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Hydroxy group-enabled highly regio- and stereo-selective hydrocarboxylation of alkynes†

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Here we present an example of utilizing hydroxy groups for regioselectivity control in the addition reaction of alkynes—a highly efficient Pd-catalyzed *syn*-hydrocarboxylation of readily available 2-alkynyl alcohols with CO in the presence of alcohols with an unprecedented regioselectivity affording 3-hydroxy-2(*E*)-alkenoates. The role of the hydroxy group has been carefully studied. The synthetic potential of the products has also been demonstrated.

Introduction

As one of the most abundant and fundamental chemical feedstock, alkynes are widely applied in biochemistry, materials sciences, pharmacology, and medicine.¹ Among many reactions, their addition reactions with another molecule, X–Y, perfectly suit the demand for green chemistry due to the 100% atom economy, thus leading to tremendous interest in this area due to the high importance of stereo-defined olefins.² However, regioselectivity is the issue when it comes to non-symmetric alkynes (Scheme 1a). Electronic and steric effects help in solving this type of problem (Scheme 1b and c).³ Using a pre-installed directing group, such as carbonates, pyridyl groups, amides, alkenes, *etc.*, is another feasible way to control regioselectivity through coordination with metal catalysts (Scheme 1d).^{4,5} As we know hydrogen bonding interactions have been widely used in organocatalysis,⁶ and recent publications also demonstrate their capacity in regioselective addition reactions.⁷ Herein, we report our recent observation on hydroxy group-enabled regioselectivity control in highly stereoselective hydrocarboxylation of readily available 2-alkynyl alcohols affording highly functionalized 3-hydroxy-2(*E*)-alkenoates (Scheme 1e).

Results and discussion

Initially, 1-phenyl-2-(pyridin-4-yl)but-3-yn-2-ol (**1a**) was treated with 8 equiv. of MeOH in the presence of 2 mol% [PdCl(π -

allyl)]₂, 6 mol% DPEphos, and 5 mol% (PhO)₂POOH with a CO balloon. Surprisingly, the expected *syn*-hydrocarboxylation product (*E*)-**2a**¹⁵ was not detected, while 66% of its regioisomeric product (*E*)-**2a** was exclusively formed unexpectedly together with 25% recovery of **1a** (Table 1, entry 1). The regio- and stereo-selectivity were further established by single-crystal X-ray diffraction analysis of (*E*)-**2a** (Fig. 1). Various palladium catalysts were then screened with no obvious improvement except for Pd(TFA)₂, which afforded 82% yield of (*E*)-**2a** (Table 1, entries 2–4). Pd(0) pre-catalysts were also examined, affording (*E*)-**2a** with 57–82% yields (Table 1, entries 5–7). Among all the ligands examined, DPEphos was still the best (Table 1, entries 8–10). When the reaction was conducted at 60 °C, the yield of (*E*)-**2a** was improved to 90% (Table 1, entry 11). Besides, the reaction could also occur efficiently without the help of (PhO)₂POOH (Table 1, entry 13).⁸

With the optimized conditions in hand and the importance of such 2-alkenoates, we set out to explore the scope of this reaction (Table 2). To our delight, this highly regioselective *syn*-hydrocarboxylation reaction delivered 3-hydroxy-2(*E*)-alkenoates as the sole product for various 2-alkynyl alcohols. Substitution of the pyridine ring at different positions made no difference (Table 2, entries 1–3). Quinolinyl-containing substrates were also compatible, efficiently furnishing (*E*)-**2d** in 71% yield (Table 2, entry 4). An electron-rich 3-aryl-substituted 2-alkynyl alcohol gave a higher yield (Table 2, entry 5). Compared with aromatic groups, 3-alkyl-substituted substrates **1f** and **1g** were less reactive and required a higher catalyst loading and temperature (Table 2, entries 6 and 7). Notably, the reaction could also be executed with more sterically hindered 2-alkynyl alcohols, delivering (*E*)-**2h** and (*E*)-**2i** in good yields (Table 2, entries 8 and 9). Interestingly, reaction with a 2-alkynyl alcohol with a *p*-nitrophenyl group instead of a pyridyl group also proceeded smoothly to give (*E*)-**2j** in 58% yield (Table 2, entry 10).

Unfortunately, this set of reaction conditions did not work very efficiently for 2-alkynyl alcohols with R¹ and R² both

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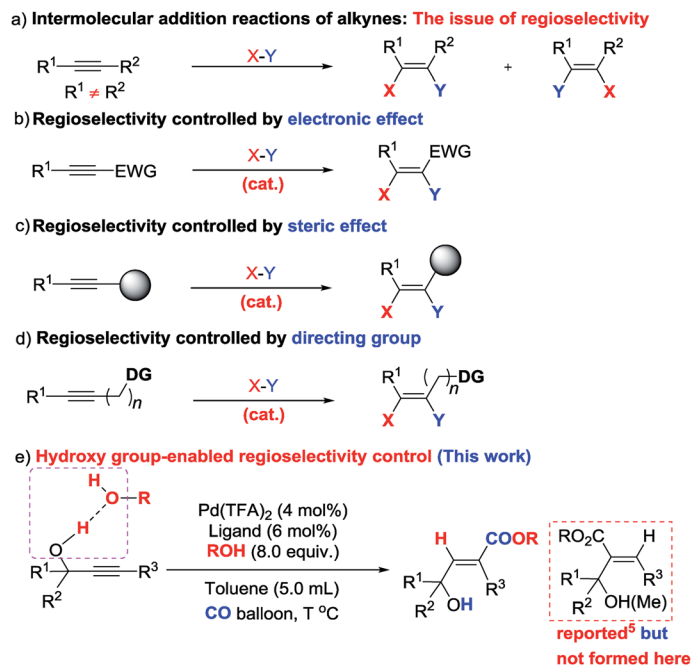
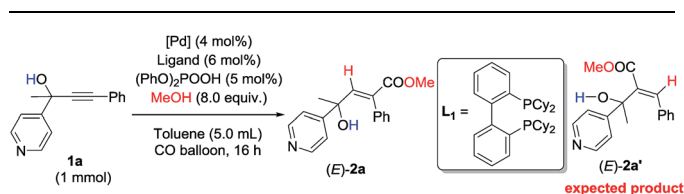
Scheme 1 Addition reactions of alkynes—approaches for regioselectivity control (only *syn*-additions are shown for clarity).

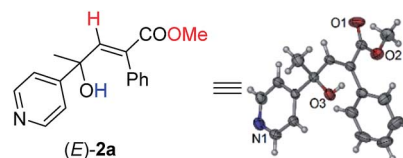
Table 1 Optimization of the reaction conditions



| Entry | [Pd] | Ligand | T/°C | (E)-2a ^a (%) | Recovery ^a (%) |
|-----------------|--|----------------|------|-------------------------|---------------------------|
| 1 | [PdCl(π -allyl)] ₂ | DPEphos | 80 | 66 | 25 |
| 2 | Pd(PPh ₃) ₂ Cl ₂ | DPEphos | 80 | 0 | 100 |
| 3 | Pd(TFA) ₂ | DPEphos | 80 | 82 | 6 |
| 4 | Pd(OAc) ₂ | DPEphos | 80 | 70 | 4 |
| 5 | Pd ₂ (dba) ₃ | DPEphos | 80 | 57 | 34 |
| 6 | Pd(<i>t</i> -Bu ₂ -PPh) ₂ | DPEphos | 80 | 78 | 12 |
| 7 | Pd(PPh ₃) ₄ | DPEphos | 80 | 82 | 15 |
| 8 | Pd(TFA) ₂ | BINAP | 80 | 26 | 67 |
| 9 | Pd(TFA) ₂ | DPPB | 80 | 33 | 43 |
| 10 | Pd(TFA) ₂ | L ₁ | 80 | 32 | 69 |
| 11 | Pd(TFA) ₂ | DPEphos | 60 | 90 | 0 |
| 12 | Pd(TFA) ₂ | DPEphos | 50 | 45 | 53 |
| 13 ^b | Pd(TFA) ₂ | DPEphos | 60 | 89 | 0 |

^a Yield and recovery were determined by ¹H-NMR analysis using CH₂Br₂ as the internal standard. ^b The reaction was carried out without (PhO)₂POOH.

being alkyl groups—the reaction of **1k** resulted in the formation of the desired (*E*)-**2k** in only 35% yield (Table 3, entry 1). Lowering the temperature increased the yield up to 49% (Table 3, entry 2). Then, the ligand effect was re-investigated to address this issue. As shown in Table 3, mono-phosphine ligands were not efficient for the hydrocarboxylation (Table 3, entries 3 and 4). It is also

Fig. 1 ORTEP representation of (*E*)-**2a**.

worth noting that the efficiency strongly depends on the electronic properties and the backbone structure of the bisphosphine ligands. Compared to 2,2'-bis(dicyclohexyl-phosphino)-

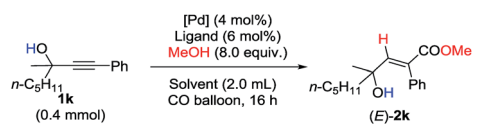
Table 2 Substrate scope-1

| Entry | R ¹ | R ² | R ³ | T/°C | (E)-2 yield ^a (%) |
|-----------------|----------------|---|--|------|------------------------------|
| 1 | Me | 4-pyridyl | Ph (1a) | 60 | 82 (2a) |
| 2 | Me | 3-Pyridyl | Ph (1b) | 60 | 80 (2b) |
| 3 | Me | 2-Pyridyl | Ph (1c) | 60 | 62 (2c) |
| 4 | Me | 3-Quinolonyl | Ph (1d) | 60 | 71 (2d) |
| 5 | Me | 4-Pyridyl | 4-MeC ₆ H ₄ (1e) | 60 | 89 (2e) |
| 6 ^b | Me | 4-Pyridyl | <i>n</i> -Bu (1f) | 70 | 86 (2f) |
| 7 ^b | Me | 4-Pyridyl | <i>n</i> -C ₈ H ₁₇ (1g) | 70 | 81 (2g) |
| 8 | Et | 4-Pyridyl | Ph (1h) | 60 | 88 (2h) |
| 9 ^c | Ph | 4-Pyridyl | <i>n</i> -Bu (1i) | 75 | 81 (2i) |
| 10 ^d | Me | 4-O ₂ NC ₆ H ₄ | <i>n</i> -C ₆ H ₁₃ (1j) | 70 | 58 (2j) |

^a Isolated yield. ^b With 6 mol% Pd(TFA)₂ and 9 mol% DPEphos. ^c With 6 mol% Pd(TFA)₂, 9 mol% DPEphos, and 6.0 mmol of MeOH for 24 h. ^d With 4 mol% Pd(TFA)₂, 8 mol% DPEphos, and 4.0 mmol of MeOH.



Table 3 Further optimization of the reaction conditions



| Entry | Ligand | Solvent | T/°C | (E)-2k ^a (%) | Recovery ^a (%) |
|-------------------|----------------|--------------------|------|-------------------------|---------------------------|
| 1 ^b | DPEphos | Toluene | 60 | 35 | 0 |
| 2 ^b | DPEphos | Toluene | 50 | 49 | 0 |
| 3 ^c | Zheda-phos | Toluene | 50 | 1 | 93 |
| 4 ^c | Sphos | Toluene | 50 | 11 | 88 |
| 5 | BINAP | Toluene | 50 | 40 | 44 |
| 6 | DPPB | Toluene | 50 | 17 | 66 |
| 7 | L ₁ | Toluene | 50 | 58 | 42 |
| 8 | BIPHEP | Toluene | 50 | 5 | 95 |
| 9 ^{b,d} | L ₁ | Toluene | 60 | 99 (95) | 0 |
| 10 ^{b,d} | L ₁ | THF | 60 | 34 | 66 |
| 11 ^{b,d} | L ₁ | 1,2-DCE | 60 | 30 | 70 |
| 12 ^{b,d} | L ₁ | CH ₃ CN | 60 | 8 | 92 |
| 13 ^{b,d} | L ₁ | DMF | 60 | 5 | 90 |
| 14 ^{b,d} | L ₁ | DMSO | 60 | — | 98 |

^a Yield and recovery were determined by ¹H-NMR analysis using CH₂Br₂ as the internal standard, and the isolated yield is shown in parentheses. ^b The reaction was carried out on a 1 mmol scale with 5 mL of toluene. ^c With 12 mol% mono-phosphine ligands. ^d With 4.0 equiv. of MeOH for 24 h.

1,1'-biphenyl (L₁), more rigid or more flexible backbone structures both made the reaction slower (Table 3, entries 5–7). Furthermore, a relatively electron-deficient ligand, BIPHEP, gave

only 5% yield of the product with 95% recovery of **1k** (Table 3, entry 8). Finally, when the reaction was carried out with 4 equiv. of MeOH at 60 °C, (*E*)-**2k** could be obtained with the highest yield (Table 3, entry 9).

Under this set of new optimal reaction conditions, more examples of 2-alkynylic alcohols were examined. As shown in Table 4, R² and R³ are both compatible with an alkyl or aryl group (Table 4, entries 1–9). The structure of (*E*)-**2q** was further confirmed by its single crystal X-ray diffraction analysis (Fig. 2). In addition, a 2-alkynylic alcohol with a four-membered cyclobutyl ring also survived affording (*E*)-**2s** in 87% yield (Table 4, entry 10). Reaction with more sterically hindered 1,1-diphenylhept-2-yn-1-ol proceeded smoothly to give (*E*)-**2t** in 86% yield and 9% recovery of **1t** (Table 4, entry 11). It is noteworthy that secondary 2-alkynylic alcohols also afforded the target products in good to excellent yields with the same regio- and stereo-selectivity (Table 4, entries 12–15). Interestingly, even the C–Br bond could survive in this reaction (Table 4, entries 2, 3, and 15). The reaction could be easily executed on a gram scale, delivering (*E*)-**2l** in 89% yield (Table 4, entry 3).

In addition to methanol, some other alcohols were also examined. Ethanol and TMSCH₂OH work well to obtain the

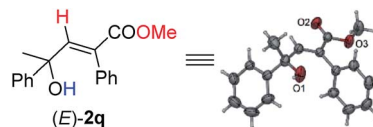
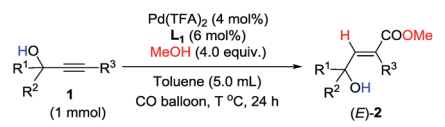
Fig. 2 X-ray crystal structure of (*E*)-**2q**.

Table 4 Substrate scope-2

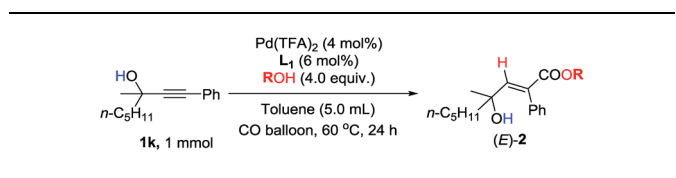


| Entry | R ¹ | R ² | R ³ | T/°C | (<i>E</i>)- 2 yield ^a /% |
|-------------------|----------------|--|--|------|--|
| 1 | Me | <i>n</i> -C ₅ H ₁₁ | Ph (1k) | 60 | 95 (2k) |
| 2 | Me | <i>n</i> -C ₅ H ₁₁ | 4-BrC ₆ H ₄ (1l) | 60 | 92 (2l) |
| 3 ^b | Me | <i>n</i> -C ₅ H ₁₁ | 4-BrC ₆ H ₄ (1l) | 60 | 89 (2l) |
| 4 ^{c,d} | Me | <i>n</i> -C ₅ H ₁₁ | <i>n</i> -Bu (1m) | 80 | 66 (2m) |
| 5 ^{e,f} | Me | <i>n</i> -Pr | <i>n</i> -C ₈ H ₁₇ (1n) | 75 | 71 (2n) |
| 6 ^{c,g} | Me | (CH ₂) ₂ CH=CH ₂ | <i>n</i> -Pr (1o) | 75 | 41 (2o) |
| 7 ^{e,h} | Me | <i>n</i> -Pr | (CH ₂) ₄ Cl (1p) | 75 | 60 (2p) |
| 8 | Me | Ph | Ph (1q) | 70 | 93 (2q) |
| 9 ^{c,i} | Me | Ph | <i>n</i> -Bu (1r) | 75 | 63 (2r) |
| 10 | | -(CH ₂) ₃ - | Ph (1s) | 25 | 87 (2s) |
| 11 ^{c,j} | Ph | Ph | <i>n</i> -Bu (1t) | 80 | 86 (2t) |
| 12 | H | <i>n</i> -C ₁₁ H ₂₃ | Ph (1u) | 60 | 93 (2u) |
| 13 ^c | H | Ph | Ph (1v) | 70 | 69 (2v) |
| 14 ^c | H | Ph | 4-MeOC ₆ H ₄ (1w) | 70 | 69 (2w) |
| 15 | H | <i>n</i> -C ₁₁ H ₂₃ | 4-BrC ₆ H ₄ (1x) | 60 | 87 (2x) |

^a Isolated yield. ^b The reaction was carried out on a 4 mmol scale. ^c With 5 mol% Pd(TFA)₂, 10 mol% L₁, and 5.0 mmol of MeOH. ^d Reaction time 48 h; 19% recovery of **1m** was detected. ^e With 6 mol% Pd(TFA)₂, 12 mol% L₁, and 5.0 mmol of MeOH. ^f Reaction time 48 h; 27% recovery of **1n** was detected. ^g 36% recovery of **1o** was detected. ^h Reaction time 48 h; 34% recovery of **1p** was detected. ⁱ Reaction time 48 h; 21% recovery of **1r** was detected. ^j Reaction time 32 h; 9% recovery of **1t** was detected.



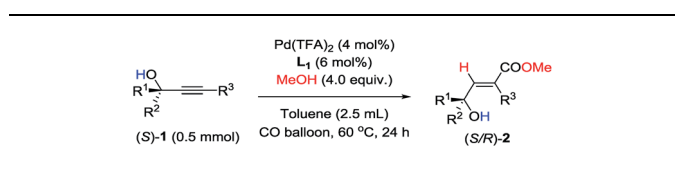
Table 5 Substrate scope-3



| Entry | ROH | Yield of (<i>E</i>)-2 ^a /% |
|----------------|-----------------------|---|
| 1 | EtOH | 95 (2ka) |
| 2 | TMSCH ₂ OH | 97 (2kb) |
| 3 ^b | i-PrOH | 76 (2kc) |
| 4 ^c | PhOH | 30 (2kd) |

^a Isolated yield. ^b 24% recovery of **1k** was determined by ¹H-NMR analysis using CH₂Br₂ as the internal standard. ^c 70% recovery of **1k** was determined by ¹H-NMR analysis using CH₂Br₂ as the internal standard.

Table 6 Palladium-catalyzed hydrocarboxylation of chiral propargylic alcohols



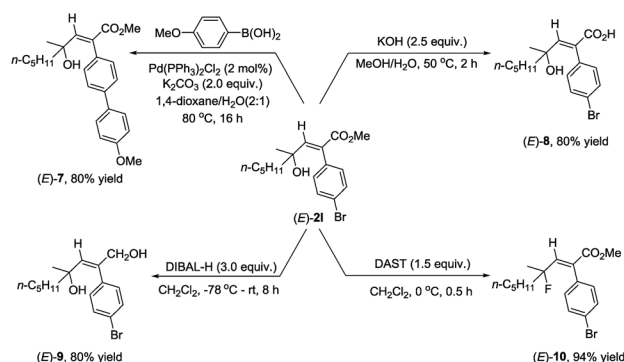
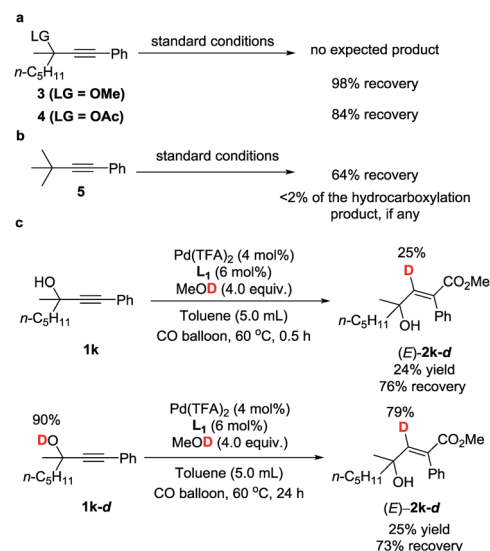
| Entry | (<i>S</i>)-1 | R ¹ | R ² | R ³ | 2 ^a | Yield/% | ee/% |
|------------------|----------------|---|----------------------------|----------------------------|------------------|---------|------|
| 1 ^{b,c} | H | <i>n</i> -C ₁₁ H ₂₃ | Ph (1u , 98) | Ph (1u , 98) | 90 (2u) | 99 | 99 |
| 2 | H | <i>n</i> -C ₁₁ H ₂₃ | 4-BrPh (1x , >99) | 4-BrPh (1x , >99) | 86 (2x) | 99 | 99 |
| 3 ^{b,d} | H | Ph | Ph (1v , >99) | Ph (1v , >99) | 68 (2v) | 99 | 99 |
| 4 ^{b,d} | H | Ph | 4-MeOPh (1w , >99) | 4-MeOPh (1w , >99) | 70 (2w) | 99 | 99 |
| 5 ^b | Me | <i>n</i> -C ₅ H ₁₁ | Ph (1k , 97) | Ph (1k , 97) | 89 (2k) | 96 | 96 |

^a Isolated yield; ee values were determined by chiral HPLC analysis. ^b The reaction was carried out at 70 °C. ^c With 4 mol% Pd(TFA)₂ and 8 mol% L₁. ^d With 5 mol% Pd(TFA)₂, 10 mol% L₁, and 5.0 equiv. of MeOH.

target products in 95–97% yield (Table 5, entries 1 and 2). Sterically hindered i-PrOH is also tolerated with 76% yield (Table 5, entry 3). Phenol behaves worse, and only 30% yield was detected (Table 5, entry 4).⁹

Furthermore, as shown in Table 6, racemization of the chiral center in substrates (*S*)-**1**¹⁰ was not observed—the reaction of optically active propargylic alcohols afforded optically active 3-hydroxy-2(*E*)-alkenoates with excellent ee values and high yields.

As we know that 2-alkenoates are important intermediates in organic synthesis, their synthetic potential has been further demonstrated for the synthesis of different stereo-defined functionalized olefins. Owing to the presence of the C–Br bond in (*E*)-**2I**, Suzuki coupling reactions could easily afford (*E*)-**7** in 80% yield.¹¹ The ester unit could be hydrolyzed with KOH at 50 °C for 2 hours to afford the corresponding acid (*E*)-**8** in 80% yield,¹² or reduced with DIBAL-H at –78 °C delivering the corresponding 1,4-diol (*E*)-**9** in 80% yield.¹³ Fluorination of the

Scheme 2 Synthetic applications of (*E*)-**2I**.

Scheme 3 Mechanistic studies.

hydroxyl group could also be easily conducted with DAST to furnish (*E*)-**10** in 94% yield¹⁴ (Scheme 2).

To gain insight into the reaction mechanism and the effect of the hydroxyl group, a couple of control experiments were conducted (Scheme 3). No desired hydrocarboxylation products were obtained when propargylic methyl ether **3**, acetate **4**, or internal alkyne **5** was utilized (Scheme 3a and b), indicating that the hydrogen bonding originating from the free hydroxyl groups in propargylic alcohol and methanol might have played a critical role in this transformation. Isotopic labeling studies reinforce the notion that methanol was the hydrogen donor (Scheme 3c). We reasoned that the low D incorporation was caused by adventitious water in the reaction mixture. Furthermore, the ¹H NMR signals of 1-phenyl-3-methyloctyn-3-ol **1k** were measured with respect to different amounts of MeOH and **1k**: an obvious shift of the hydroxy signal in **1k** and MeOH was observed, indicating hydrogen bonding between the two hydroxyl groups (Fig. 3).

In addition, kinetic studies were also carried out. Linear relationships were obtained for ln{c₀/(c₀ – [(*E*)-**2k**]}) vs. reaction time (c₀ is the initial concentration of **1k**), even with 10-fold



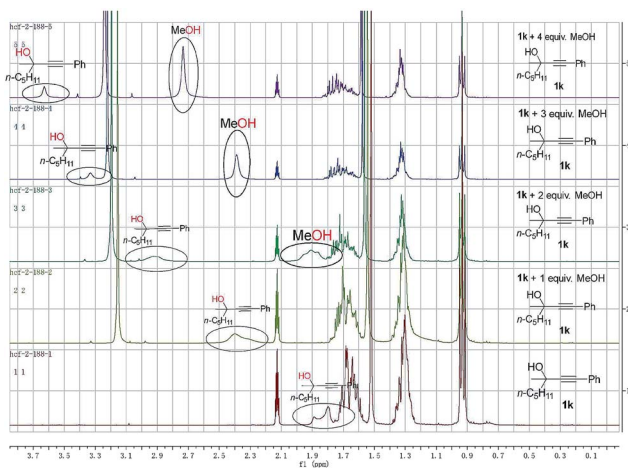


Fig. 3 NMR investigation on hydrogen bonding.

excess of MeOH to ensure pseudo zero order in MeOH, indicating first-order dependence of the reaction rate with respect to propargylic alcohol (Fig. 4b). An experiment was also carried out to measure the rate of H/D-scrambling. By adding MeOD into the solution of **1k** in CDCl_3 and then subjecting the mixture to ^1H NMR analysis immediately, the H/D-exchange process was found to reach an equilibrium state within 3 minutes (for details, see the ESI[†]), which is much faster than the rate of this hydrocarboxylation reaction (Fig. 4a).

Based on this, parallel reactions of **1k** and **1k-d** in separate reaction vessels monitored by ^1H NMR analysis of the reaction profile could help determine the value of k_{H} and k_{D} , and then the KIE was calculated to be $k_{\text{H}}/k_{\text{D}} = 16$ (Fig. 5), indicating the primary isotope effect of H/D.

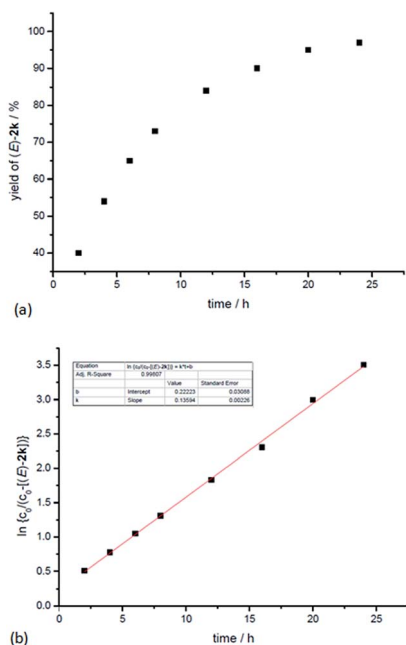
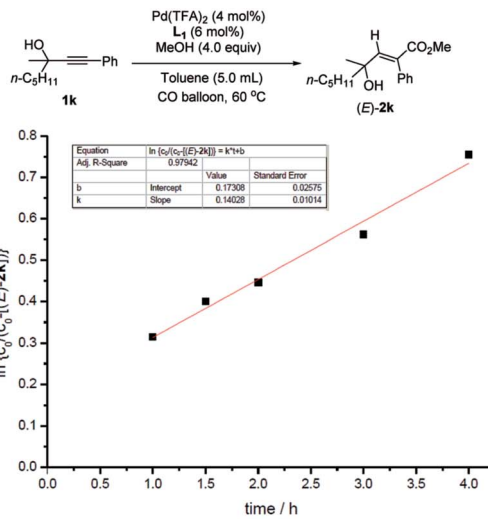
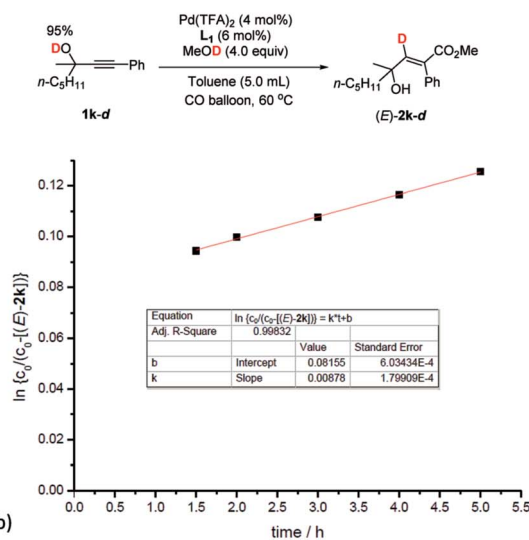


Fig. 4 Determination of the reaction order of propargylic alcohol. (a) Yield of (*E*)-**2k** vs. time. (b) $\ln\{c_0/(c_0 - [(E)\text{-}2k])\}$ vs. time (*R*-squared is the coefficient of determination).



(a)



(b)

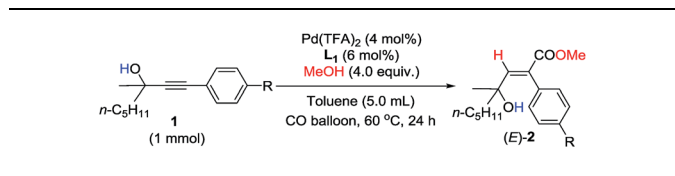
Fig. 5 Kinetic isotope effect experiments. (a) Linear function fit for the reaction rate of **1k** to obtain k_{H} . (b) Linear function fit for the reaction rate of **1k-d** to obtain k_{D} . $k_{\text{H}}/k_{\text{D}} = 16$.

In order to further identify the rate-determining step, the electronic effect of substrates on the Pd-H insertion step was investigated (Table 7). Then, kinetic studies of the substrates with different substituents on the *para*-position of the phenyl ring such as Br, CO_2Me , Me, and OMe were carried out. Linear relationships were obtained for $\ln\{c_0/(c_0 - [(E)\text{-}2k])\}$ vs. reaction time, and show significantly different reaction rates, that is, the more electron-rich the substituent is, the faster the reaction rate is (Fig. 6). These results also indicate that Pd-H insertion has a large effect on the reaction rate. However, we are still not able to exclude the oxidative addition of O-H with Pd as the rate-determining step.

In order to further unveil the mechanism, solvents without hydrogen bonding^{7b} were also screened—lower yields were detected in comparison with the data for toluene. The stronger the polarity of the solvent is, the lower the yield would be, and nothing but a large amount of substrate recovery was observed



Table 7 Electronic effect investigation



| Entry | R | Yield of (E)-2 ^a /% |
|----------------|----------------------------------|--------------------------------|
| 1 | H (1k) | 95 (2k) |
| 2 | Br (1l) | 92 (2l) |
| 3 ^b | CO ₂ Me (1y) | 85 (2y) |
| 4 | Me (1z-A) | 96 (2z-A) |
| 5 | OMe (1z-B) | 97 (2z-B) |

^a Isolated yield. ^b 14% recovery of **1y** was detected.

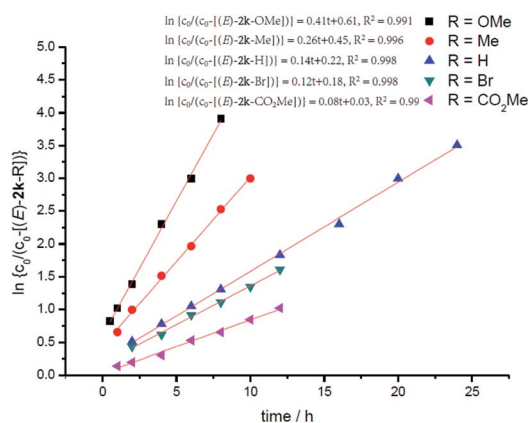
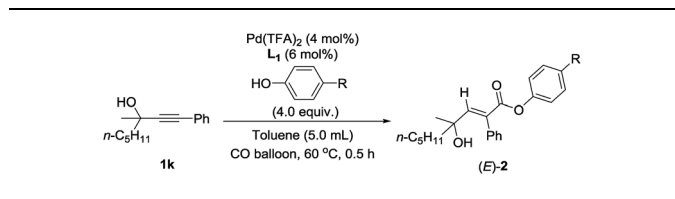


Fig. 6 $\ln\{c_0/(c_0 - [(E)-2k-R])\}$ vs. time (R -squared is the coefficient of determination).

when using DMSO, further supporting the irreplaceable role of hydrogen bonding in this transformation (Table 3, entries 10–14).

Other than this, a Hammett study with phenols bearing various substituents has also been carried out (Table 8). The negative value for ρ points out that the rate-determining step favors phenols with electron-donating groups (Fig. 7).¹⁵ This seems reasonable to us because phenols with electron-donating groups would result in a higher electron density on the oxygen atom, thus leading to stronger hydrogen bonding with the hydrogen atom in the hydroxyl group and/or nucleophilicity (see step 3 in Scheme 4).

Based on these studies, a plausible mechanism is proposed (Scheme 4). Hydrogen bonding between the hydroxyl group of methanol and that of 2-alkynol combined with the coordination of the C–C triple bond to the Pd⁰ species would form complex A. Subsequent oxidative addition of the O–H bond in methanol with Pd⁰ in A affords complex B. Subsequent regioselective *syn*-hydropalladation of the C–C triple bond delivers the H atom to the sp carbon atom closer to the hydroxy group in **1k**, and then nucleophilic attack of CO by the methoxy anion generates **Int 2**. Reductive elimination would then furnish (E)-**2k** and regenerate the Pd⁰ species to finish the catalytic cycle. Of course, further studies are needed to fully verify this mechanism.

Table 8 Hammett study with phenols bearing various substituents^a

| Entry | R | σ (ref. 16) | Yield of (E)-2/% |
|-------|--------------------|--------------------|--------------------|
| 1 | H | 0 | 11 (2kd) |
| 2 | MeO ₂ C | 0.45 | 3.5 (2ke) |
| 3 | Me | −0.17 | 14 (2kf) |
| 4 | MeO | −0.27 | 16 (2kg) |
| 5 | Cl | 0.23 | 6 (2kh) |

^a Yield and recovery were determined by ¹H-NMR analysis using CH₂Br₂ as the internal standard.

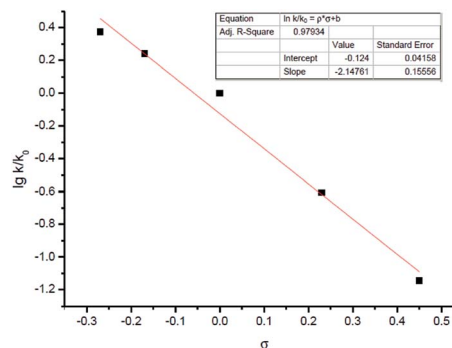
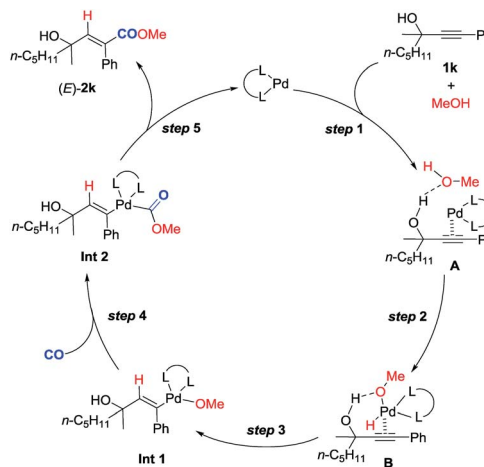


Fig. 7 Hammett equation of phenols with varying acidities.



Scheme 4 Plausible reaction mechanism.

Conclusions

In summary, we have developed hydroxy group-enabled highly regio- and stereo-selective hydrocarboxylation of 2-alkynyl alcohols, exploiting a previously unrecognized regioselectivity control strategy. The remarkable substrate scope, atom economy, and good to excellent yields make this reaction a facile synthetic



method to produce highly functionalized 3-hydroxy-2(*E*)-alkenoates and the observed regioselectivity may arise from hydrogen bonding, which needs further investigation. Due to the versatility of the functionality in the products, the importance of the stereoselective construction of C=C bonds, and the nature of regioselectivity control, this method will be of high interest to organic and medicinal chemists. Further studies in this area are currently ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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