. F.; Newlander, K. A.; Burgess, J. L.; Eggleston, D. S.; Nichols, A. *Tetrahedron* **1993**, *49*, 3479.

(44) Felder, D.; Carreon, M. del P.; Gallani, J.-L.; Guillon, D.; Nierengarten, J.-F.; Chuard, T.; Deschenaux, R. *Helv. Chim. Acta* **2001**, *84*, 1119.

TABLE 3. MoO_2Cl_2-Catalyzed Acetylation, Pivalation, and Benzoylation of Alcohols, Amines, and Thiols



entry	substrate[a]	time, h	yield,[b] %
1	$Ph(CH_2)_2OH$	0.1 (12/26[c])	100 (99/92[c])
2	$PhCH{=}CHCH_2OH$	0.3 (8/12)	98 (96/98)
3		0.7 (15/38)	95 (90/97)
4		6 (40/--)	98 (91/--)
5		2 (36/74)	99 (94/92)
6	*tert*-BuOH[d]	2 (12/24)	94 (99/99)
7	Ph_3COH[d]	2 (12/24)	98 (99/97)
8		1 (24/--)	99 (91/--)
9		4 (20/70)	99 (98/98)
	X = O, NH, S	0.5 (2.5/50/36[e])	98 (97/99/95[e])
		12 (144/80)	97 (96/100)
10	$PhCH_2NH_2$	0.1 (0.3/1/0.2[e])	99 (99/99/95[e])
11	$(i\text{-Pr})_2NH$	0.4	97
12	*tert*-$BuNH_2$	0.1 (0.2/2/1[e])	99 (99/99/98[e])
13	$PhCH_2SH$	4 (14/8)	100 (95/98)
14	*tert*-BuSH	18 (42/26)	98 (97/100)

[a] 1.5 equiv of anhydride was used unless otherwise stated. [b] Isolated yields and characterized spectroscopically. [c] The data in parentheses correspond to pivalations and benzoylations, respectively, unless otherwise stated. [d] Carried out in refluxed toluene with 1 equiv of $EtN(i\text{-Pr})_2$. [e] The third item in parentheses corresponds to *t*-Boc protection.

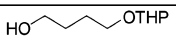
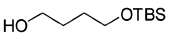
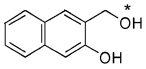
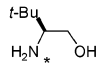
The Effects of Protic Nucleophiles. With the optimal catalyst $Mo(O)_2Cl_2$ in hand, nucleophilic acyl substitutions of acetic, pivalic anhydride (representing two steric extremes), and benzoic anhydride with protic nucleophiles (e.g., alcohols, amines, and thiols) of varying steric and electronic demands were examined. In all cases the chemical yields of acylations were ≥90%, Table 3.

MoO_2Cl_2-catalyzed acylations are more reactive by up to 14 times than the corresponding $V(O)(OTf)_2$-catalyzed ones.[22a] In particular, benzoylations of secondary alcohols by MoO_2Cl_2 are far more efficient than those catalyzed by $V(O)(OTf)_2$ where heating becomes essential. In general, acetylations of alcohols proceed much faster by 5−120 times than the corresponding pivalations. In turn,

pivalations of alcohols proceed faster by 1.5−3.5 times than the corresponding benzoylations. On the other hand, acetylations of thiols and amines are merely 2−12 and 2−5 times faster than the corresponding pivalations, respectively, presumably due to their increasing nucleophilicities. In turn, pivalations of amines proceed faster by 3−20 times than the corresponding benzoylations presumably due to the more acidic nature of the resultant benzoic acid (compared with acetic or pivalic acid) during the benzoylation. The partial proton transfer from benzoic acid to amine substrates may be responsible for slowing down the benzoylation. Notably, acylations of thiols are more sensitive to steric than to electronic attributes of anhydrides. The pivalations of thiols proceed slower by 1.6−1.8 times than the corresponding benzoylations!

Acylations went smoothly with primary (entries 1−2), secondary (entries 3−5), and acid-sensitive allylic (entry 2) and benzylic (entry 8) alcohols. No trace of allylic[19,45] or pinacol[46] rearrangement byproducts was observed in the case of cinnamyl alcohol and stilbene-type diol (entries 2 and 8). Acylation of tertiary alcohols turns out to be more challenging. Tertiary alcohols such as *tert*-butyl alcohol[47] and trityl alcohol[48] were completely inert toward acylation in catalytic MoO_2Cl_2 at ambient temperature for more than 48 h. In addition, only about 10% conversion was observed when both the acetylations were carried out in refluxing CH_2Cl_2 for 24 h. We figured that the intrinsic steric hindrance associated with tertiary alcohols may tend to interrupt the product formation. Nevertheless, a modified protocol by adding 1 equiv of $(i\text{-Pr})_2$NEt, a sterically hindered base, into the reaction media allows one to achieve complete acetylations of respective *tert*-butyl alcohol and trityl alcohol in refluxed toluene in 2 h (24 h in CH_2Cl_2) (entries 6 and 7, Table 3). A control reaction in the absence of catalytic MoO_2Cl_2 under otherwise similar reaction conditions did not lead to any appreciable product formation in 2 days.[49] In addition, both the corresponding pivalations and benzoylations reach full conversions in refluxed toluene in 12 and 24 h, respectively. On the other hand, the corresponding *tert*-butylamine and *tert*-butanethiol are fairly reactive (entries 12 and 14) under standard NAS conditions. Aromatic alcohols, amines,[50] and thiols (e.g., 2-hydroxy-, 2-amino-, and 2-thionaphthalenes) are amenable to acylations in essentially quantitative yields (entry 9). The acylation substrate scope is somewhat limited to the application of sterically demanding diisopropylamine. It works only for the unbranched alkanoic anhydrides (entry 11). In addition, the useful *t*-Boc protections for aliphatic and aromatic amines (the third data in entry 9b, entries 10 and 12) also proceeded smoothly in ≥95% yields.

TABLE 4. Selected Examples for Acetylation, Pivalation, and Chemoselective Acylation of Functionalized Substrates Catalyzed with 1 mol % of MoO_2Cl_2

entry	substrate[a]	time, h	yield,[b] %
1		6 (13)	95 (95)
2		1 (15)	98 (99)
3	cellulose[c]	6	95
4		3[d](49/12[e])	98 (99/98[e])
5		2[f] (6/12/12[g])	99 (99/96/99)
6		0.5 (1/12/10)	100 (100/96/99)

[a] 1.5 equiv of anhydride was used unless otherwise stated. [b] Isolated yields and characterized spectroscopically. [c] Carried out at 100−110 °C in HOAc/Ac_2O. [d] Asterisk signifies the reactive site. [e] The data in parentheses correspond to pivalation and benzoylation, respectively, unless otherwise stated. [f] For effective monoacylation, 0.95 equiv of anhydride was used. [g] The third item in parentheses represents *t*-Boc protection.

The Scope of Functional Group Compatibility. Besides a diverse of functional groups such as alkene, ester (including lactone and α,β-enoate), ketone, acetonide, imide, and lactol examined previously with vanadyl triflate,[51] the current acylation protocol also tolerates protic nucleophiles bearing acid-sensitive THP ether and base-sensitive TBS ether (entries 1−2, Table 4). The high catalytic efficacy of MoO_2Cl_2 was further demonstrated in the peracetylation of the most challenging scenario-cellulose (averaged ca. 300 OH groups!), entry 3, Table 4. The peracetylation went to completion in 6 h in Ac_2O/HOAc mixture (in 1/1 ratio) at elevated temperature (100−110 °C).[52] It should be noted that cellulose acetate is commercially made from processed wood pulp. The pulp is processed using acetic anhydride to form acetate flake from which products are made. Another technique for producing cellulose acetate involved treating cotton with acetic acid/Ac_2O, using sulfuric acid as a catalyst. In both processes, the reactions were carried out below 40 °C leading to cellulose acetate with acetate content of up to ca. 40%. Major applications for cellulose acetate include textiles and fibers, spectacle frames, lacquers, handles for tools, film media, transparent sheeting, specialty papers, and filter media. The

(45) A mixture of products was obtained under usual conditions (acid chloride/pyridine). For its effective acetylation mediated by TMSOTf, lower reaction temperature (−10 °C in ethyl acetate) was required (ref 9).

(46) Conventional procedures ($(RC(O))_2O$/base) led to only pinacol rearrangement product.

(47) (a) $Ce(OTf)_3$: Dalpozzo, R.; Nino, A. De; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett.* **2003**, *44*, 5621. (b) $AlPW_{12}O_4$: Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F.; Amani, K. *Chem. Commun.* **2003**, *6*, 764. (c) $Bi(OTf)_3$: Mohammadpoor-Baltork, I.; Aliyan, H.; Khosropour, A. R. *Tetrahedron* **2001**, *57*, 5851. (d) $CoCl_2$: Ahmad, S.; Iqbal, J. *J. Chem. Soc., Chem. Commun.* **1987**, *2*, 114. (e) DMAP/CCl_4: Kamijo, T.; Yamamoto, R.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1983**, *31*, 3724.

(48) (a) $Bi(OTf)_3$: Mohammadpoor-Baltork, I.; Aliyan, H.; Khosropour, A. R. *Tetrahedron* **2001**, *57*, 5851. (b) $K_5CoW_{12}O_{40}$-$3H_2O$: Habibi, M. H.; Tangestaninejad, S.; Mirkhani, V.; Yadollahi, B. *Synth. Commun.* **2002**, *32*, 863. (c) Sn(IV) tetraphenylporphyrin perchlorate: Tangestaninejad, S.; Habibi, M. H.; Mirkhani, V.; Moghadam, M. *Synth. Commun.* **2002**, *32*, 1337.

(49) Direct heating of acetic anhydride and *tert*-butyl alcohol to give *tert*-butyl acetate in moderate 59% yield was reported: Kammoun, N.; Bigot, Y. Le; Delmas, M.; Boutevin, B. *Synth. Commun.* **1997**, *27*, 2777.

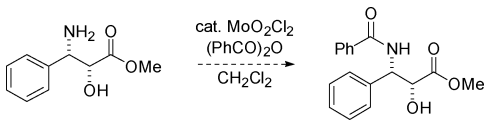
(50) (a) Conversion of aniline to acetanilide failed in $Cp^*_2Sm(thf)_2$-mediated acetylation. (b) Ishii, Y.; Takeno, M.; Kawasaki, Y.; Muromachi, A.; Nishiyama, Y.; Sakaguchi, S. *J. Org. Chem.* **1996**, *61*, 3088.

(51) See Table 4′ in the Supporting Information for a complete functional group compatibility study including the substrates that were previously examined in vanadyl triflate catalyzed NAS.

(52) Pivalations did not work properly due to the poor solubility of these substrates in pivalic anhydride.

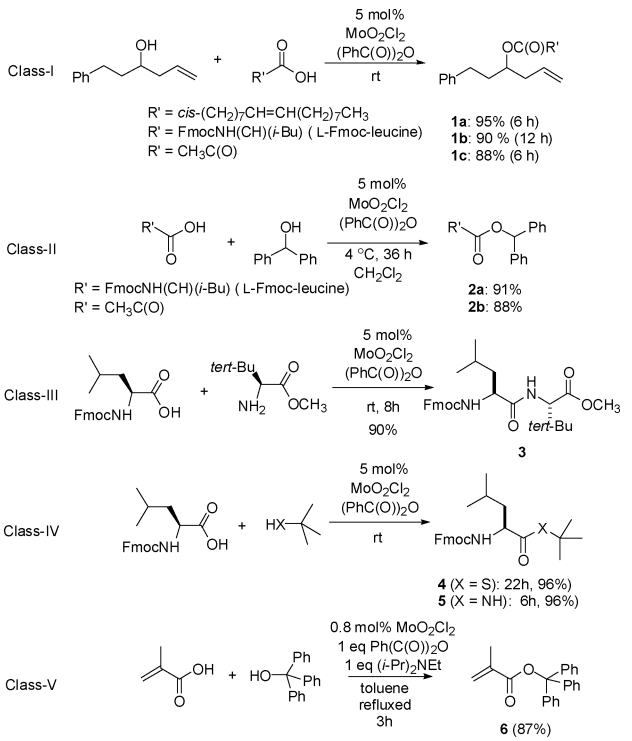
current new protocol provides essentially colorless cellulose triacetate (TAC) of high purity directly with greater than 90% acetate content due to mild catalyst attribute.[53] More importantly, the acetate content can be judiciously tuned by heating TAC in hot MeOH or EtOH in catalytic MoO_2Cl_2, which is potentially useful for optical materials applications.[54]

Chemoselectivity. By taking advantage of the differential reactivity between nucleophiles, we were able to carry out chemoselective acylation (including acetylation, pivalation, and benzoylation) of 3-hydroxymethyl-2-naphthol. Its primary hydroxyl group was acylated with complete chemoselectivity and in ≥98% yields (entry 4, Table 4). Further stirring with excess of acetic and pivalic anhydride (10 equiv) for another 18 and 72 h (50 °C) furnished the corresponding diacetylated and dipivalated products in 87% and 89% yields, respectively. Unlike the DMAP-catalyzed acylation, a complete reversal of chemoselectivity was observed in this case. Notably, acetylation of *tert*-leucinol and 2-amino-2-methyl-1-propanol at the sterically hindered amino moiety was highly selective (entries 5 and 6). The corresponding *N*-acetylated and *t*-Boc-protected products were furnished in ≥99% yields. In addition, the analogous *N*-pivalation and *N*-benzoylation also proceeded with complete selectivity (≥96% yields). Selective *N*-acylation (ca. 80−88% in terms of selectivity) of 1,2-amino alcohols bearing a secondary hydroxyl group has been achieved by conventional methods (Et_3N or pyridine).[55] However, chemoselective *N*-acylations of 1,2-amino alcohols bearing primary hydroxyl groups and with sterically hindered amino groups as shown in entries 5 and 6 are challenging. The desired products were isolated in only 20% yields by using the pivalic anhydride/pyridine protocol! Remarkably, chemoselective benzoylations of 3-hydroxymethyl-2-naphthol, *tert*-leucinol, and 2-amino-2-methyl-1-propanol also work extremely well (entries 4−6) with essentially 100% selectivity. In marked contrast, chemoselective benzoylations catalyzed by vanadyl triflate were less satisfactory (73−83% selectivity).[22a] The exclusive chemoselectivity in the benzoylation of amino alcohol substrates allows for its potential application to the Taxol C-13 side-chain synthesis by direct *N*-benzoylation of the 3-phenylisoserine ester without protecting any existing secondary alcohol functionalities.[56]



In Situ Mixed-Anhydride Approach. Since benzoic anhydride is the least reactive anhydride, one may carry out acylation directly with fatty acid in the presence of benzoic anhydride. By this protocol, the in situ generated mixed anhydride−MoO_2Cl_2 adduct acts as the real acylation reagent.[57] So far, we have examined five different substrate classes. As representative examples for class I, the respective oleic acid, Fmoc-L-leucine, or pyruvic acid was treated with 1-phenethyl-3-buten-1-ol (1.1 equiv) in the presence of benzoic anhydride (1.1 equiv) in CH_2Cl_2 with 5 mol % of MoO_2Cl_2 for 6−12 h. The resultant oleate, leucinate, and pyruvate (**1a**−**c**) were produced smoothly in 88−95% yields, Scheme 2. Satisfactory results were also achieved for class II substrates by reacting respective Fmoc-L-leucine and pyruvic acid with diphenylmethanol, a useful protective group for acids, as the nucleophile.[58] Conventionally, the direct coupling between an acid and diphenylmethanol require the use of *p*-TSA in refluxed benzene/toluene[59] or stoichiometric coupling agents under neutral conditions (e.g., Ph_3P/DEAD[60]) or basic media (e.g., DCC,[61] cyanuric acid,[62] and *O*,*O*′-di(2-pyridyl)-thiocarbonate[63] in pyridine with DMAP). Since diphen-

SCHEME 2. Acylations with Mixed Anhydride Approaches toward Oleate, Pyruvate, Dipeptide, *tert*-Butylthio Ester, *N*-*tert*-Butylamide, and Trityl Methacrylate Syntheses



(53) (a) Brownish cellulose acetate was obtained by using conventional procedures before purification. (b) Cellulose acetate with 55% acetate content could be synthesized at 80 °C for 12 h in catalytic MoO_2Cl_2.

(54) Unpublished results from this laboratory.

(55) (a) Matsumoto, H.; Matsuda, T.; Nakata, S.; Mitoguchi, T.; Kimura, T.; Hayashi, Y.; Kiso, Y. *Bioorg. Med. Chem.* **2001**, *9*, 417. (b) Matsumoto, H.; Sohma, Y.; Kimura, T.; Hayashi, Y.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 605.

(56) The documented procedure required the use of benzoyl chloride at −78 °C and Et_3N and then gradually warmed to ambient temperature; see: Palomo, C.; Arrieta, A.; Cossio, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6429.

(57) *p*-Nitrobenzoic anhydride has been utilized in macrolactonization of ω-hydroxy acids catalyzed by $Sc(OTf)_3$, see: ref 18a.

(58) Sagami. US 4086136, 1978; *Chem. Abstr.* **1978**, *89*, 180369w.

(59) (a) Paredes, R.; Agudelo, F.; Taborda, G. *Tetrahedron Lett.* **1996**, *37*, 1965. (b) Vyas, D. M.; Skonezny, P. M.; Jenks, T. A.; Doyle, T. W. *Tetrahedron Lett.* **1986**, *27*, 3099.

(60) (a) Barlos, K.; Kallitsis, J.; Mamos, P.; Patrianakou, S.; Stavropoulos, G. *Liebigs Ann. Chem.* **1987**, 633. (b) Sivvas, E.; Voukelatou, G.; Kouvelas, E. D.; Francis, G. W.; Aksnes, D. W.; Papaioannou, D. *Acta Chem. Scand.* **1994**, *48*, 76.

(61) (a) Anaya, J.; Barton, D. H. R.; Caballero, M. C.; Gero, S. D.; Grande, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2137. (b) Sliskovic, D. R.; Picard, J. A.; Roark, W. H.; Essenburg, A. D.; Krause, B. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 713.

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ylmethyl esters are similar in acid lability to *tert*-butyl esters and can be readily cleaved under mild Brønsted acids (e.g., HCl in CH_3CN[64]), warmed organic acids (e.g., CF_3CO_2H, AcOH, and HCO_2H) or by methanolic NaOH, the current applications signify a handy approach toward diphenylmethyl ester synthesis under mild reaction conditions by using benzoic anhydride as the coupling agent. In addition, pyruvates with chiral prosthetic groups arising from secondary alcohols are useful substrates for asymmetric synthesis, particularly in reduction, addition, and aldol reactions. Their syntheses by direct couplings between pyruvic acid and appropriate alcohols have been similarly achieved by several conventional methods as just mentioned.[65] The example as illustrated in the case of **2b** offers a powerful and mild alternative for their syntheses. Notably, the mixed anhydride approach by using benzoic anhydride in the presence of catalytic MoO_2Cl_2 or $V(O)(OTf)_2$ is unprecedented and all these demonstrations are so far unachievable by all the conventional (e.g., DMAP) and metal triflate-based catalysts reported to date.

tert-Butylthio esters and *N*-*tert*-butylamides are popular derivatives of protected acids. The former compounds can be unmasked by treatment with polymer-supported SO_3H,[66a] Br_2/aq THF,[66b] or in aqueous $LiOH/H_2O_2$.[67] The later compounds can be readily unmasked in aqueous acids (e.g., aqueous H_2SO_4 or 6 N HCl in protic solvents[68] and TFA[69]) or bases (e.g., aqueous NaOH/EtOH[69a]). In addition, *tert*-butylthio esters can be readily functionalized to amides,[70] esters,[71] and thio acids.[72] The mixed-anhydride technique was thus further applied to dipeptide[73] (class III), *tert*-butylthio ester,[74] and *N*-*tert*-butylamide (class IV) syntheses, as illustrated in the direct coupling of Fmoc-L-leucine with methyl L-*tert*-leucinate, *tert*-butanethiol, and *tert*-butylamine in 90%, 96%, and 96% yields, respectively. Classical ways of accessing these functional molecules from the corresponding acids also require either initial stoichiometric mixed-anhydride formation (e.g., with $CF_3(CO)_2O$[75] or $ClCO_2R$[70c,76]) and subsequent reaction with the respective nucleophile (a two-step procedure) or the use of a stoichiometric coupling agent like DCC/EDC,[77] $(EtO)_2P(O)$-CN,[78] 1,1′-carbonyldiimidazole,[79] and PyBOP[80] (a one-pot procedure) in basic media. Furthermore, trityl methacrylate (class V) can also be readily synthesized by combining the mixed anhydride approach with the modified acylation protocol especially for tertiary alcohols at elevated temperature. Conventionally, this substrate class can only be made through a combination of trimethylsilyl methacrylate and trityl fluoride or trityl silyl ether in the presence of SiF_4 or TMSOTf.[81] The newly devised recipe proves to be more handy and practical in terms of large scale preparation. Notably, these five substrate classes are important in view of their potential chiral template[82] (class I), combinatorial[83] (class II), peptide[84] (class II and III), medicinal[85] (class II and IV, e.g., the

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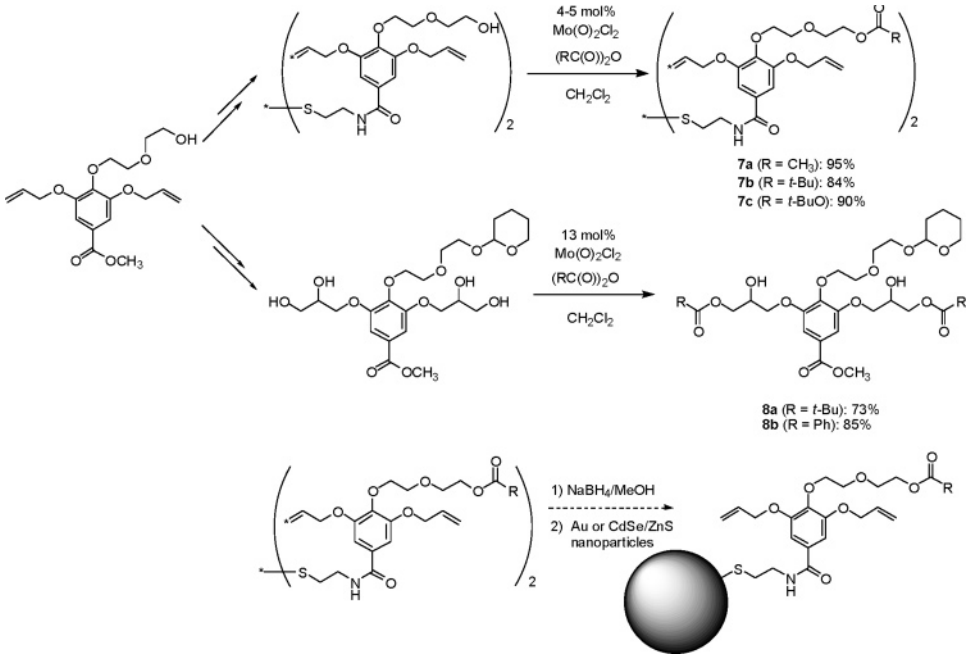
SCHEME 3. Applications to Highly Functionalized Molecules



tert-butyl amide side chain in Propecia[86]), biochemical[87] (class IV), and chiral polymer[88] (class V) applications. Therefore, the current approach represents a new practical one-pot procedure by using relatively cheap benzoic anhydride as the coupling agent and catalytic MoO_2Cl_2 to directly construct a myriad array of C−O, C−N, and C−S bonds for molecules of biologically and industrial interests at ambient temperature.

Mechanistic Insights. To clarify if $MoOCl_2(O_2CR)_2$ **I** was actually involved in MoO_2Cl_2-catalyzed NAS, we have prepared it from respective $MoOCl_4$ with silver pivalate in a 1:2 ratio in anhydrous CH_2Cl_2 or benzene. Its identity and purity were fully secured by ^1H NMR, ^{13}C NMR,[89] and ESI-MS analyses (Figure 2). When it was subjected to the same NAS reaction conditions, the reaction catalyzed by 5 mol % $MoOCl_2(Piv)_2$ **I** exhibit matching reaction rate (3.5 h, 97% yield) as that mediated by MoO_2Cl_2 (3.4 h, 98%). In addition, MoO_2Cl_2 was recovered from the aqueous workup in greater than 95% for both catalytic processes and a control experiment with addition of 2,6-di-*tert*-butyl-4-methylpyridine (20 mol %) as a proton scavenger only slightly slows down the test NAS, excluding the involvement of HCl-mediated catalysis.

Applications to Highly Functionalized Substrates. As a final demonstration for the synthetic utility of the catalytic protocol, we have carried out acylations on a highly functionalized substrate which contain allyl ether, amide, disulfide, and ethylene glycol ether units. The resultant acetylation, pivalation, and *t*-Boc formation products **7a**−**c** were furnished in 84−95% chemical yields without any intervention of disulfide bond cleavage,[90] sulfide, or olefin oxidation, Scheme 3. More importantly, chemoselective pivalation and benzoylation at the two primary hydroxyl units for a tetraol system derived from the same starting methyl ester can also be achieved. Furthermore, once the disulfide bond in **7a**−**c** is cleaved

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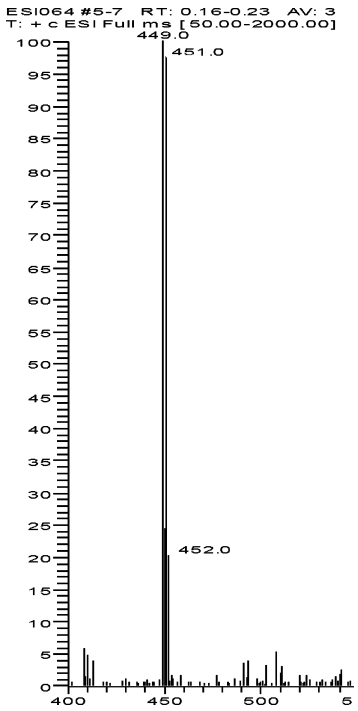

FIGURE 2. ESI-MS analyses of $MoOCl_2(Piv)_2$-**I**: *m/e* 450 ($M + CH_3CN + Na^+$).

by reduction, the resultant products are potentially useful as anchors to gold or CdSe/ZnS nanoparticles.

Conclusions. By judicious screening of group VIb oxometallic species, we have unraveled the amphoteric catalytic behavior of MoO_2Cl_2 in nucleophilic acyl substitutions with a diverse array of anhydrides. The catalytic utility of oxomolybdenum complexes in olefin metathesis,[91] olefin epoxidation,[92] and sulfide oxidation[93] has been well elucidated in the literature. The current study opens a new entry toward their extensive uses in C−X bond-forming events, i.e., NAS of anhydrides with functionalized protic nucleophiles. Besides the $V(O)X_2$ family, both MoO_2Cl_2 and $MoOCl_4$ represent a new type of water-tolerant and recoverable oxometallic chlorides.[94] The acylation protocol allows for exclusive chemo-selective acylations at systems (e.g., diol and amino alcohol) where other catalysts showed less satisfactory results and tolerates many delicate structural, substrate, and functional group variations. NAS of anhydrides by thiols and amines that were relatively unexplored by conventional catalytic means were also briefly examined with success. The efficient mixed anhydride approach demonstrated by using stoichiometric benzoic anhydride and catalytic MoO_2Cl_2 (or $V(O)(OTf)_2$[95]) to target naturally occurring and biomedicine-related substrates was not precedented and so far unachievable by conventional catalysts and metal triflates reported to date. The new approach augurs well for their potential and extensive applications. Control experiments with freshly prepared $MoOCl_2(O_2CBu^t)_2$ strongly indicate the involvement of an oxomolybdenum dialkanoate intermediate **I** before being attacked by a protic nucleophile, which is in-situ-generated by NAS of a given anhydride with either amphoteric Mo=O (i.e., Mo^+-O^-) units in MoO_2Cl_2. Investigations toward their uses in new catalytic systems as well as asymmetric variants of this catalytic process are underway and will be reported in due course.

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Supporting Information Available: Representative experimental procedures, spectral data, and ^1H and ^{13}C NMR spectra for all of the acylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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