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ARTICLE

Vanadyl Species-Catalyzed, Complementary β -Oxidative Carbonylation of Styrene Derivatives with Aldehydes

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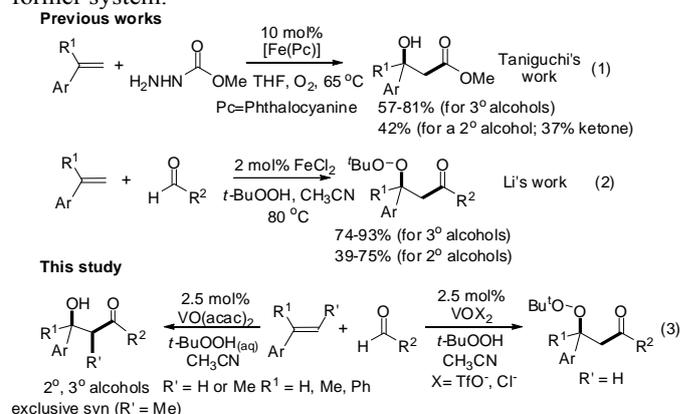
A series of oxometallic species and metal acetylacetonates (acac) was examined as catalysts for oxidative carbonylation of styrene with benzaldehyde by using *t*-butylhydroperoxide as co-oxidant in warm acetonitrile. Among them, VO(acac)₂ and vanadyl(IV) chloride were found to be the only catalyst class to achieve the cross-coupling processes by judicious turning 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 aldehyde C-H bond were involved in the tandem processes with 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 precisely and regioselectively install 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, Crick 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 benign concern, operational efficiency and simplicity.³ However, these carbonylation methodologies were mainly utilized to construct β -unfunctionalized ketones, further functionalization of the inert C(sp³)-H bond at the carbon β to the carbonyl is required for building up further molecular complexity, thus somewhat limiting their extensive applications. To meet this ultimate need, an efficient and direct, β -oxidative carbonylation of alkenes remain to be explored. Along this line, several seminal works 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

aldehyde C_{sp}²-H bond in the presence of *tert*-butyl hydroperoxide (TBHP) oxidant,⁶ which provided a complementary means to access this type of products through the radical-mediated, oxidative coupling as compared to some existing powerful coupling manipulations.⁷ By utilizing iron(II) triggered radical and Fenton process, Taniguchi⁸ and Li⁹ independently identified unique and efficient synthetic protocols of β -hydroxy and β -peroxy carbonyl compounds from vinyl arenes and aldehydes in the presence of O₂ or TBHP co-oxidant [Eq. (1) and (2)]. Among these studies, acyl radicals (or alkoxycarbonyl radicals) were formed as reactive intermediates by 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.



β -Hydroxycarbonyl compounds, the well-known aldol products,¹⁰ constitute key structural templates in many polyketides¹¹ 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 chemistry¹³ 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 with varying only the vanadyl counter ions. In contrast with the two iron-catalyzed processes mentioned above,^{6,7} this new complimentary combination of catalytic methods provides an expedient tool to selectively access either radical processes by using the same set of coupling reagents with judicious turning of the electrostatic attribute of a given vanadyl catalyst [Eq. 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 fact of 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 remain 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 couplings between styrene derivatives and aldehydes without resorting to any halides or halide equivalents.⁵

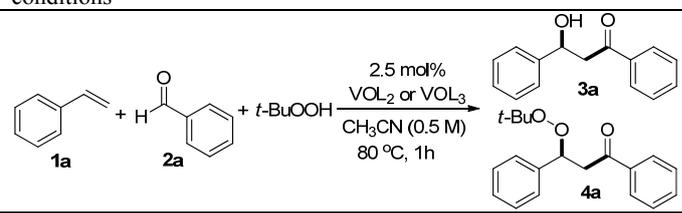
We started out by using styrene **1a** and benzaldehyde **2a** (3.0-5.0 equiv) as a test coupling system in the presence of anhydrous TBHP (3.0 equiv in decane) with a diverse array of oxometallic species at 80 °C. Among these oxometallic species and solvents examined, group 5B, oxovanadium species were found to be the most chemoselective and efficient catalysts than group 6B (e.g., 13-18% yields by CrO₂Cl₂ and MoO₂Cl₂) and group 4B (e.g., < 3% by TiOCl₂ and HfOCl₂) in acetonitrile (See Supporting Information, 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 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 carbonylative β -hydroxylation product **3a** (43-75% yields in entries 7-10 and 12).

Among the three vanadyl species bearing electronegative ligands (i.e., ⁻OTf, Cl⁻, and AcO⁻) examined, VOCl₂·3H₂O 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 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 anion also led to a 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 by 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 β -diketonate ligand (i.e., acac⁻ \approx 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 V=O unit in delivering the hydroxyl group at the β -position. Oxidovanadium(V) catalysts such as VOCl₃ and VO(OPr)₃ also showed the similar ligand effects. Namely, more Lewis acidic VOCl₃ led to the β -peroxidation product **4a** (68% yield), whereas more basic VO(OPr)₃ furnished the β -hydroxyketone **3a** (64% yield; entries 11 and 12) albeit with less catalytic efficiencies presumably due to their moisture sensitivity.

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 ₂ O ^c	trace	71
2	VOCl ₂ ·3H ₂ O	5	80
3	VOCl ₂ ·3H ₂ O / bipy ^d	37	6
4	VOCl ₂ ·3H ₂ O / phen ^e	23	trace
5	VOCl ₂ ·3H ₂ O / salen ^f	68	7
6	VO(OAc) ₂ ·3H ₂ O ^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(<i>O</i> Pr) 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 ₂ O ^o	trace	43

^a Reaction condition: 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: acetylacetonate. ⁱ tmhd: 2,2,6,6-tetramethyl heptan-2,5-dione. ^j hfacac: 1,1,1,5,5,5-hexafluoropentane-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.

The final optimized conditions 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 was completed 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 larger excess of TBHP (at least 3 equiv) is essential to facilitate the β -peroxidation pathway.

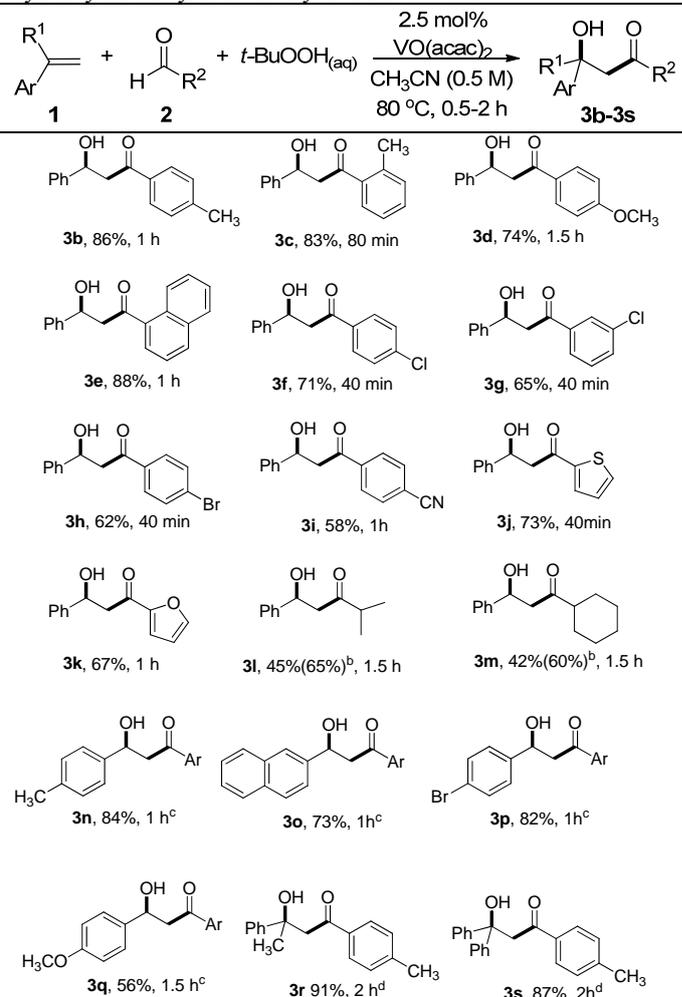
The fully optimized β -hydroxycarbonylation protocol proved amenable to a diverse range of aldehyde and styrene type substrate combinations (Scheme 1). In marked contrast, Pd(II) catalyzed, β -hydroxyphosphonylation and β -hydroxy-carboxylation of styrene proceeded in only 34% and 42% isolated yields, 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 (**1e**) substrates reacted most efficiently, affording the corresponding β -hydroxyketones (**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 CDCl₃ 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 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 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 successfully 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 SI).

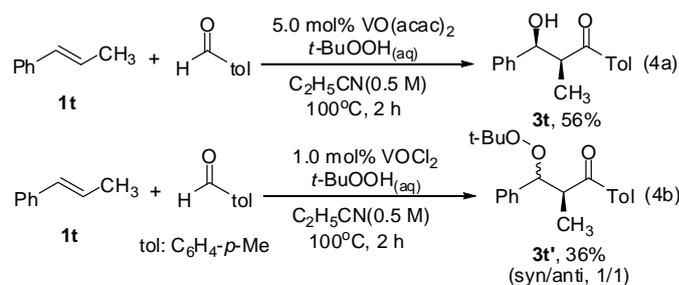
Styrenyl substrates bearing *p*-substituents (**1n–q**), α -methyl-, α -phenyl-, and β -methyl-styrenes were also investigated. It was found that the coupling efficiencies to *p*-substituted styrenes were satisfactory in all cases except **1q** which bears *p*-methoxy group. The products of pharmaceutical 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 exclusive syn diastereoselectivity even at elevated temperature (100 °C) and longer reaction time (2h) in propanonitrile presumably due to β -methyl steric effect [eq. (4a)].

Scheme 1. Substrate scope in the VO(acac)₂-catalyzed β -hydroxy-carbonylation of styrene derivatives^a

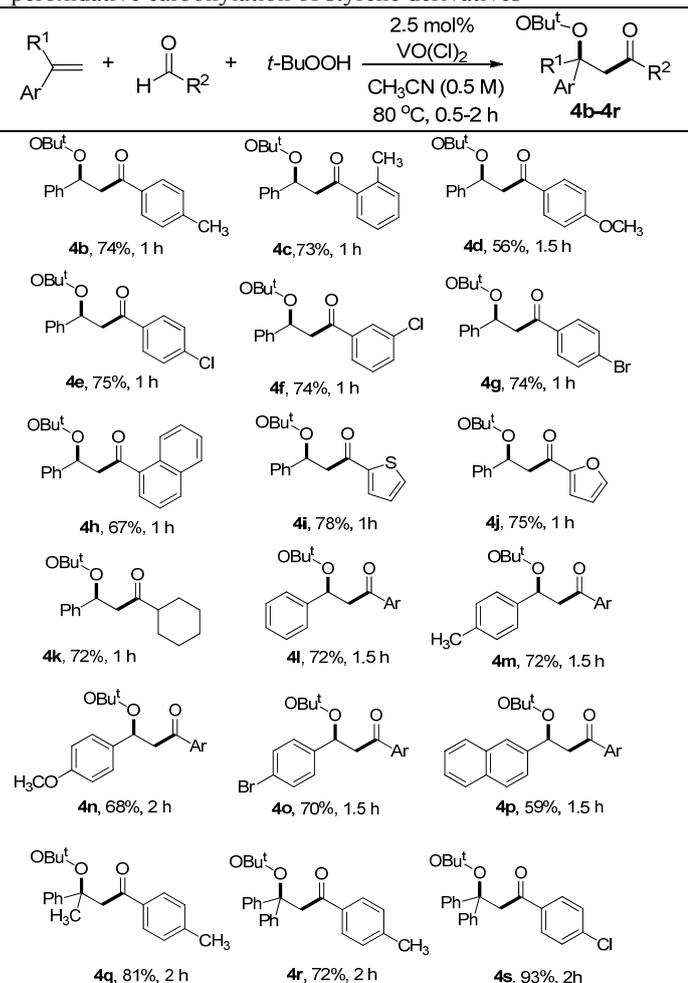


^a Reaction condition: **1** (1 mmol), **2** (5 mmol), VO(acac)₂ (0.025 mmol), 70% aqueous *t*-BuOOH (3 mmol), acetonitrile (2 mL), 80 °C, under N₂. Yields of isolated products are given. ^b 5 mol% of VO(acac)₂ was used. ^c Ar = 3,4-di-methylphenyl. ^d Reaction temperature: 90 °C.

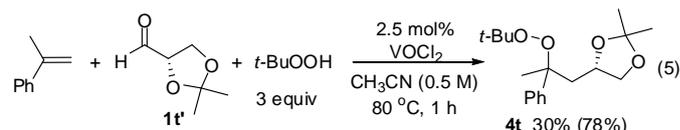


By taking advantage of the differential catalytic activity between the two final vanadyl catalysts, we also carried out the complementary functionalization of styrene derivatives (Scheme 2). Their β -peroxidative carbonylations by using 2.5 mol% of VOCl_2 under the established conditions (Table 1, entry 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 characters of aldehyde reactants because minor epoxide formations from the initial coupling products were 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 [eq (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

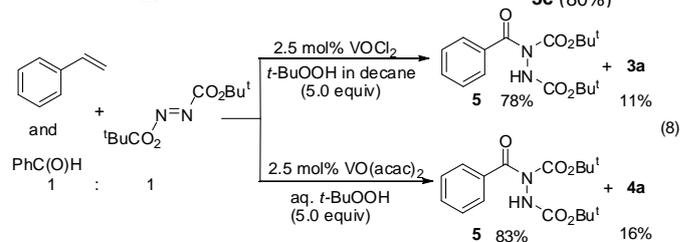
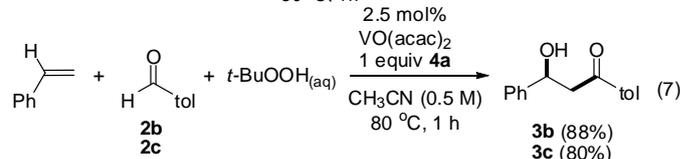
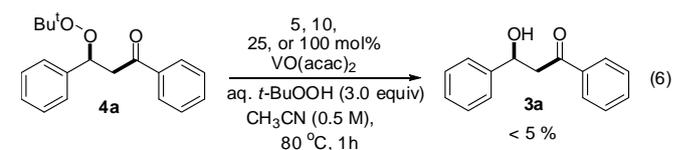


^a Reaction condition: **1** (1 mmol), **2** (5 mmol), VOCl_2 (0.025 mmol), *t*-BuOOH (3 mmol, 5 M in decane), acetonitrile (2 mL), 80 °C, under N_2 . Yields of isolated products are given.



On the other hand, 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 in 2h in propanonitrile [eq. (4b)]. The result indicated a different operating mechanism involved in $\text{V}(\text{O})\text{Cl}_2$ catalyzed reaction.

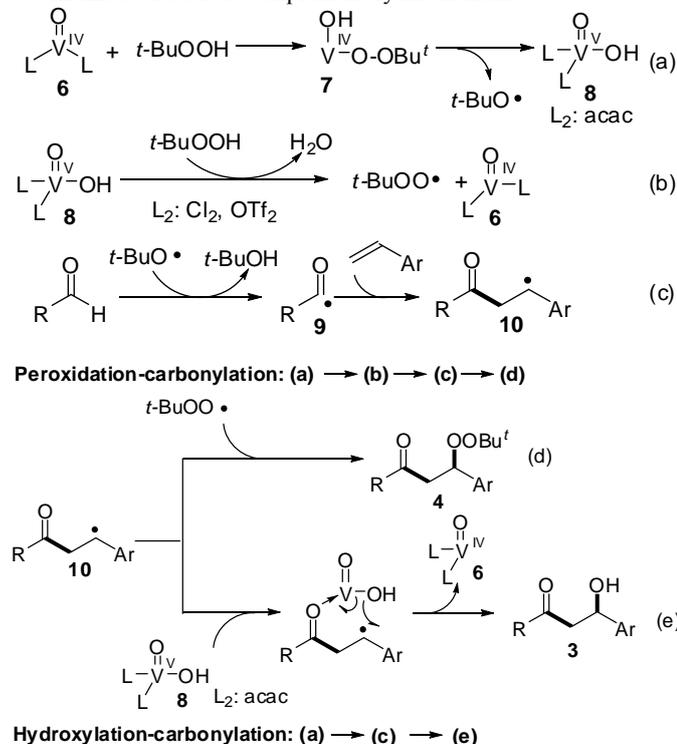
Notably, treatment of **4a** with 3.0 equiv TBHP in the presence of 5, 10, 25, and even 100 mol% $\text{VO}(\text{acac})_2$ afforded less than 5% of **3a** [Eq. (6)]. Furthermore, the cross coupling reactions between *p*-tolualdehyde (or *o*-tolualdehyde) and styrene in the presence of 1 equiv of **4a** led only to **3b** (or **3c**) with negligible amount of **3a** under similar catalytic conditions [Eq. (7)]. Both control experiments ruled out the possibility of **4a** as the intermediate *en route* to **3a** in the β -carbonylative hydroxylation of styrene [Eq. (6)]. Furthermore, when 1.0 equiv of di-*tert*-butyl azodicarboxylate (DtBAD) was added to the individual peroxidation and hydroxylation reaction as a radical trapping reagent,²³ the coupling product **5** between benzoyl radical 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 radical mechanism [Eq. (8)].



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 a 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 a homolytic cleavage of the O-O bond with a concomitant electron transfer [step (a)]. Vanadyl(V) hydroxide-8 further reacts with an additional TBHP to produce *t*-butylperoxy radical [*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 Haber-Weiss mechanism may be responsible for the chemoselective carbonylative peroxidation. Firstly, hydrogen atom abstraction of an aldehyde by *t*-butoxy radical (*t*-BuO•) produced by step-(a) would afford an acyl radical-**9**. 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)].

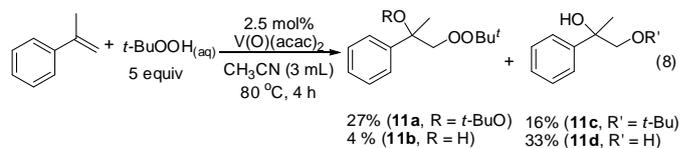
Scheme 3. Plausible complementary mechanisms



Conversely, the vanadyl(V) hydroxide **8** may act as a source of hydroxyl radical²⁶ 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 V(O)(acac)₂ catalyst (Table 1, entry 14). In addition, the product distribution of VOCl₂ 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 experiment with an equal amount of VO(acac)₂ and TBHP in refluxing acetonitrile was maintained for 1h. Complex-**8** (VO(acac)₂-OH) was indeed formed as evidenced by electrospray ionization mass analysis of the mixture (see SI). Furthermore, the addition of α-methylstyrene to that reaction mixture for 4h 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 [eq (8)]. The formation of **11c** further supports the formation of *t*-butoxy radical 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 the **8** with benzylic radical-**10** [Scheme 3, (a)→(c)→(e)] to afford the β-hydroxyketone **3** with concomitant release of the initial catalyst **6** and completion of the catalytic cycle.



Conclusions

In conclusion, we have developed the 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-hydroxy ketone product-**3a** under similar reaction conditions. Conversely, moisture tolerant VOCl₂ serves as an alternative catalytic system for FeCl₂ and provides an additional advantage for aliphatic aldehydes bearing 2° alkyl groups. The new complementary methodologies are attractive because desirable β-hydroxy and β-peroxyketones can be provided selectively by using the same set of coupling partners. The exclusive syn selectivity observed in eq-4 also suggests that vanadyl species-associated radical might be involved in the coupling reaction. Further investigations on their detailed mechanisms and asymmetric variants of this radical, oxidative coupling transformation are underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, structural proofs, and spectral data for all new compounds are provided, See DOI: 10.1039/b000000x/

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