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Vanadyl species-catalyzed complementary β-oxidative carbonylation of styrene derivatives with aldehydes†

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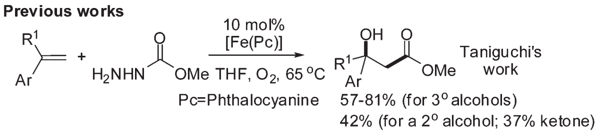
A series of oxometallic species and metal acetylacetonates (acac) was examined as catalysts for oxidative carbonylation of styrene with benzaldehyde using *t*-butylhydroperoxide as the co-oxidant in warm acetonitrile. Among them, VO((acac)$_2$ and vanadyl(IV) chloride were found to be the only catalyst class to achieve cross-coupling processes by judiciously tuning the ligand electronic attributes, leading to β-hydroxylation– and β-peroxidation–carbonylation of styrene, respectively, in a complementary manner. Mechanistic studies indicated that vanadyl-associated acyl radicals generated by *t*-butoxy radical-assisted, homolytic cleavage of the aldehyde C–H bond were involved in tandem processes with an exclusive *syn* diastereoselectivity in the case of β-methylstyrene.

Introduction

Transition metal-catalyzed direct vicinal difunctionalization of alkenes is one of the most attractive strategies because it allows precise and regioselective installation of two substituents across a C=C double bond. Among them, oxidative double functionalization of alkenes (*e.g.*, dihydroxylation,[1a,b] aminohydroxylation,[1c] and oxidative difunctionalization[1d,e]) has become an important tactic in organic synthesis. These new advances enable chemists to assemble complex building blocks of biological and medicinal interests in a single operation from common alkene feedstock.[1] In the last decade, significant advances have been achieved in the carbonylation of olefins catalyzed by transition metal complexes derived from Rh, Co, Ru and Pd.[2] On the other hand, Caddick and co-workers have revealed an impressive radical-type hydroacylation of activated alkenes under aerobic and catalyst-free conditions, which demonstrate the power of the oxidative cross-coupling strategy in view of its environmental benignity, operational efficiency and simplicity.[3] However, these carbonylation methodologies were mainly utilized to construct β-unfunctionalized ketones; further functionalization of the inert C(sp^3)–H bond at the carbon β to the carbonyl is required for building up further molecular complexity, thus somewhat limiting their extensive application. To meet this ultimate need, an efficient and direct β-oxidative carbonylation of alkenes remains to be explored. Along this line, several seminal studies on the β-amino and β-hydroxy carbonylation of olefins have been developed in recent years.[4,5]

Very recently, Lei and co-workers developed a straightforward approach for the synthesis of α,β-unsaturated ketones by copper(II)-catalyzed direct coupling of alkenes with the aldehyde C$_{sp2}$–H bond in the presence of the *tert*-butyl hydroperoxide (TBHP) oxidant,[6] which provided a complementary means to access this type of product through the radical-mediated oxidative coupling as compared to some existing powerful coupling manipulations.[7] By utilizing the iron(II) triggered radical and Fenton process, Taniguchi[8] and Li[9] independently identified unique and efficient synthetic protocols for β-hydroxy and β-peroxy carbonyl compounds from vinyl arenes and aldehydes in the presence of O$_2$ or the TBHP co-oxidant [eqn (1) and (2)]. Among these studies, acyl radicals (or alkoxycarbonyl radicals) were formed as reactive intermediates by the redox Fenton cycle and triggered the tandem acyl radical–alkene–oxidant (oxygen or TBHP) three-component coupling reactions. However, high loadings of the expensive iron phthalocyanine (Fe(Pc)) and carbazates were required. In addition, further oxidation at the 2° hydroxyl groups of the products may limit the synthetic utility of the former system.



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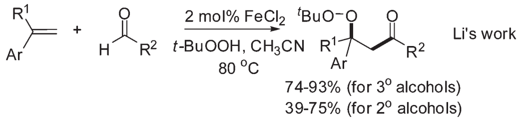

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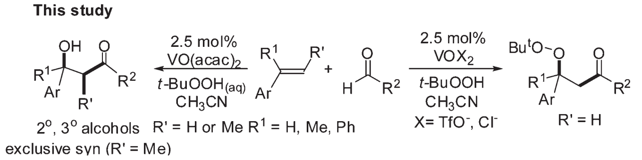
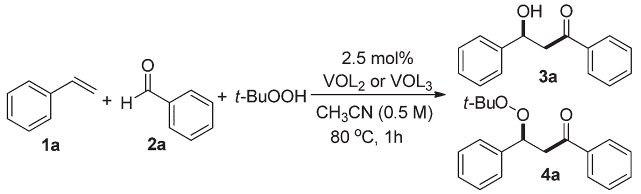


(3)

β-Hydroxycarbonyl compounds, the well-known aldol products,[10] constitute key structural templates in many polyketides[11] and are also valuable for the subsequent synthesis of *syn*- or *anti*-1,3-diols through judicious reduction on the ketone moiety.[12] As part of our continuing efforts in vanadyl species mediated oxidative coupling chemistry[13] and recent interests in the functionalization of C–H bonds, herein we describe two new classes of oxidative β-peroxy-carbonylation and β-hydroxy-carbonylation of alkenes, respectively, catalyzed by two individual oxovanadium/TBHP systems by varying only the vanadyl counter ions. In contrast to the two iron-catalyzed processes mentioned above,[6,7] this new complementary combination of catalytic methods provides an expedient tool to selectively access either radical process using the same set of coupling reagents with judicious tuning of the electrostatic attributes of a given vanadyl catalyst [eqn (3)]. Vanadyl species have been well adopted to catalyze reactions like polymerization, oxidations of alcohols, amines, and sulfides, as well as allylic alcohol and olefin epoxidation.[14,15] Despite the *in situ* perbenzoic acid generation by aerobic oxidation of benzaldehyde for olefin epoxidation catalyzed by vanadyl species,[16] their ability as catalysts for aldehyde C–H activation remains elusive even with ample success particularly in 3° C–H activation.[17] To our delight several vanadyl species turned out to efficiently catalyze the oxidative coupling between styrene derivatives and aldehydes without resorting to any halides or halide equivalents.[5]

We started out by using styrene **1a** and benzaldehyde **2a** (3.0–5.0 equiv.) as a test coupling system in the presence of anhydrous TBHP (3.0 equiv. in decane) with a diverse array of oxometallic species at 80 °C. Among these oxometallic species and solvents examined, group 5B oxovanadium species were found to be the most chemoselective and efficient catalysts compared to group 6B (*e.g.*, 13–18% yields by CrO_2Cl_2 and MoO_2Cl_2) and group 4B (*e.g.*, <3% by $TiOCl_2$ and $HfOCl_2$) in acetonitrile (see ESI, Table S1†). Notably, the structural identities of the β-oxidative carbonylation products catalyzed by the vanadyl catalysts highly depend on their counter ion attributes and thus the amphoteric nature of the resulting vanadyl species (*i.e.*, V=O *vs.* $^+$V–O$^-$). Namely, more electronegative counter anions (*e.g.*, $^-$OTf and Cl$^-$) and thus more electron-deficient vanadyl species led to the β-peroxidative carbonylation product **4a** (68–80% yields as in entries 1, 2 and 11 of Table 1). On the other hand, more basic counter anions (*e.g.*, acetylacetonate analogues and Oi-Pr) and thus more electron-rich vanadyl species furnished the carbonylative β-hydroxylation product **3a** (43–75% yields in entries 7–10 and 12).

Table 1 Vanadyl species-catalyzed selective β-hydroxylation- or β-peroxidation–carbonylation of styrene: optimization of reaction conditions[a]



Entry	Catalyst	Yield of **3a**^{b} (%)	Yield of **4a**^{b} (%)
1	$VO(OTf)_2$–$5H_2O^c$	Trace	71
2	$VOCl_2$–$3H_2O$	5	80
3	$VOCl_2$–$3H_2O$/bipy^d	37	6
4	$VOCl_2$–$3H_2O$/phen^e	23	Trace
5	$VOCl_2$–$3H_2O$/salen^f	68	7
6	$VO(OAc)_2$–$3H_2O^g$	32	6
7	$VO(acac)_2{}^h$	75	Trace
8	$VO(tmhd)_2{}^i$	73	Trace
9	$VO(hfacac)_2{}^j$	43	Trace
10	$VO(dbm)_2{}^k$	58	Trace
11	$VOCl_3$	—^{q}	68
12	$VO(O^iPr)_3$	64	<5
13	$VO(acac)_2{}^l$	82 (84)^m	—^{q}
14	$VO(acac)_2{}^{l,m}$ (5 mol%)	89	—^{q}
15	$VO(acac)_2{}^{l,m,n}$	65	—^{q}
16	$VO(acac)_2{}^{l,m,o}$	72	—^{q}
17	$VO(acac)_2$/BHT^p	Trace	—^{q}
18	$VOCl_2$–$3H_2O^o$	Trace	43

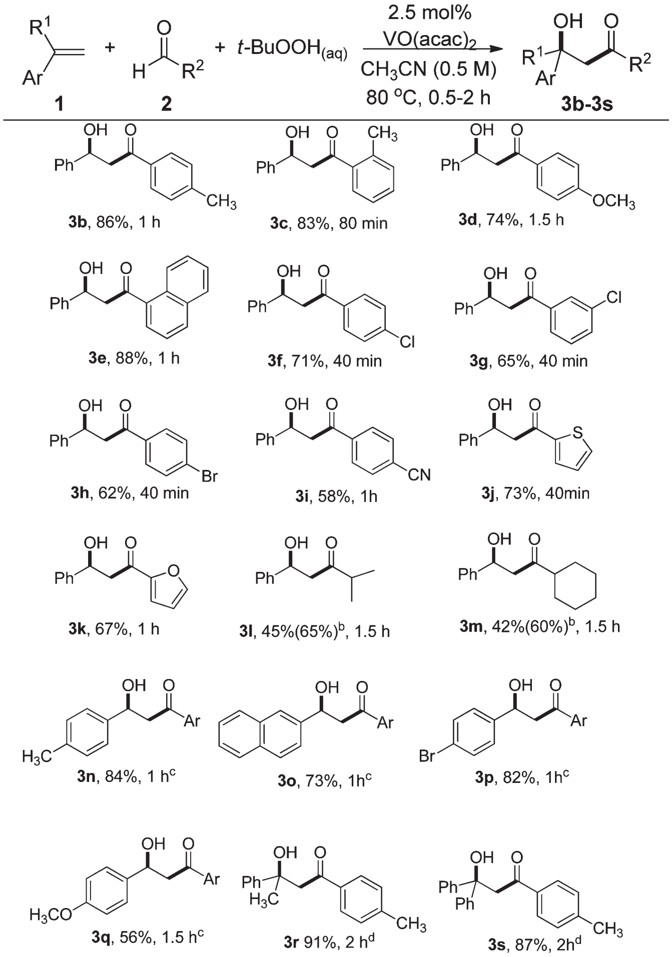
[a] Reaction conditions: styrene (1 mmol), aldehyde (5 mmol), 5 M *tert*-BuOOH in decane (3 mmol), MeCN (2 mL), 80 °C. [b] Isolated yield. [c] OTf: trifluoromethanesulfonate. [d] bipy: 2,2′-bipyridine (2.5 mol%). [e] phen: 1,10-phenanthroline (2.5 mol%). [f] salen: *N*,*N*′-bis(salicylidene)-ethylenediamine (2.5 mol%). [g] OAc: acetate. [h] acac: acetylacetone. [i] tmhd: 2,2,6,6-tetramethyl heptan-2,5-dione. [j] hfacac: 1,1,1,5,5,5-hexafluoropentan-2,5-dione. [k] dbm: dibenzoylmethane. [l] 3.0 equiv. of 70% *tert*-BuOOH in water was used. [m] Slow addition of TBHP over 30 min. [n] 65 °C. [o] Styrene/aldehyde/*tert*-BuOOH$_{(aq.)}$ ratio: 1/3/2, 80 °C. [p] One equiv. of 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added. [q] Not detected.

Among the three vanadyl species bearing electronegative ligands (*i.e.*, $^-$OTf, Cl$^-$, and AcO$^-$) examined, $VOCl_2$–$3H_2O$ provided the best yield of **4a** (80%, entry 2), despite with a trace amount (5%) of β-hydroxyketone **3a** isolated. Increasing the electron density of the vanadyl centre by adding basic, bidentate ligands like 2,2′-bipyridine or 1,10-phenanthroline resulted in a significant loss of catalytic activities with a reversal of product distribution (37 and 23% yields of **3a** as in entries 3 and 4). Further increasing the electron density of the vanadyl centre by employing the covalent Salen-type (*N*,*N*′-bis(salicylidene)ethylenediamine) ligand improved the yield of **3a** to 68% (entry 5), along with a discernible amount of β-peroxyketone **4a** (7%). Vanadyl species which bears weakly basic acetate counter anions also led to preferential formation of **3a** albeit in poorer yield (32%, entry 6).

Based on these ligand effects, we further optimized the production of **3a** in the model reaction using tetradentate, oxovanadium bis(acetylacetonate) [VO(acac)$_2$] and its derivatives. As expected, oxovanadium β-diketonate species bearing more basic ligands predominantly gave the β-hydroxylation product **3a** in 43–75% yields. Notably, the product yields are proportional to the basicity of the β-diketonate ligand (*i.e.*, acac$^-$ ≈ tmhd$^-$ > dbm$^-$ > hfacac$^-$; entries 7–10 in Table 1). Therefore, the less hindered VO(acac)$_2$ was selected as the best catalyst in view of its catalytic reactivity, commercial price, and availability (75% yield, entry 7). It should be noted that metal acetylacetonates derived from Fe(II), Co(II), Cu(II), Rh(II), and Pd(II) did not provide any discernible product **3a** under similar conditions, indicating the essential role of the V=O unit in delivering the hydroxyl group at the β-position. Oxidovanadium(V) catalysts such as VOCl$_3$ and VO(OPr^i)$_3$ also showed similar ligand effects. Namely, more Lewis acidic VOCl$_3$ led to the β-peroxidation product **4a** (68% yield), whereas more basic VO(OPr^i)$_3$ furnished the β-hydroxyketone **3a** (64% yield; entries 11 and 12) albeit with less catalytic efficiencies presumably due to its moisture sensitivity.

The final optimized condition for the β-hydroxylative carbonylation of styrene was to use 3.0 equiv. of 70% aqueous TBHP instead of dry TBHP in the presence of 5.0 equiv. of benzaldehyde with 2.5 mol% of VO(acac)$_2$ at 80 °C. The desired β-hydroxyketone **3a** was afforded in 84% yield (Table 1, entry 13). Slow addition of aqueous TBHP over 30 min and doubled catalyst loading (*i.e.*, 5 mol%) further increased the yield of **3a** to 89% and the β-peroxidation was completely suppressed [*cf.* entry 13 (parenthesis) with entry 14]. The yield of **3a** was reduced to 65% when the reaction temperature was lowered to 65 °C (entry 15). Decreasing the substrate and oxidant stoichiometry to 1.0/3.0/2.0 (styrene/benzaldehyde/TBHP) reduced the yield of **3a** by 10–12% (entry 16). Therefore, 2.0 equiv. of TBHP was still sufficient to achieve a satisfactory production of β-hydroxyketone **3a**. These results indicated that the β-peroxidation pathway can be suppressed with insufficient loading of TBHP or with a more basic catalyst. Notably, when 2,6-di-*tert*-butyl-4-methylphenol (BHT, 1.0 equiv.), a radical scavenger,[18] was introduced, the test reaction completely shut down, suggesting the involvement of a radical process of this coupling reaction (entry 17). In contrast, the chemical yield of the VO(Cl)$_2$-catalyzed β-peroxidation was dropped to half (*i.e.*, 43%) with the reduced substrate and oxidant stoichiometry (entry 18), which revealed that a larger excess of TBHP (at least 3 equiv.) is essential to facilitate the β-peroxidation pathway.

The fully optimized β-hydroxycarbonylation protocol proved amenable to a diverse range of aldehyde and styrene type substrate combinations (Scheme 1). In marked contrast, Pd(II) catalyzed, β-hydroxyphosphonylation and β-hydroxy-carboxylation of styrene proceeded in only 34% and 42% isolated yields, respectively, along with extensive dehydration and/or hydroxyl oxidation (37% yield).[8,19] Aromatic aldehydes bearing electron-donating or -stabilizing groups such as methyl (**1b–c**), methoxy (**1d**), and benzo-fused (**1d**) substrates reacted most efficiently, affording the corresponding β-hydroxyketones

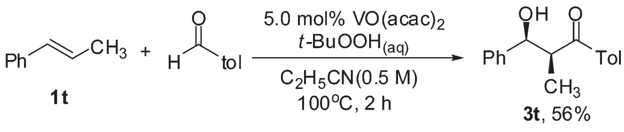


Scheme 1 Substrate scope in the VO(acac)$_2$-catalyzed β-hydroxycarbonylation of styrene derivatives^a. ^{a}Reaction conditions: **1** (1 mmol), **2** (5 mmol), VO(acac)$_2$ (0.025 mmol), 70% aqueous *t*-BuOOH (3 mmol), acetonitrile (2 mL), 80 °C, under N$_2$. Yields of the isolated products are given. ^{b}5 mol% of VO(acac)$_2$ was used. ^{c}Ar = 3,4-di-methylphenyl. ^{d}Reaction temperature: 90 °C.

(**3b–e**) in 74–86% isolated yields albeit with 30%–50% longer reaction time due to the steric and/or electronic effects of the substituent. Notably, these products are somewhat acid sensitive. They tend to undergo dehydration to form the corresponding enones (30–34%) even upon standing in CDCl$_3$ for 24 h. Electron-deficient, halogen- or cyano-containing, as well as hetero-aromatic aldehydes (**1f–k**) were well adapted to the reaction conditions. The desired products **3f–k** were obtained in 58–73% yields in a shorter reaction time (40 min to 1 h).

Aliphatic aldehydes proved more recalcitrant due to facile decomposition of the incipient acyl radicals to the corresponding alkyl radicals under the reaction conditions.[20] Beside aliphatic aldehydes bearing 1° alkyl groups (*e.g.*, pentanal), those with α-branching groups (*e.g.*, isopropyl and cyclohexyl in **1l,m**) also showed satisfactory results. Higher catalyst loading (5 mol%) and a longer reaction time (1.5 h) were required to achieve satisfactory yields (60–65%) of products **3l,m**. Nevertheless, these two cases turned out to be the only successful aliphatic aldehyde examples reported to date. In contrast, both pivaldehyde (a 3° alkyl group) and phenylethanal (a benzyl group) led to the α-hydroxyalkylation products in 68% yields (see ESI†).

Styrenyl substrates bearing *p*-substituents (**1n–q**), α-methyl-, α-phenyl-, and β-methyl-styrenes, were also investigated. It was found that the coupling efficiencies to *p*-substituted styrenes were satisfactory in all cases except for **1q** which bears the *p*-methoxy group. The products of pharmaceutical interests (*i.e.*, **3n–3p** and **3q**) were isolated in good (73–84%) and moderate (56%) yields, respectively.[21] To our expectation, α-substituted styrenes like **1r** and **1s** were high yielding substrates (87–91% yield) presumably due to the involvement of even more stable 3° radical intermediates and complete prevention of over oxidation. Furthermore, the more challenging substrate, *trans*-β-methyl styrene, was also able to produce the corresponding coupling product **3t** with an exclusive *syn* diastereoselectivity even at an elevated temperature (100 °C) and a longer reaction time (2 h) in propanonitrile presumably due to the β-methyl steric effect [eqn (4a)].



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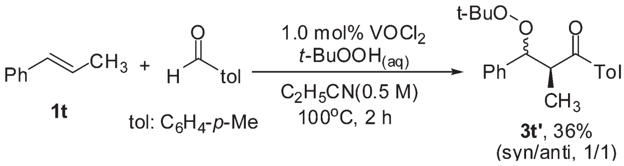
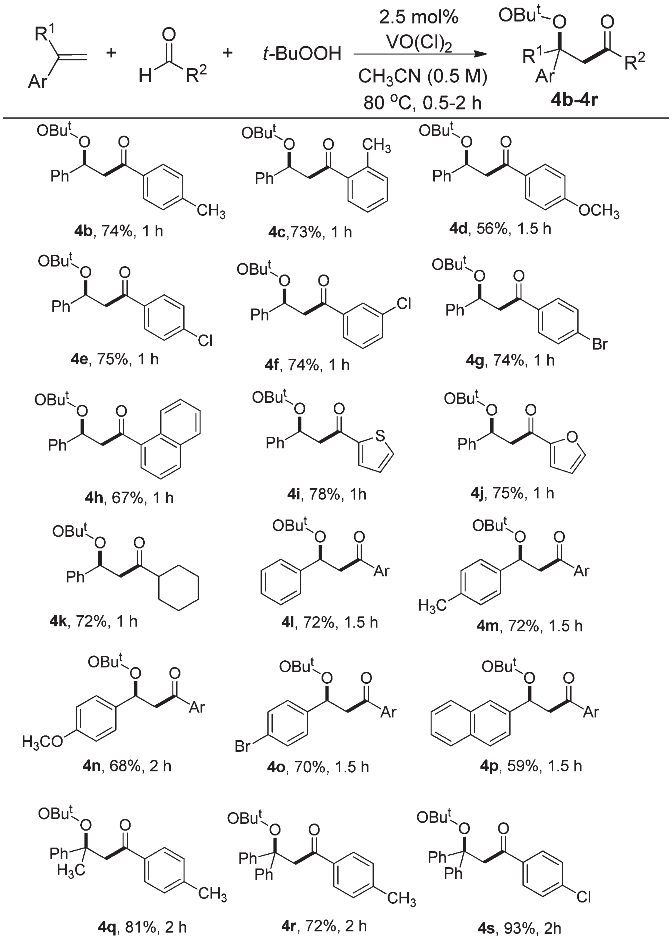
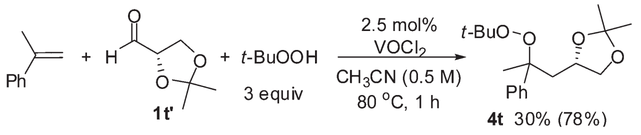


(4b)

By taking advantage of the differential catalytic activity between the two final vanadyl catalysts, we also carried out the complementary functionalization of styrene derivatives (Scheme 2). Their β-peroxidative carbonylations using 2.5 mol % of $VOCl_2$ under the established conditions (Table 1, entry 2, styrene/benzaldehyde/TBHP, 1/5/3) were performed for the same substrate classes. Comparative results are compiled in Scheme 2. There was no direct correlation between the yields of the peroxide products and the electronic characteristics of aldehyde reactants because minor epoxide formation from the initial coupling products was observed in several cases. Beside electron rich or hindered cases (**1d** and **1h**), most aromatic aldehydes led to the products **4b–h** in 73–75% yields which were comparable to or slightly higher than those catalyzed by $FeCl_2$. In the cases of hetero-aromatic and aliphatic aldehydes which were not studied before, the peroxides **4i–k** were furnished in 72–78% yields. As a potentially useful extension, acetonide-protected glyceraldehyde was tested under similar reaction conditions. The desired, volatile products **4t** were produced in 78% conversion (in 30% isolated yield) as a 1 : 1 mixture of diastereomers [eqn (5)].[22] *p*-Substituted styrenes led to the β-peroxy carbonylated products **4l–p** in 59–72% yields. Expectedly, α-methyl and α-phenyl styrenes afforded even better yields (72–93%) in the β-peroxy ketone formation (**4q–s**).



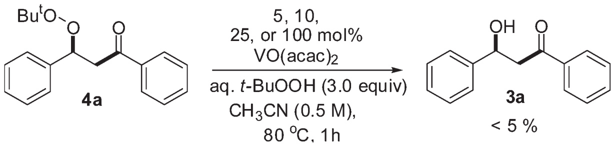
Scheme 2 Substrate scope in the $VOCl_2$-catalyzed β-peroxidative carbonylation of styrene derivatives[a]. [a]Reaction conditions: **1** (1 mmol), **2** (5 mmol), $VO(Cl)_2$ (0.025 mmol), *t*-BuOOH (3 mmol, 5 M in decane), acetonitrile (2 mL), 80 °C, under N_2. Yields of the isolated products are given.



(5)

On the other hand, the reaction of *trans*-β-methyl styrene with *p*-tolualdehyde led to the corresponding coupling product **3t′** with 1 : 1 (*syn* : *anti*) diastereoselectivity at 100 °C for 2 h in propanonitrile [eqn (4b)]. The result indicated a different operating mechanism involved in the $V(O)Cl_2$ catalyzed reaction.

Notably, treatment of **4a** with 3.0 equiv. TBHP in the presence of 5, 10, 25, and even 100 mol% $VO(acac)_2$ afforded less than 5% of **3a** [eqn (6)]. Furthermore, the cross-coupling reactions between *p*-tolualdehyde (or *o*-tolualdehyde) and styrene in the presence of 1 equiv. of **4a** led only to **3b** (or **3c**) with a negligible amount of **3a** under similar catalytic conditions [eqn (7)]. Both control experiments ruled out the possibility of **4a** as the intermediate *en route* to **3a** in the β-carbonylative hydroxylation of styrene [eqn (6)]. Furthermore, when 1.0 equiv. of di-*tert*-butyl azodicarboxylate (DtBAD) was added to the individual peroxidation and the hydroxylation reaction as a radical trapping reagent,[23] the coupling product **5** between benzoyl radicals and DtBAD was obtained in 78–83% yields in both cases along with the desired products **3a** and **4a** in 11 and 16% yields. The results strongly implicated that both the reactions proceeded through the radical mechanism [eqn (8)].



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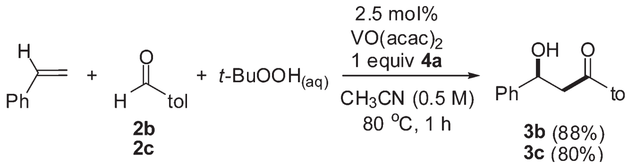

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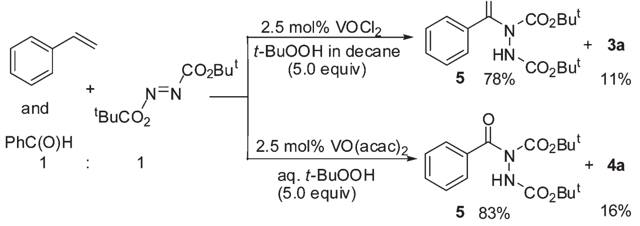

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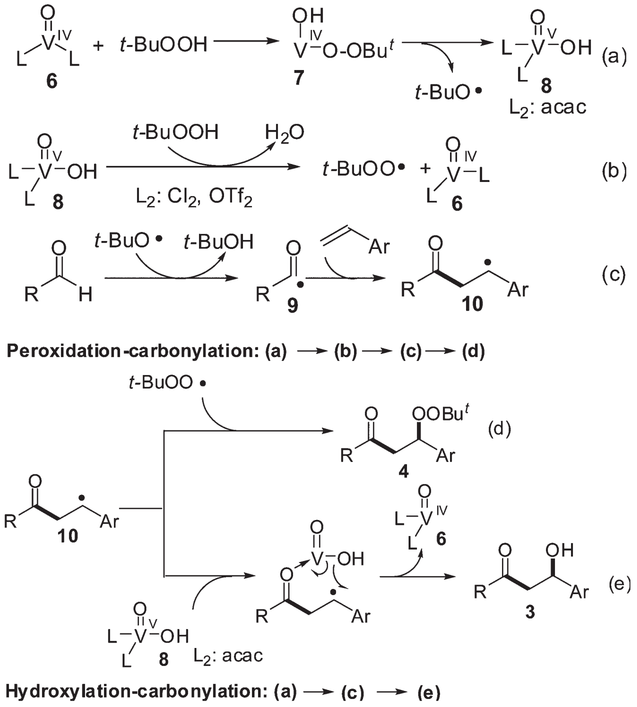
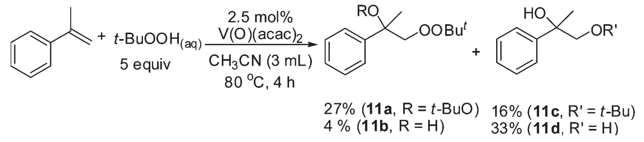


Scheme 3 Plausible complementary mechanisms.

Several mechanistic features governing vanadium-catalyzed oxygen transfer reactions such as epoxidation, C–H bond hydroxylation, and other oxidation reactions have been documented.[15,24] Among them, vanadyl alkylperoxy complex **7** generated by vanadyl(IV) **6**-triggered, Haber–Weiss decomposition of TBHP [steps (a) and (b) in Scheme 3] is widely considered as the key intermediate in vanadyl(IV)/TBHP catalytic systems;[25] complex-**7** is oxidatively decomposed to vanadyl(V) hydroxide **8** through homolytic cleavage of the O–O bond with concomitant electron transfer [step (a)]. Vanadyl(V) hydroxide **8** further reacts with an additional TBHP to produce *t*-butylperoxy radicals [*t*-BuOO$^•$, step (b)] with a concomitant formation of H_2O. The two-step decomposition of TBHP coupled with a one-electron change of the vanadyl centre associated with the Haber–Weiss mechanism may be responsible for the chemoselective carbonylative peroxidation. Firstly, hydrogen atom abstraction of an aldehyde by the *t*-butoxy radical (*t*-BuO$^•$) produced by step (a) would afford an acyl radical **9**. The subsequent addition of **9** to a styrene type substrate would produce a more stable, benzylic type radical **10** [step (c)]. Radical **10** would be trapped by an incipient *t*-BuOO$^•$ to facilitate the peroxidation–carbonylation product **4** formation and bring back the initial vanadyl(IV) catalyst **6** [Scheme 3, (a)→(b)→(c)→(d)].

Conversely, the vanadyl(V) hydroxide **8** may act as a source of hydroxyl radicals[26] in the chemoselective hydroxylation of radical **10**, presumably due to its increased stability under the influence of basic or electron-rich ligand(s).[27] This hypothesis is consistent with our observations that the formation of *t*-BuOO$^•$ *via* vanadyl(V) hydroxide **8**-induced decomposition of TBHP [step (b)] can be suppressed by reducing the amount of TBHP (Table 1, entry 13, parenthesis) or increasing the loading of the V(O)(acac)$_2$ catalyst (Table 1, entry 14). In addition, the product distribution of $VOCl_2$ mediated catalysis was reversed from peroxy **4** to the corresponding β-hydroxyketone **3** when the incipient **8** was stabilized by introducing basic or covalent ligand(s) (Table 1, entries 3–5). These results support the important role of **8** in the hydroxylation pathway.

To support the increased stability of vanadyl(V) hydroxide **8** under the influence of the acac ligand, a control sample with an equal amount of VO(acac)$_2$ and TBHP in refluxing acetonitrile was maintained for 1 h. Complex **8** (VO(acac)$_2$–OH) was indeed formed as evidenced by electrospray ionization mass analysis of the mixture (see ESI†). Furthermore, the addition of α-methylstyrene to that reaction mixture for 4 h led to the formation of 1,2-di-*t*-butylperoxylation and 1,2-dihydroxylation products, **11a** and **11d**, in 27% and 33% yields along with 1-hydroxy-2-*t*-butylperoxy and 1-hydroxy-2-*t*-butoxy adducts, **11b** and **11c**, in 4 and 16% yields [eqn (8)]. The formation of **11c** further supports the formation of *t*-butoxy radicals and vanadyl(V) hydroxide **8** through pathway (a). Therefore, the V(O)(acac)$_2$-catalyzed hydroxylation–carbonylation of styrene may proceed through a direct coupling of **8** with benzylic radical **10** [Scheme 3, (a)→(c)→(e)] to afford β-hydroxyketone **3** with concomitant release of the initial catalyst **6** and completion of the catalytic cycle.



(8)

Conclusions

In conclusion, we have developed tandem and complementary β-hydroxylation–carbonylation and β-peroxidation–carbonylation of styrenes by simply adjusting the ligand environment of a vanadyl centre. Notably, V(O)(acac)$_2$ is the only acac-bearing, oxometallic species that works for this chemistry. Other metallic acac species like Fe(acac)$_2$, Fe(acac)$_3$, Co(acac)$_2$, Cu(acac)$_2$, Rh(acac)$_2$, and Pd(acac)$_2$ did not lead to any discernible β-hydroxyketone product **3a** under similar reaction conditions. Conversely, moisture tolerant VOCl$_2$ serves as an alternative catalytic system for FeCl$_2$ and provides an additional advantage for aliphatic aldehydes bearing 2° alkyl groups. The new complementary methodologies are attractive because the desirable β-hydroxy and β-peroxyketones can be provided selectively by using the same set of coupling partners. The exclusive *syn* selectivity observed in eqn (4) also suggests that vanadyl species-associated radicals might be involved in the coupling reaction. Further investigations on the detailed mechanisms and asymmetric variants of this radical, oxidative coupling transformation are underway.

Acknowledgements

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Notes and references

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