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Pd(II)-Catalyzed Cascade Wacker−Heck Reaction: Chemoselective Coupling of Two Electron-Deficient Reactants

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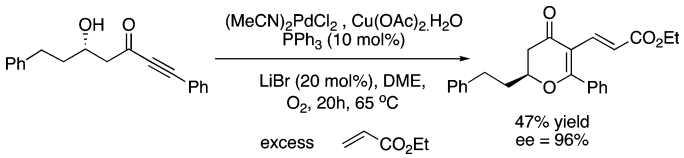

A novel palladium(II)-catalyzed oxy-carbopalladation process was developed allowing for the orchestrated union of hydroxy ynones with ethyl acrylate, two electron-deficient reactants. With β-hydroxy ynones, this cascade Wacker−Heck process gave access to highly functionalized tri- or tetrasubstituted dihydropyranones featuring an unusual dienic system. For diastereomerically pure and for enantioenriched β-hydroxyynones, these reactions proceed without affecting the stereochemical integrity of the existing stereocenters. In addition, tetrasubstituted furanones can be prepared when α-hydroxyynones and ethyl acrylate are used as starting materials. The dihydropyranones and furanones obtained upon cyclization are novel compounds, but structurally related carbohydrate derivatives featuring a similar dienic system have been used as starting materials for the construction of polyannulated products, suggesting that these cascade Pd(II)-mediated oxidative heterocyclizations are of value for various synthetic applications.

Introduction

Palladium(0)-catalyzed cascade reactions are used extensively in synthesis for the construction of highly functionalized carbo- and heterocycles.[1] Very often, these transformations involve a reactive σ-alkyl Pd intermediate, which can undergo further transformations prior to a terminal reductive process. Depending on the reactants and the reaction conditions, it is possible to trap these transient σ-alkyl Pd species by the insertion of carbon monoxide or olefins, by nucleophilic attack, or through various cross-coupling reactions.[2] Pd(II)-catalyzed cascade reactions were recently selected as key steps for the total synthesis of important biologically active targets. Tietze et al. reported an elegant enantioselective synthesis of vitamin E relying on a domino Wacker−Heck sequence, starting with an oxidative cyclization for the construction of the chroman framework, followed by an intermolecular olefin insertion for the attachment of part of the chain of vitamin E.[3] An alternative Wacker−Heck process was developed by Rawal et al. to construct a key fragment necessary for the total synthesis of mycalamide A.[4] In this study, the desired pyran ring featuring an exocyclic double bond was the result of an intramolecular Heck reaction of a σ-alkyl palladium species, arising from an intermolecular Wacker reaction of an enol ether with methanol. The successful outcome of these cascade reactions is likely the result of combined inter- and intramolecular processes involving electronically complementary olefinic partners. Recently, we have shown that the palladium(II)-mediated oxidative cyclization of β-hydroxy enones led to the formation of di- or trisubstituted dihydropyranones in high yields.[5] This transformation did not take place for hydroxyenones possessing a substituent on the sp^2 hybridized carbon α to the carbonyl group, a limitation

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(1) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (c) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453−3516. (d) Heumann, A.; Réglier, M. *Tetrahedron* **1996**, *52*, 9289−9346.

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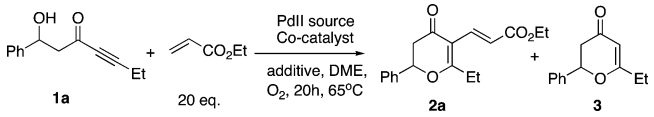
SCHEME 1. Wacker−Heck Oxidative Heterocyclization of Hydroxy Ynones



preventing access to dihydropyranones substituted at this carbon. To overcome this limitation, we devised a palladium(II)-catalyzed Wacker−Heck reaction starting from β-hydroxy ynones. Upon oxidative heterocyclization, these substrates should lead to σ-alkenyl Pd intermediates, which cannot β-eliminate, but could undergo olefin insertion to form trisubstituted dihydropyranones featuring an alkenyl substituent α to the carbonyl. Herein, we report the feasibility of this Pd(II)-catalyzed cascade process involving the union of structurally diverse hydroxy ynones and ethyl acrylate, two electron-deficient reactants. To the best of our knowledge, the cascade processes reported to date, which feature a Pd(II)-catalyzed oxidative heterocyclization, all involve at least one electron-rich olefinic partner.[3,4,6] The products resulting from the cascade reactions reported herein are unusual functionalized dihydropyranones and furanones, which are not accessible upon Pd(II)-catalyzed oxidative heterocyclization of the corresponding adequately substituted α- or β-hydroxy enones.

Results and Discussion

Optimization Studies. Our initial studies focused on the development of an optimum set of reaction conditions for the palladium-mediated coupling of ethyl acrylate with β-hydroxyynone **1a**, a compound prepared in 78% yield by aldol condensation of the commercially available 3-hexyn-2-one with benzaldehyde (Scheme 1, Table 1). The results of our optimization study are summarized in Table 1. The key to success lies in the optimum combined choice for the catalyst, the solvent, and the additives. Under the reaction conditions used for the oxidative cyclization of hydroxyenones ($PdCl_2$, CuCl, Na_2HPO_4, O_2, 65 °C),[5] the reaction of the β-hydroxyynone **1a** in the presence of 20 equiv of ethyl acrylate led to the formation of the desired adduct **2a** in 27% yield (entry 1). The addition of 10 mol % of PPh_3 led to an increased yield of 41%, possibly due to the ability of this additive to stabilize the σ-alkenyl Pd intermediate, therefore promoting the carbopalladation step (entry 2).[7] An increase in the loading of Na_2HPO_4 or CuCl was not beneficial (entries 3 and 4). When $Pd(TFA)_2$ was used as the catalyst in the presence of benzoquinone as the co-oxidant, compound **2a** was isolated in 40% yield (entry 6). The use of $(MeCN)_4Pd(BF_4)_2$ and $Cu(OAc)_2{\cdot}H_2O$ in combination with K_2CO_3 and PPh_3 led to the formation of a new product identified as the disubstituted dihydropyranone **3**, in addition to the desired trisubstituted dihydropyranone **2a**, in 38% and 28% yield, respectively (entry 7). The dihydropyranone **3** was the result of a base-mediated 6-*endo-dig* process or a palladium-catalyzed ring closure followed by protonolysis of the σ-alkenyl Pd intermediate. Interestingly, the addition of LiBr[6] minimized the formation of **3** and increased the yield of **2a** to 43% yield (entry 8). In the presence of $(MeCN)_2PdCl_2$, compound **3** could not be detected in the crude reaction mixture (entry 9). After extensive experimentation, it was found that the reaction of **1a** with ethyl acrylate was best performed at 65 °C in DME in the presence of 20 mol % of LiBr and 10 mol % of $(MeCN)_2PdCl_2$, $Cu(OAc)_2{\cdot}H_2O$ and PPh_3, under an atmospheric pressure of oxygen leading to the dihydropyranone Heck trapping product **2a** in a reasonable 58% isolated yield (entry 11). Ligands such as triethylamine, sparteine, pyridine, or DMSO, commonly used for other Pd(II)-mediated oxidative cyclizations, were tested in an attempt to improve further the chemical yield, but none of these reactions led to significant improvement (entries 14−17).[8]

TABLE 1. Optimization Studies for the Ring Closure of 1a into 2a

entry	Pd source (mol %) co-oxidant (mol %)	additives (mol %)	yield (%)
1	$PdCl_2$ (10) CuCl (10)	Na_2HPO_4 (10)	27
2	$PdCl_2$ (10) CuCl (10)	Na_2HPO_4 (10), PPh_3 (10)	41
3	$PdCl_2$ (10) CuCl (100)	Na_2HPO_4 (10), PPh_3 (20)	20
4	$PdCl_2$ (10) CuCl (10)	Na_2HPO_4 (100), PPh_3 (20)	34
5	$Pd(TFA)_2$ CuCl (10)	Na_2HPO_4 (10), PPh_3 (10)	37
6[a]	$Pd(TFA)_2$ benzoquinone (400)	PPh_3 (20)	40
7	$(MeCN)_4Pd(BF_4)_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	K_2CO_3 (10), PPh_3 (20)	28 (38[b])
8	$(MeCN)_4Pd(BF_4)_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	K_2CO_3 (10) PPh_3 (10), LiBr (20)	43 (27[b])
9	$(MeCN)_2PdCl_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	K_2CO_3 (10) PPh_3 (10), LiBr (20)	42
10	$(MeCN)_2PdCl_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	PPh_3 (20), LiBr (20)	50
11	$(MeCN)_2PdCl_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	PPh_3 (10), LiBr (20)	58
12[c]	$(MeCN)_2PdCl_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	PPh_3 (10), LiBr (20)	48
13[c]	$(MeCN)_2PdCl_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	PPh_3 (20), LiBr (20)	50
14	$(MeCN)_2PdCl_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	Et_3N (10), LiBr (20)	50
15	$(MeCN)_2PdCl_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	sparteine (10), LiBr (20)	40
16	$(MeCN)_2PdCl_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	pyridine (10), LiBr (20)	33
17	$(MeCN)_2PdCl_2$ (10) $Cu(OAc)_2{\cdot}H_2O$ (10)	DMSO (10), LiBr (20)	38

[a] Reaction carried out under argon atmosphere. [b] Yield of side product **3**. [c] Reaction carried out for 48 h.

Synthesis of Tri- and Tetrasubstituted Dihydropyranones. The reaction was subsequently carried out with β-hydroxyynones **1b**−**f**, which were all converted to the desired products resulting from the cascade Wacker−Heck process with chemical yields ranging from 44% to 56% (Table 2). All of the products were formed as single geometrical *E*-isomers for the exocyclic double bond. No starting material or side products resulting from a 6-*endo-dig* ring closure, not followed by a Heck coupling, were detected in the crude reaction mixtures.

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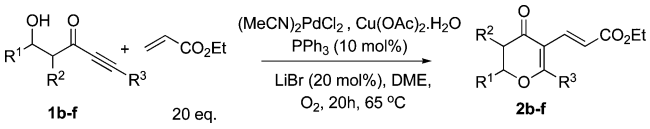
(6) (a) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130−3131. (b) Scarborough, C. C.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 3251−3254. (c) Minami, K.; Kawamura, Y.; Koga, K.; Hosokawa, T. *Org. Lett.* **2005**, *7*, 5689−5692. (d) Trudeau, S.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5465−5468. (e) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371−3373. (f) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3367−3370. (g) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *Chem. Eur. J.* **2005**, *11*, 5708−5712. (h) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809−812. (i) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn* **1989**, *62*, 2050−2054.

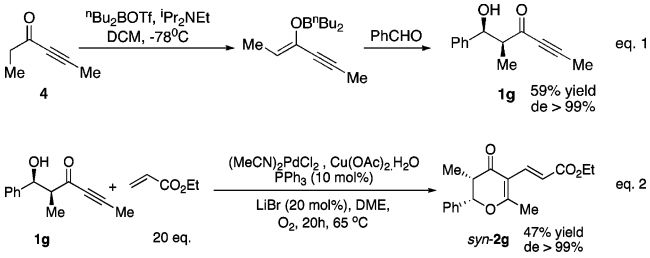
(7) A ^{31}P NMR of the crude reaction mixture after filtration of the Cu salts revealed that no peaks corroborating with PPh_3 or $OPPh_3$ were detected; the fate of PPh_3 over the course of this reaction is still unknown. The ^{31}P NMR spectra are provided in the Supporting Information.

TABLE 2. Wacker−Heck of β-Hydroxy Ynones 1b−f



entry	substrate	R^1	R^2	R^3	product	yield (%)
1	**1b**	4-$NO_2C_6H_4$	H	Et	**2b**	52
2	**1c**	4-$MeOC_6H_4$	H	Et	**2c**	56
3	**1d**	4-$MeOC_6H_4$	H	Me	**2d**	55
4	**1e**	$Ph(CH_2)_2$−	H	Et	**2e**	44
5	**1f**	−C_4H_4−		Me	**2f**	50

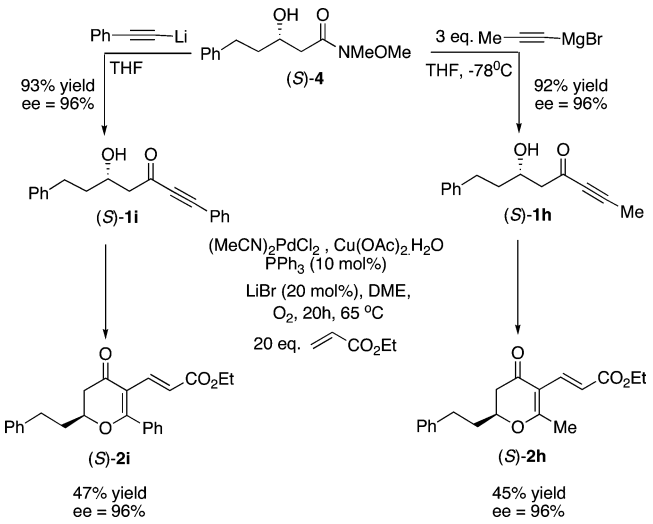
SCHEME 2. Pd(II)-Mediated Synthesis of Tetrasubstituted *syn*-Dihydropyranone 2g



We also cyclized the *syn*-β-hydroxyynone **1g** readily prepared in 59% yield and with excellent diastereoselectivity (>99% de) from 4-hexyn-3-one **4** and benzaldehyde using a *n*-Bu_2BOTf- and *i*-Pr_2EtN-mediated aldol reaction (Scheme 2, eq 1).[9] Applying the optimized conditions for the Wacker−Heck cyclization process, the desired tetrasubstituted *syn*-dihydropyranone **2g** was formed in 47% yield without affecting the relative stereochemistry of the two existing stereocenters (>99% de) (Scheme 2, eq 2).

With the successful outcome of the domino Wacker−Heck coupling, we subsequently examined the stereochemical integrity of enantiopure hydroxy ynones (*S*)-**1h** and (*S*)-**1i** upon heterocyclization followed by C−C bond formation. Direct catalytic asymmetric aldolizations leading to enantiopure β-hydroxyynones are rare, and the few reactions reported to date, although elegant, are limited in scope.[10] We therefore opted for an operationally simple route to ynones (*S*)-**1h** and (*S*)-**1i** using as starting material the known enantiopure Weinreb amide (*S*)-**4** prepared from the corresponding β-hydroxy ester.[5] This ester

SCHEME 3. Synthesis and Cascade Oxidative Heterocyclization of (*S*)-1h and (*S*)-1i



was readily available enantioenriched using a Baker's yeast-mediated catalytic asymmetric reduction.[11] The reaction of 1-propynylmagnesium bromide or the lithium anion of phenylacetylene with (*S*)-**4** led to the formation of the desired β-hydroxy ynones (S)-**1h** and (*S*)-**1i** in excellent yields. Both products were obtained with an ee of 96%. Upon cyclization in the presence of an excess of ethylacrylate, the desired dihydropyranones (*S*)-**2h** and (*S*)-**2i** were formed in 45% and 47% yield, respectively, and with enantiomeric excesses of 96%, leading us to conclude that this cascade Wacker−Heck process occurred with no detectable racemization (Scheme 3).

Synthesis of Tetrasubstituted Furan-3(2*H*)-ones. The domino cyclization reaction was also applied to α-hydroxyynones **6a**−**c**, which were prepared in four steps from ethyl 2-hydroxy-2-methylpropanoate. The cyclization of α-hydroxyynones with alkyl or aryl substituents on the triple bond in the presence of an excess of ethyl acrylate gave the corresponding tetrasubstituted furanones **7a**−**c** in isolated yields ranging between 52% and 65%. For susbtrate **6c** with a phenyl substituent capping the alkyne, the side product **8** resulting from a noncascade 5-*endo-dig* cyclization was isolated in 26% yield in addition to the desired product **7c**, which was formed in 65% yield (Scheme 4).

Mechanism. A plausible mechanism for the palladium(II)-catalyzed Wacker−Heck process presumably involves initial coordination of the metal to the triple bond, resulting in intramolecular nucleophilic attack by the proximal hydroxy group (oxypalladation). This leads to the formation of a σ-alkenyl palladium intermediate, which cannot undergo β-hydride elimination. This intermediate can further react in a subsequent carbopalladation process with ethyl acrylate present in large excess. After β-hydride elimination, the tri- or tetrasubstituted dihydropyranone is formed with concomitant formation of a palladium hydride species which upon reductive elimination would allow Pd(0) to re-enter the catalytic cycle after oxidation by molecular oxygen. The side product **3** resulting from the cyclization of **1a** can be formed upon a 6-*endo-dig* ring closure followed by rapid protonolysis of the σ-alkenyl palladium intermediate, preventing subsequent Heck

(8) For selected Pd(II) heterocyclizations featuring the use of different additives, see: (a) Tietze, L. T.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453−3516. (b) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem.* **2004**, *2*, 2551−2554. (c) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (d) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164−166. (e) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625−655. (f) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892−2895. (g) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907−2908. (h) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063−5064. (i) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584−3585. (j) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298−5300. (k) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2310. (l) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063−5064. (m) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578−9579.

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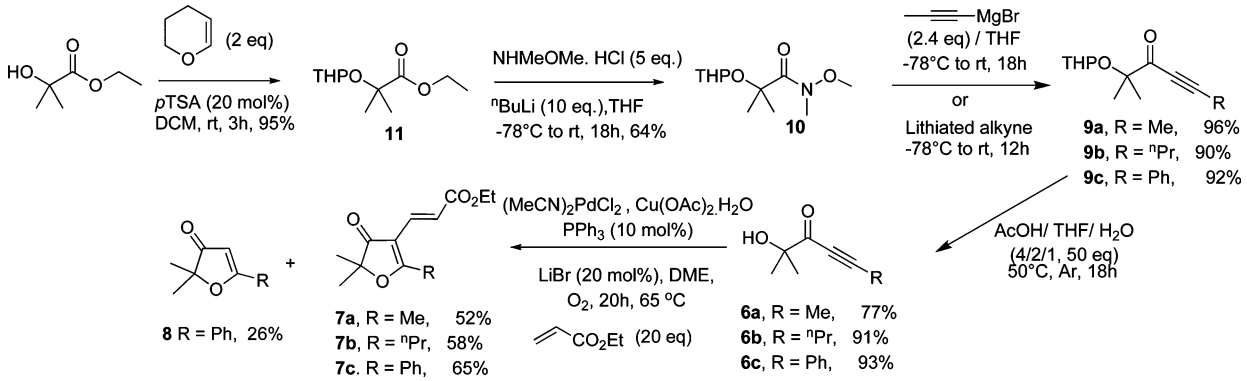
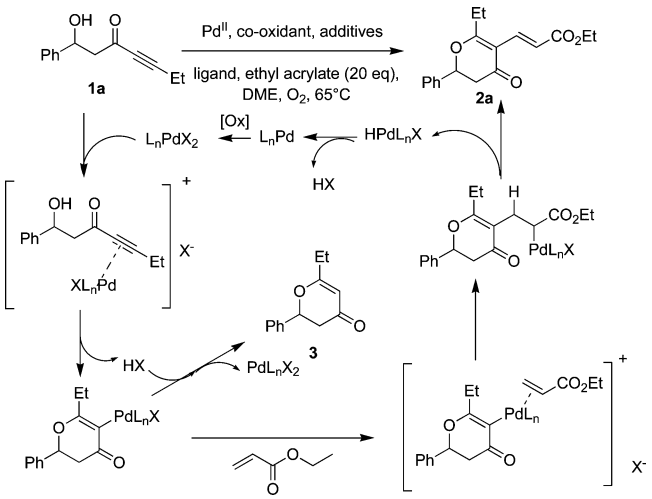
SCHEME 4. Synthesis and Heterocyclization of α-Hydroxy Ynones 6a−c



SCHEME 5. Oxy-/Carbopalladation Reaction Mechanism



coupling. An alternative reaction pathway could be a base-mediated ring-closure process.[12] Notably, a control experiment carried out without Pd(II) catalyst led only to recovered starting material contaminated with a side product resulting from dehydration of the hydroxy ynone (Scheme 5).[13]

Conclusion

In conclusion, we have developed a novel palladium(II)-catalyzed Wacker−Heck process, which chemoselectively couples two electron-poor substrates to afford novel trisubstituted dihydropyranones or furanones. These compounds are unknown, but structurally related carbohydrate derivatives featuring a similar dienic system have been used in natural product synthesis.[14] This chemistry belongs to a growing class of Pd-(II)-catalyzed oxidative heterocyclizations, an area of research which has reappeared at the forefront of organometallic catalysis. Further work is undergoing in our laboratories to study the synthetic potential of these unusual products and to develop alternative palladium-catalyzed cascade reactions involving electron-deficient ynones.

Experimental Section

General Procedure A: Aldol Reaction. To a precooled (0 °C) solution of diisopropylamine (1.5 equiv) in anhydrous THF was added *n*-BuLi (1.6M in hexanes, 1.5 equiv). The solution was stirred for 30 min at 0 °C and then cooled to −78 °C, and 3-hexyn-2-one was added dropwise (1.3 equiv) in THF via cannula. The solution was stirred for 20 min at −78 °C, and then the corresponding aldehyde (1 equiv) was added in THF via cannula. The resulting solution was stirred for 15 min. Then, it was quenched with a saturated ammonium chloride solution and allowed to warm at room temperature. The organic layer was separated and the aqueous layer was partitioned with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and filtered under suction, and solvent was removed in vacuo. The resulting residue was further purified by silica gel chromatography.

General Procedure B: Preparation of *β*-Hydroxy Ynones by Addition of a Grignard Reagent to a Weinreb Amide. To a flask charged with the Weinreb amide (1 equiv) in THF was added at −78 °C dropwise 1-propynylmagnesium bromide (0.5 M in THF, 2.4 equiv). The mixture was warmed to room temperature overnight and then quenched with NH_4Cl at 0 °C. The organic layer was separated, and the aqueous layer was partitioned with ethyl acetate. The organic layers were combined and dried over $MgSO_4$. After filtration, solvent was removed in vacuo. The resulting residue was further purified by silica gel chromatography.

General Procedure C: Preparation of *β*-Hydroxy Ynones by Addition of a Lithiated Alkyne. To a flask charged with the correspondent alkyne (1.1 equiv) in THF was dropwise added *n*-BuLi (2.5 M in THF, 1.1 equiv) at 0 °C for 30 min. Then, the Weinreb amide in THF was added dropwise at −78 °C. The mixture was warmed to room temperature overnight and quenched with NH_4Cl at 0 °C. The organic layer was separated, and the aqueous layer was partitioned with ethyl acetate. The organic layers were combined and dried over $MgSO_4$. After filtration, solvent was removed in vacuo. The resulting residue was further purified by silica gel chromatography.

General Procedure D: Deprotection of the THP Group. To a flask charged with the protected alcohol (1 equiv) was added at

(12) For *6-endo-dig* cyclization not catalyzed by palladium complexes, see: (a) Hashimoto, S.; Ban, M.; Yanagiya, Y.; Sakata, S.; Ikegami, S. *Tetrahedron Lett.* **1991**, *32*, 4027−4030. (b) Hashimoto, S.; Sonegawa, M.; Sakata, S.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1987**, *1*, 24−25. (c) Dreessen, S.; Schabbert, S.; Schaumann, E. *Eur. J. Org. Chem.* **2001**, *2*, 245−251. (d) Pflieger, D.; Muckensturm, B. *Tetrahedron Lett.* **1990**, *31*, 2299−2300. (e) Pflieger, D.; Muckensturm, B. *Tetrahedron* **1989**, *45*, 2031−2040. (f) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115−8116. (g) García, H.; Iborra, S.; Primo, J. *J. Org. Chem.* **1986**, *51*, 4432−4436. (h) Lavallée, J.-F.; Berthiaume, G.; Deslongchamp, P.; Grein, F. *Tetrahedron Lett.* **1986**, *27*, 5455−5458.

(13) During our optimization study, we found that the cyclization of 6-hydroxy-8-phenyloct-2-yn-4-one (±)-**1h** in the presence of $PdCl_2$, CuCl, Na_2HPO_4, Cu powder (10 mol %), ethyl acrylate (20 equiv), O_2, DME, 65 °C led to the formation of the desired dihydropyranone (±)-**2h** along with a side product never observed otherwise, the acyclic (2*E*)-ethyl 8-hydroxy-4-methyl-6-oxo-10-phenyldeca-2,4-dienoate (9% yield). However, this result was not reproducible (reactions attempted several times, side product observed once).

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room temperature a mixture of acetic acid/water/THF (4/2/1, 50 equiv) under Ar. The mixture was heated at 50 °C for 24 h, and then solvent was evaporated in vacuo and the residue was further purified by silica gel chromatography.

General Procedure E: Palladium-Catalyzed Domino Wacker−Heck Reaction. To a flask charged with the ligand, base, co-oxidant, additive, and catalyst was added the substrate in DME, followed by ethyl acrylate in DME. The vessel was then degassed and the atmosphere replaced by oxygen. The reaction was heated at 65 °C under oxygen atmosphere for 24 h. The mixture was filtered through a mixture of sand and Celite or silica. The filtrate was evaporated in vacuo, and the residue was further purified by silica gel chromatography.

1-Hydroxy-1-phenylhept-4-yn-3-one (1a). Compound **1a** was obtained from benzaldehyde (0.35 mL, 3.47 mmol) and 3-hexyn-2-one (0.57 mL, 5.20 mmol) according to general procedure **A**. Purification by silica gel chromatography (hexane/EtOAc, 9:1) yielded the product (545 mg, 78% yield) as a pale yellow oil: R_f (hexane/EtOAc, 1:1) = 0.46; δ_{1H} (400 MHz, $CDCl_3$) 1.22 (3H, t, J = 7.6 Hz), 2.39 (2H, q, J = 7.6 Hz), 2.94 (1H, dd, J = 17.5, 3.4 Hz), 2.97 (1H, d, J = 3.3 Hz), 3.04 (1H, dd, J = 17.5, 9.1 Hz), 5.25 (1H, ddd, J = 9.1, 3.4, 3.3 Hz), 7.27−7.40 (5H, m); δ_{13C} (400 MHz, $CDCl_3$) 12.6 (CH_3), 12.7 (CH_2), 54.0 (CH_2), 69.8 (CH), 80.2 (C), 97.1 (C), 125.7 (2 × CH), 127.8 (CH), 128.6 (2 × CH), 142.4 (C), 186.9 (C); ν_{max} (film/cm^{-1}) 3031, 2982, 2941, 2213, 1668; *m*/*z* (HRMS, FI) found 202.0989 ([M]$^+$), $C_{13}H_{14}O_2$ requires 202.0994.

1-Hydroxy-1-(4-methoxyphenyl)hex-4-yn-3-one (1d). Compound **1d** was obtained from 3-hydroxy-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methylpropanamide[15] (300 mg, 1.22 mmol) and 1-propynylmagnesium bromide (0.5 M in THF, 6 mL) in THF according to general procedure **B**. Purification by silica gel chromatography (hexane/EtOAc, 3:1) yielded the product (203 mg, 77% yield) as a pale yellow oil: R_f (hexane/EtOAc, 2:1) = 0.30; δ_{1H} (400 MHz, $CDCl_3$) 2.03 (3H, s), 2.88 (1H, dd, J = 17.2, 3.4 Hz), 2.90 (1H, d, J = 3.3 Hz), 3.02 (1H, dd, J = 17.3, 9.2 Hz), 3.80 (3H, s), 5.18 (1H, ddd, J = 8.9, 3.3, 3.2 Hz), 6.88 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.6 Hz); δ_{13C} (400 MHz, $CDCl_3$) 4.1 (CH3), 53.9 (CH2), 55.3 (CH3), 80.2 (C), 91.7 (C), 113.9 (2 × CH), 127.0 (2 × CH), 134.6 (C), 159.2 (C), 186.8 (C); ν_{max} (film/cm^{-1}) 3479, 2985, 2838, 2218, 1699, 1597, 1512; *m*/*z* (HRMS, FI) found 217.0875 ([M]$^+$), $C_{13}H_{13}O_3$ requires 217.0865.

***syn*-1-Hydroxy-2-methyl-1-phenylhex-4-yn-3-one (1g).** To a stirred solution of diisopropylethylamine (1.3 equiv) and di-*n*-butylboron triflate (1 M solution in DCM, 1.2 equiv) in anhydrous DCM (10 mL) at −78 °C was added hex-4-yn-3-one **4** (1 equiv) in dry DCM (2 mL). The reaction mixture was warmed to 0 °C and stirred for 2 h, before it was cooled to −78 °C again and benzaldehyde (2.5 equiv) was added. The reaction mixture was then maintained at −78 °C for 2 h and at −26 °C for 16 h. The resulting reaction mixture was quenched by addition of methanol (2 mL/mmol), a pH 7 (PBS) buffer solution (2 mL/mmol), and a H_2O_2 peroxide solution (30% sol, 2 mL/mmol) at 0 °C. Stirring was continued for 1 h. Then, the mixture was partitioned between H_2O (30 mL), and DCM (3 × 30 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was further purified by silica gel chromatography (hexane/diethyl ether, 1:1) and yielded the product (160 mgs, 59% yield, >99% de) as a colorless oil; R_f (hexane/diethyl ether, 1:1) = 0.45; δ_{1H} (400 MHz, $CDCl_3$) 1.15 (3H, d, J = 7.2 Hz), 2.05 (3H, s), 2.70 (1H, d, J = 3.3 Hz), 2.87 (1H, qd, J = 7.2, 3.5 Hz), 5.30 (1H, dd, J = 3.4, 3.3 Hz), 7.24−7.38 (5H, m); δ_{13C} (400 MHz, $CDCl_3$) 4.2 (CH_3), 9.5 (CH_3), 55.0 (CH), 72.6 (CH), 79.6 (C), 92.3 (C), 125.9 (2 × CH), 127.4 (CH), 128.3 (2 × CH), 141.6 (C), 191.3 (C); ν_{max} (film/cm^{-1}) 3457, 3031, 2982, 2938, 2217, 1667, 1494, 1453; *m*/*z* (HRMS, ESI) found 225.0886 ([M + Na]$^+$), $C_{13}H_{14}NaO_2$ requires 225.0886.

(*S*)-5-Hydroxy-1,7-diphenylhept-1-yn-3-one (1i). Compound **1i** was obtained from (*S*)-**4** (350 mg, 1.48 mmol) and phenylacetylene (445 μL, 4.1 mmol) according to general procedure **C**. Purification by silica gel chromatography (hexane/EtOAc, 4:1) yielded the product (380 mg, 93% yield) as a pale yellow solid: mp = 45−50 °C; R_f (hexane/EtOAc, 9:1) = 0.28; The enantiomeric excess of the product **1i** was determined to be 96% ee by HPLC analysis [column, DAICEL CHIRALCEL OD (0.46 cm Φ × 25 cm); eluent, hexane/Pr^{i}OH = 9/1; flow rate, 1.0 mL/min; retention time: 28.5 min (minor), 69.9 min (major)]: $[\alpha]^{18}_D$ +17.7 (*c* 1.0, $CHCl_3$); δ_{1H} (400 MHz, $CDCl_3$) 1.79 (1H, dddd, J = 16.6, 9.6, 7.0, 4.2 Hz), 1.90 (1H, dddd, J = 17.2, 9.1, 8.4, 5.4 Hz), 2.71−2.86 (2H, m), 2.88−2.93 (2H, m), 4.24 (1H, m), 7.15−7.66 (10H, m); δ_{13C} (400 MHz, $CDCl_3$) 31.7 (CH_2), 38.0 (CH_2), 52.0 (CH_2), 66.9 (CH), 87.8 (C), 91.9 (C), 125.9 (CH), 128.46 (2 × CH), 128.49 (2 × CH), 128.7 (2 × CH), 131.0 (CH), 133.2 (2 × CH), 141.7 (C), 187.6 (C); ν_{max} (film/cm^{-1}) 3449, 3026, 2928, 2203, 1666, 1490, 1299; *m*/*z* (HRMS, ESI) found 301.1199 ([M + Na]$^+$), $C_{19}H_{18}NaO_2$ requires 301.1199.

(*E*)-Ethyl-3-(6-ethyl-4-oxo-2-phenyl-3,4-dihydro-2*H*-pyran-5-yl)acrylate (2a). Compound **2a** was obtained from **1a** (62 mg, 0.25 mmol) according to general procedure **E**. Purification by silica gel chromatography (hexane/EtOAc, 4:1) yielded the product as a pale yellow oil: R_f (hexane/EtOAc, 4:1) = 0.30; δ_{1H} (400 MHz, $CDCl_3$) 1.25 (3H, t, J = 7.4 Hz), 1.32 (3H, t, J = 7.1 Hz), 2.65 (1H, dq, J = 14.4, 7.5 Hz), 2.69 (1H, dq, J = 14.4, 7.5 Hz), 2.74 (1H, dd, J = 16.7, 3.4 Hz), 2.95 (1H, dd, J = 16.7, 14.0 Hz), 4.23 (2H, q, J = 7.1 Hz), 5.43 (1H, dd, J = 14.2, 3.5 Hz), 6.97 (1H, d, J = 15.8 Hz), 7.34−7.45 (6H, m); δ_{13C} (100 MHz, $CDCl_3$) 11.7 (CH_3), 14.4 (CH_3), 26.2 (CH2), 43.4 (CH2), 60.2 (CH2), 80.3 (CH), 110.8 (C), 119.9 (CH), 126.0 (2 × CH), 128.9 (2 × CH), 129.0 (CH), 135.2 (CH), 137.5 (C), 168.3 (C), 180.4 (C), 190.4 (C); ν_{max} (film/cm^{-1}) 1646; *m*/*z* (HRMS, ESI) found 301.1440 ([M + H]$^+$), $C_{18}H_{21}O_4$ requires 301.1459.

6-Ethyl-2-phenyl-2*H*-pyran-4(3*H*)-one (3).[16] Isolated side product of the above reaction. Purification by silica gel chromatography (hexane/EtOAc, 4:1) yielded the product as a pale yellow oil. The NMR data of this compound are in agreement with the literature.[16]

2-Hydroxy-2-methylhex-4-yn-3-one (6a). Compound **6a** was obtained from **9a** (580 mg, 2.75 mmol) according to general procedure **D**. Purification by silica gel chromatography (hexane/EtOAc, 3:2) yielded the product (267 mg, 77%) as a colorless oil: R_f (hexane/EtOAc, 3:2) = 0.40. δ_{1H} (400 MHz, C_6D_6) 1.31 (3H, s), 1.44 (6H, s), 3.70 (1H, br s); δ_{13C} (C_6D_6) 3.2 (CH3), 26.5 (2 × CH_3), 77.1 (C), 77.4 (C), 95.2 (C), 192.1 (C); ν_{max} (film/cm^{-1}) 3476, 2980, 2219, 1672, 1361, 1255, 1175; *m*/*z* (HRMS, FI) found 127.0749 ([M + H]$^+$) $C_7H_{11}O_2$ requires 127.0759.

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Supporting Information Available: Experimental data for substrates **1b**,**c**,**e**−**h**, **2b**−**i**, **5**, **6b**, **7a**−**c**, **9a**−**c**, and **10**. ^{1}H NMR and ^{13}C spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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