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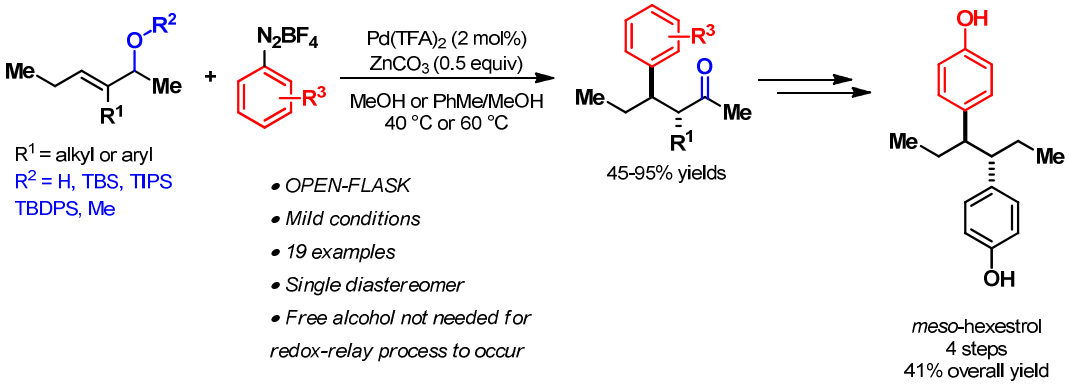
ABSTRACT GRAPHIC



ABSTRACT

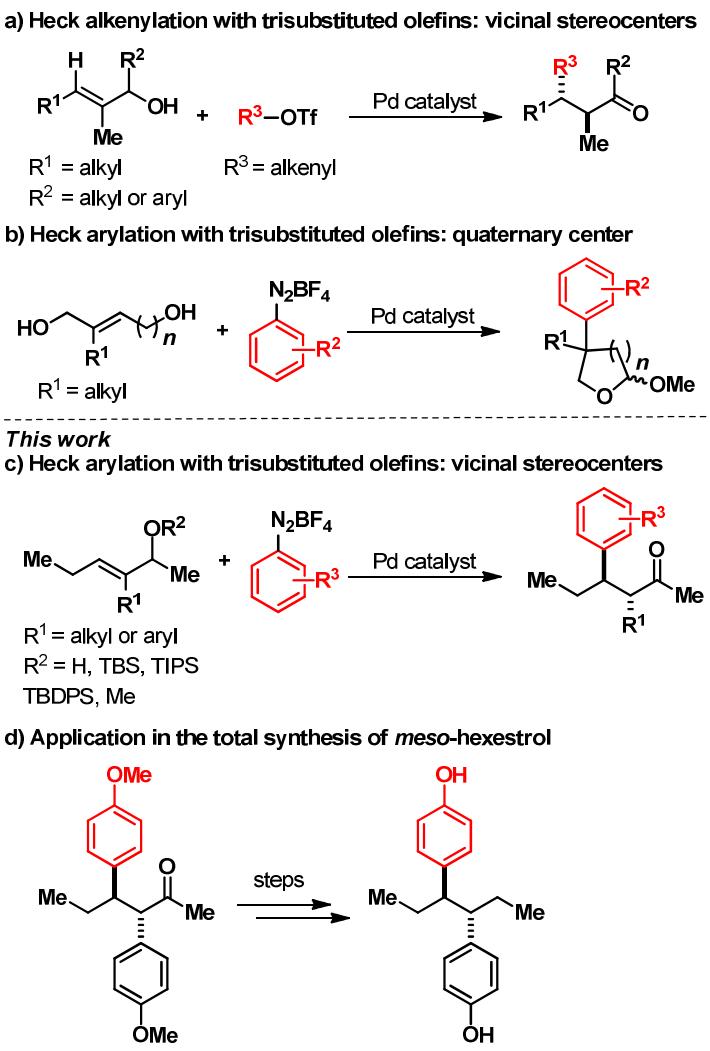
Novel palladium-catalyzed redox-relay Heck arylation reactions of trisubstituted allylic alkenols were developed employing silyl and methyl ethers. The reactions proceeded under mild conditions in moderate to high yields in excellent *anti* diastereoselectivity to form α,β-disubstituted methyl ketones containing two contiguous stereocenters. The new redox-relay arylations using silyl and methyl ethers of the starting alkenols demonstrates that the presence of a free hydroxyl group is not a *sine qua non* condition for an effective redox-relay process as previously thought. Deuterium labeled alkenols **2-*d*-10a**, **2-*d*-10b**, and **2-*d*-10c** permitted to track the palladium-hydride reinsertion steps in the conversion of the starting free alcohols, silyl, and methyl ethers into the corresponding methyl ketone **3-*d*-11a**, with 100% deuterium retention. Moreover, the synthetic potential of the method was demonstrated with a straightforward synthesis of the *meso*-hexestrol in 4 steps, in 41% overall yield from alkenol **10a**.

1. INTRODUCTION

The construction of contiguous stereogenic centers in a controlled manner is a key issue in organic synthesis. Methods involving aldol reactions,[1] Michael additions,[2] and pericyclic[3] reactions as single transformations or in tandem have been instrumental in addressing this challenge. On the other hand, the application of Heck reactions to assemble these structural frameworks are relatively rare, with the notable exception of a recently reported Heck alkenylation of alkenols reported by Sigman using vinyl triflates (Scheme 1a).[4] Therefore, construction of contiguous stereogenic centers by Heck reactions, in particular Heck arylations, constitutes a considerable task as it involves the functionalization of rather congested tertiary substituted double bonds. Application of palladium-catalyzed coupling of arenediazonium salts to olefins (Heck-Matsuda reaction) has emerged as a powerful tool in recent years due to its ability to add structural complexity under operationally simple conditions. Our research group[5] and others[6] have made significant contributions to extend the application of the Heck-Matsuda reactions to more complex olefinic systems and to the enantiocontrolled construction of stereogenic centers. In this context, we recently described the arylation of trisubstituted olefin using aryldiazonium salts as electrophiles to yield quaternary stereocenters with excellent levels of enantio- and regioselectivity[5b] (Scheme 1b). The preference for the arylation at the most substituted carbon might be explained by the electronic bias of the double bond due to the distal polarization promoted by the hydroxyl group, resulting in the delivery of the aryl group to the more electron rich sp^2 carbon. β-Elimination and palladium-hydride reinsertion yield the corresponding aldehyde, which cyclizes in the methanolic medium to furnish the corresponding methyl lactol.

Herein, we report the arylation of trisubstituted allylic alcohols and their silyl and methyl ether derivatives for the direct construction of methyl ketones decorated with two continuous stereogenic centers in a straightforward way (Scheme 1c). The Heck arylations using silyl and methyl ethers instead of free alkenols constitute the first examples extending the so-called redox-relay process in Heck reactions. The synthetic potential of these Heck reactions is demonstrated by a new strategy to the total synthesis of *meso*-hexestrol (Scheme 1d).[7] Hexestrol and its derivatives exhibited a variety of biological activities[8] and they are considered effective inhibitors of microtubule assembly.[9]

Scheme 1. Heck reaction of trisubstituted alkenols.



2. RESULTS AND DISCUSSION

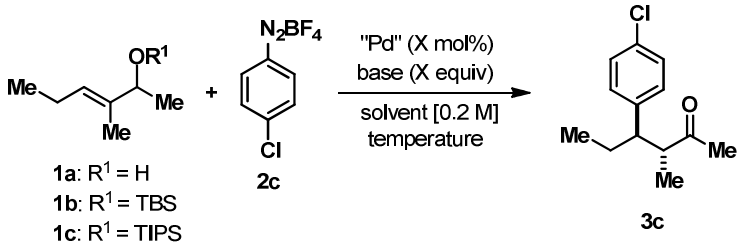
Our studies began with the Heck-Matsuda reaction between (*E*)-3-methylhex-3-en-2-ol (**1a**) and 4-chlorobenzenediazonium tetrafluoroborate (**2c**) as model coupling partners. Initially, we used our previously developed catalytic system,[10] $Pd(TFA)_2$ (10 mol%), 0.5 equiv. of $ZnCO_3$ as base, in MeOH at 40 ^{o}C, without ligands (Table 1, entry 1) which provided the methyl ketone **3c** in moderate yield (65%) as a single diastereoisomer with 1,2-*anti* relationship. The reaction was also performed at 60 °C without any significant improvement (entry 2).

To evaluate the importance of the free alcohol functionality in the formation of redox-relay product, we also carried out the Heck-Matsuda reaction with the corresponding silyl

ethers **1b** and **1c**. Previous results from our laboratory have shown the compatibility of silyl ethers with the redox-relay process.[5a] Gratifyingly, the reaction of the TBS ether **1b** and TIPS ether **1c** with the arenediazonium salt **2c** provided ketone **3c** as single stereoisomer in excellent yields of 98% after only 15 minutes (entries 3 and 4). These results prompted further investigations regarding the palladium source, the solvent and the base of the reaction (entries 5-14).

Replacement of $Pd(TFA)_2$ by other palladium sources, such as $Pd_2(dba)_3$ or $Pd(acac)_2$ (entries 5 and 6) resulted in lower reaction yields of 70% and 64%, respectively. Except by using MeOH, DMC, and EtOH (entries 3, 8 and 12), all the other solvents furnished the Heck product **3c** in lower yields. Exchange of the $ZnCO_3$ base by DTBMP and Rochelle's salt, provided the Heck product **3c** in excellent yields of 92% and 88% (entries 13 and 14), thus allowing some flexibility regarding the choice of the base. Maintaining the conditions display in entry 3, but changing the temperature to 40 ^oC led to slightly extend in the reaction (30 min), but with an almost quantitative yield for the reaction (entry 15). The Heck-Matsuda reaction maintained excellent performance at a lower catalyst loading of 5 mol% and 2 mol% (95% and 89% yields, entries 16 and 17), whereas a significant decrease in chemical yield to 73% and longer reaction times were observed with 1 mol% of catalyst (entry 18).

Table 1. Evaluation of the reaction under "ligandless" conditions



1a: R^1 = H
1b: R^1 = TBS
1c: R^1 = TIPS

2c

3c

entry	R^1	[Pd] (mol%)	solvent	base (equiv)	temp. (^oC)	t (min)	yield (%)[a]
1	H	$Pd(TFA)_2$ (10)	MeOH	$ZnCO_3$ (0.5)	40	15	65
2	H	$Pd(TFA)_2$ (10)	MeOH	$ZnCO_3$ (0.5)	60	15	58
3	**TBS**	**$Pd(TFA)_2$ (10)**	**MeOH**	$ZnCO_3$ (0.5)	**60**	**15**	**98**
4	TIPS	$Pd(TFA)_2$ (10)	MeOH	$ZnCO_3$ (0.5)	60	15	98
5	TBS	$Pd_2(dba)_3$ (10)[b]	MeOH	$ZnCO_3$ (0.5)	60	30	70
6	TBS	$Pd(acac)_2$ (10)	MeOH	$ZnCO_3$ (0.5)	60	30	64
7	TBS	$Pd(TFA)_2$ (10)	PhMe	$ZnCO_3$ (0.5)	60	*o.n.*[c]	23
8	TBS	$Pd(TFA)_2$ (10)	DMC	$ZnCO_3$ (0.5)	60	360	70

9	TBS	$Pd(TFA)_2$ (10)	THF	$ZnCO_3$ (0.5)	60	*o.n.*	5
10	TBS	$Pd(TFA)_2$ (10)	DMF	$ZnCO_3$ (0.5)	60	*o.n.*	28
11	TBS	$Pd(TFA)_2$ (10)	MeCN	$ZnCO_3$ (0.5)	60	*o.n.*	15
12	TBS	$Pd(TFA)_2$ (10)	EtOH	$ZnCO_3$ (0.5)	60	360	82
13	TBS	$Pd(TFA)_2$ (10)	MeOH	DTBMP[d] (1.0)	60	15	92
14	TBS	$Pd(TFA)_2$ (10)	MeOH	Rochelle's salt (1.0)	60	15	88
15	TBS	$Pd(TFA)_2$ (10)	MeOH	$ZnCO_3$ (0.5)	40	30	99
16	TBS	$Pd(TFA)_2$ (5)	MeOH	$ZnCO_3$ (0.5)	40	75	95
17	**TBS**	**$Pd(TFA)_2$ (2)**	**MeOH**	**$ZnCO_3$ (0.5)**	**40**	**90**	**89**
18	TBS	$Pd(TFA)_2$ (1)	MeOH	$ZnCO_3$ (0.5)	40	360	73

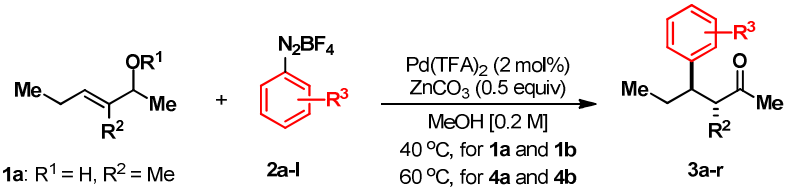
[a] Determined by ^1H NMR using internal standard. [b] dba = dibenzylideneacetone. [c] *o.n.* = overnight. [d] DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

With the optimized conditions in hand, the reaction scope was explored with several arenediazonium salts (Table 2). The reactions of olefin **1b** with electron-rich and electron-deficient arenediazonium salts furnished the corresponding arylated products **3a-r** as a single diastereomer in moderate to excellent yields (up to 95%). Lower chemical yields were observed for the benzenediazonium salt and for the ortho-substituted arenediazonium salts (compounds **3g**, **3h** and **3i**).

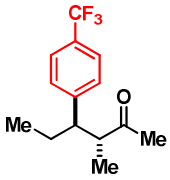
The efficiency of the newly developed method was also evaluated with respect to the substituent R^2 of the olefin by replacing the methyl group by an aryl group (Table 2). Thus, olefins **4a** (free OH group) and **4b** (TBS protected alcohol) were synthesized and submitted to the optimized Heck-Matsuda condition to provide the corresponding arylated products **3m-r** as a single diastereomer in all cases in variable yields depending on the aryldiazonium salt employed.

The relative *anti* stereochemistry of the Heck product was determined from single crystal X-ray analysis of compound **3m** and was extended to the other Heck products (see the Supporting Information for details).[11]

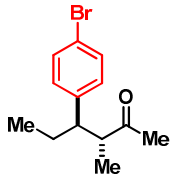
Table 2. Scope of the Heck-Matsuda arylation



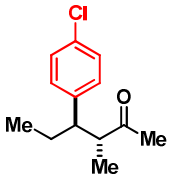
1a: R^1 = H, R^2 = Me
1b: R^1 = TBS, R^2 = Me
4a: R^1 = H, R^2 = Ph
4b: R^1 = TBS, R^2 = Ph



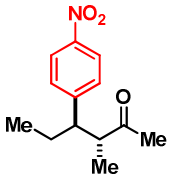
3a
from 1b: 80%



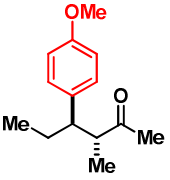
3b
from 1b: 85%



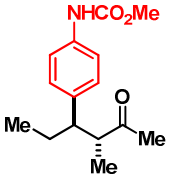
3c
from 1b: 87%



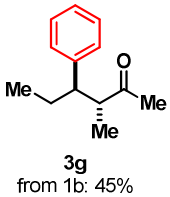
3d
from 1b: 95%
from 1b (Pd 1 mol%): 88%
from 1a: 88%



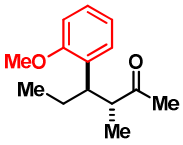
3e
from 1b: 87%
from 1a: 65%



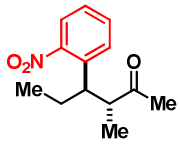
3f
from 1b: 60%



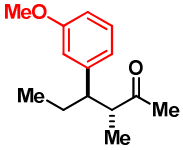
3g
from 1b: 45%



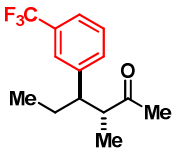
3h
from 1b: 55%



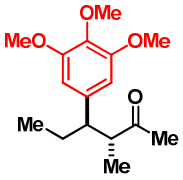
3i
from 1b: 45%



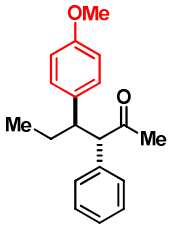
3j
from 1b: 77%



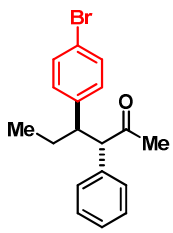
3k
from 1b: 80%



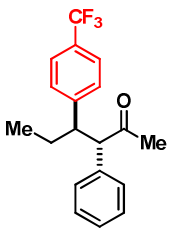
3l
from 1b: 75%
from 1a: 65%



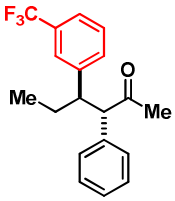
3m
from 4b: 70%
from 4a: 59%



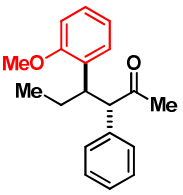
3n
from 4b: 75%



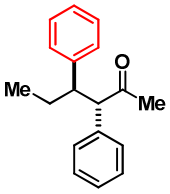
3o
from 4b: 77%



3p
from 4b: 60%



3q
from 4b: 50%



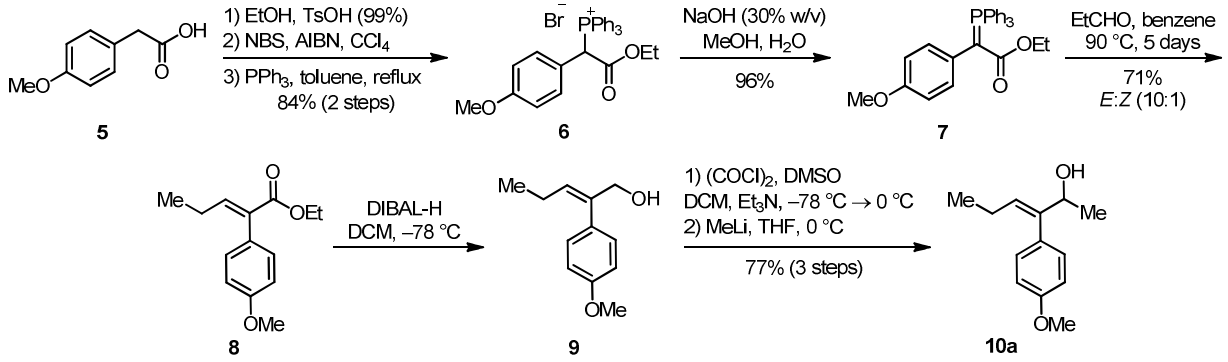
3r
from 4b: 60%

[a] Conditions: **1a-b**, **4a-b** (0.2 mmol), **2a-l** (0.4 mmol), $Pd(TFA)_2$ (2 mol%), $ZnCO_3$ (0.1 mmol), MeOH (1 mL). [b] Isolated yields.

On the synthetic point of view, the high regio- and diastereoselectivities of the method allowed its application as key step in the total synthesis of *meso*-hexestrol (**14**). We commenced the synthesis with a reliable way to prepare the critical alkenol **10a** bearing a 4-OMe-phenyl group from the commercially available carboxylic acid **5** in a multigram scale (Scheme 2). Esterification of carboxylic acid **5** with EtOH and TsOH (99% yield),[12] followed by bromination of the corresponding ester with NBS and AIBN[13], and nucleophilic substitution with PPh_3, provided the phosphonium salt **6** in 84% of yield over two steps.[14]

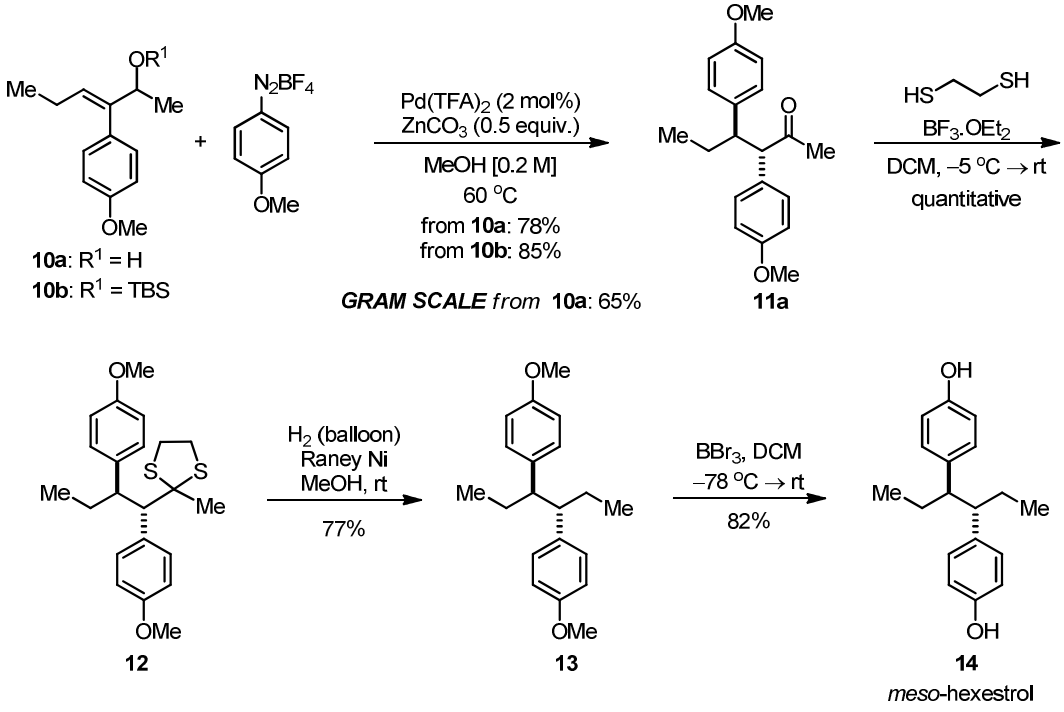
Treatment of phosphonium salt **6** with NaOH provided phosphorane **7** in 96% yield.[14] Next, the Wittig coupling between phosphorane **7** and propionaldehyde gave the unsaturated ester **8** in 71% yield (*E*:*Z* 10:1).[15] The reduction of ester **8** with DIBAL-H[16] followed by oxidation under Swern conditions,[16] and treatment with MeLi provided the olefin **10a** in 77% of yield over three steps. The configuration of double bond of product **10a** as *E* was confirmed by NOESY analysis.

Scheme 2. Preparation of *E*-olefin 10a.



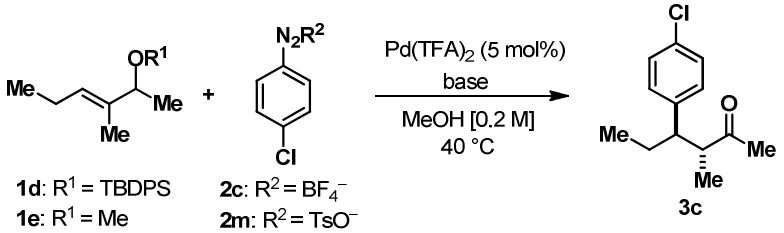
In the sequence, gram-scale Heck-Matsuda arylation of *E*-olefin **10a** with 4-methoxybenzenediazonium salt provided methyl ketone **11a** as a single diastereoisomer in 78% isolated yield (Scheme 3). Heck-Matsuda arylation of TBS ether **10b** improved the yield of **11a** to 85%, as expected from previous experiments. Treatment of methyl ketone **11a** with 1,2-ethanedithiol and $BF_3.OEt_2$ furnished dithiane **12** in quantitative yield, which underwent desulfurization with Raney Nickel[17] to afford the diarylated hexane **13** in 77% yield. Finally, demethylation of the compound **13** with BBr_3 gave *meso*-hexestrol (**14**) in 82% yield.[18] The stereoselective synthesis of *meso*-hexestrol (**14**) was accomplished in 4 steps from olefin **10a** in 41% overall yield.

Scheme 3. Diastereoselective total synthesis of *meso*-hexestrol.



The intriguing and to a certain extent unexpected[19] results obtained with the alkenol silyl ethers displayed in Table 2, in many instances affording results superior to the free allylic alcohol, prompted us to reinvestigate this transformation in more details to obtain some mechanistic insights. One obvious question was the purposely formation of a silyl enol ether intermediate, which could, in principle, furnish the methyl ketone **3c** upon workup or in the reaction medium. Alternatively, we speculated that a variant of the regular redox-relay process could be operative in this case. To investigate the former hypothesis - the existence of a silyl enol ether intermediate - we submitted the more stable TBDPS silyl ether **1d** to the same reaction conditions (Table 3, entry 1) hoping to isolate or detect the putative silyl enol ether intermediate, but only the Heck product **3c** was isolated in 72% yield.

Table 3. The redox-relay process on trisubstituted silyl and methyl alkenols



1d: R^1 = TBDPS **2c**: $R^2 = BF_4^-$ **3c**

1e: R^1 = Me **2m**: $R^2 = TsO^-$

entry	R^1	R^2	base (equiv)	t (min)	yield (%)[a]
1	TBDPS[b]	BF_4^-	$ZnCO_3$ (0.5)	120	72
2	Me	BF_4^-	$ZnCO_3$ (0.5)	60	74
3	Me	BF_4^-	proton-sponge (1.0)	60	59
4	Me	BF_4^-	$ZnCO_3$ (0.5) + DTBMP (1.0)	60	62
5	Me	TsO^-	$ZnCO_3$ (0.5)	60	66
6	TBDPS	TsO^-	$ZnCO_3$ (0.5)	90	40
7[c]	TBDPS	TsO^-	$ZnCO_3$ (0.5)	300	–[d]

[a] Isolated yields. [b] TBDPS = *tert*-butyldiphenylsilyl. [c] Toluene was used as solvent. [d] Compound **3c** not observed.

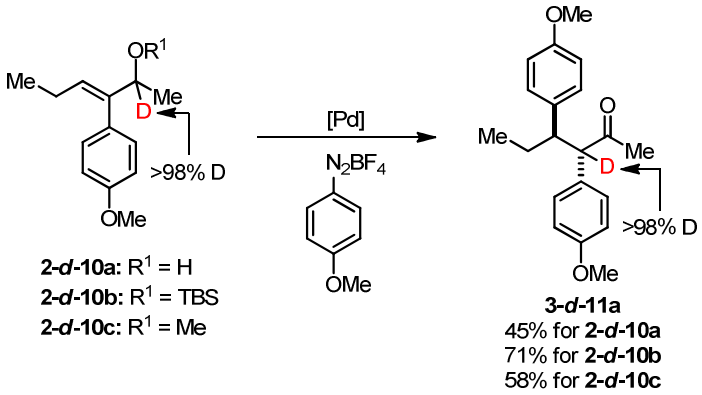
At this point we considered that either the residual acidity of the reaction medium or the presence of fluoride ions from the BF_4^- arenediazonium salt counterion could be responsible for the conversion of the silyl enol ether into the corresponding ketone. To circumvent this potential pathway, we also synthesized the methyl ether **1e**, which we expected to be more stable under the reaction conditions. Surprisingly, the Heck-Matsuda reaction of methyl ether **1e** led to ketone **3c** cleanly in a good 74% yield (Table 3, entry 2). To ensure that ketone **3c** was not being generated by methanolysis of a putative methyl enol ether under some local mild acidic conditions, either proton-sponge or an additional equivalent of DTBMP was used as base. As shown in entries 3 and 4 (Table 3), ketone **3c** was obtained in 59% and 62% yield, respectively, suggesting that H^+ formation during the Heck reaction is apparently not responsible for converting the supposed methyl enol ether into the ketone. Heck-Matsuda arylation of ether **1e** using 4-chlorobenzenediazonium tosylate also led to ketone **3c** in 66% indicating no need of a fluoride source in the redox process (Entry 5). However, a lower yield was obtained in the case of TBDPS ether and 4-chloro benzenediazonium tosylate (Entry 6). When the reaction was carried out in toluene and in the absence of a fluoride source (use of arenediazonium tosylate salt **2m**, entry 7)

formation of compound **3c** was not observed, even after 5 hours. We took this result as an additional evidence for the role of methanol and/or fluoride ion in the redox-relay step.

Taken together, these data suggest that a weakly acidic medium is not responsible to convert the enol ethers intermediates into the methyl ketones **3**. Therefore, the silyl and methyl groups are probably removed in a latter step after palladium-hydride reinsertion into the enol ether intermediate, implying that redox-relay processes might occur with functional groups other than a free alcohol.

To unequivocally validate the hypothesis that a redox-relay process can be operative with other functional groups apart from the conventional conversion of a hydroxyl group into a carbonyl group,[20] we synthesized compounds **2-*d*-10a−2-*d*-10c** bearing a deuterated carbinol center and submitted them to the standard conditions shown in Table 2. All deuterium-labeled derivatives led to the Heck-Matsuda methyl ketone **3-*d*-11a** in good yields with full incorporation of the deuterium at the internal α–carbonyl position. The location of the deuterium was clearly confirmed by ^{1}H NMR of methyl ketone **3-*d*-11a** by the absence of a doublet centered at 3.89 ppm which was indicative of the methine in non-deuterated methyl ketone **11a** used as standard. ^{1}H NMR spectrum has also permitted to measure >98% deuterium incorporation at the α-carbonyl position (Scheme 4) (see the Supporting Information for details). These results constitute unequivocal indication that redox-relay processes can indeed occur with silyl and methyl ethers.

Scheme 4. Evaluation of deuterium migration in the redox-relay step.



2-*d*-10a: R^1 = H
2-*d*-10b: R^1 = TBS
2-*d*-10c: R^1 = Me

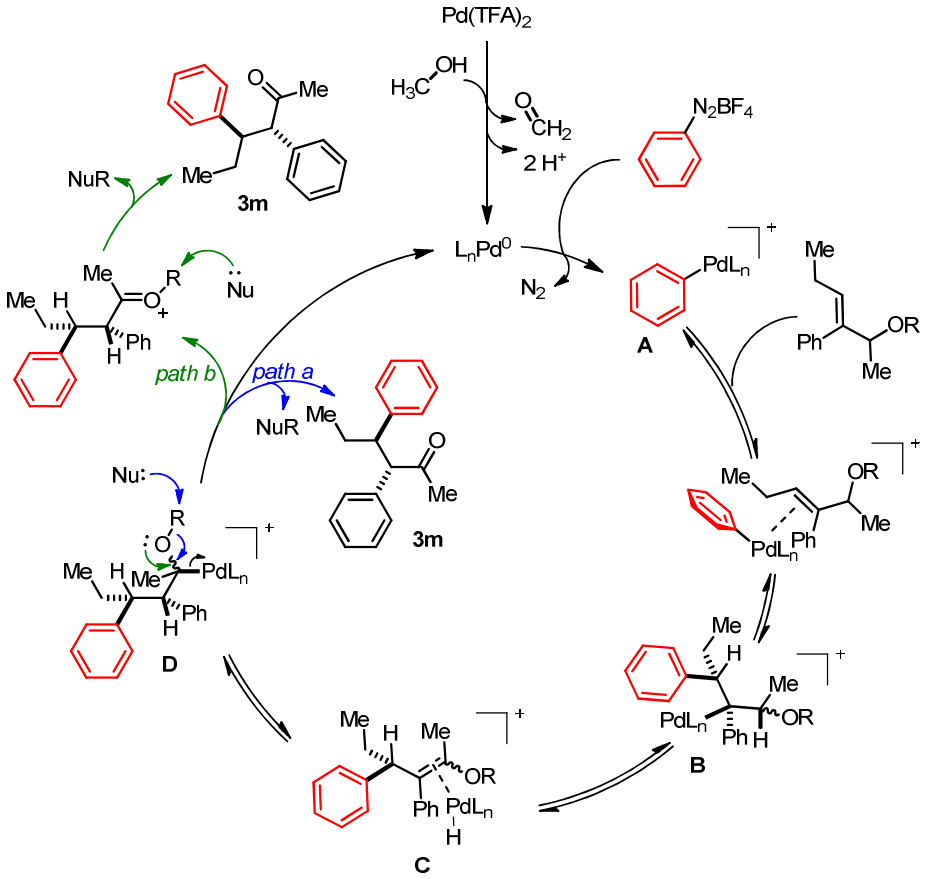
3-*d*-11a
45% for **2-*d*-10a**
71% for **2-*d*-10b**
58% for **2-*d*-10c**

A rationalization for the formation of Heck-Matsuda product is shown in Scheme 5. The catalytic cycle starts with the oxidative addition of the palladium complex to the aryldiazonium salt furnishing the cationic aryl palladium **A**. After complexation of the olefin to complex **A**, *syn*-carbopalladation occurs, generating intermediate **B**. The more acidic

carbinol hydrogen then becomes available for β-syn-elimination furnishing palladium enol ether (silyl or methyl) as intermediate **C**. Palladium hydride reinsertion provides the isomeric intermediate **D**, which in the case of silyl and methyl ethers, undergoes either a nucleophilic-assisted redox-relay process (path a), or an anchimeric-assisted palladium reductive elimination (path b) followed by solvolysis and/or fluorination of the silyl/methyl group bound to an oxonium intermediate. Both pathways would lead to the formation of the ketone product and regeneration of palladium(0).

The high *anti* diastereoselectivity observed can be explained by the nature of palladium hydride chain walking. Since the β-elimination (B to C, Scheme 5) occurs at the same face of migratory insertion step (A to B), the re-insertion step onto the enol ether intermediate (C to D) leads the β-group in an *anti* position with respect to the aryl group coming from the corresponding diazonium salt. The high *anti* diastereoselectivity strongly suggests that the re-insertion step occurs intramolecularly.

Scheme 5. Proposed mechanism. R = H, Me, TBS, TIPS, TBDPS. Nu = MeOH or [F⁻].



3. CONCLUSION

We have developed efficient palladium-catalyzed redox Heck arylation reactions of trisubstituted allylic alkenols and its corresponding silyl and methyl ethers. The reaction proceeded under mild conditions in moderate to high yields in excellent *anti* diastereoselectivity to form α,β-disubstituted methyl ketones containing two contiguous stereocenters. The successfully redox-relay processes achieved with silyl and methyl ethers as starting alkenols **1b**-**1e**, **4b** and **10b** show that the presence of a free hydroxyl group is not a *sine qua non* condition for an effective redox-relay process. Deuterium labeled alkenols **2-*d*-10a**, **2-*d*-10b**, and **2-*d*-10c** allowed to track the palladium-hydride reinsertion steps in the conversion of the starting silyl/methyl ethers into the corresponding methyl ketone **3-*d*-11a**, thus confirming that silyl and methyl ethers can indeed undergo late oxidation in Heck-Matsuda reactions. Due to its increase in structural complexity, the method was successfully applied in a straightforward synthesis of the *meso*-hexestrol (4 steps) in 41% overall yield from alkenol **10a**. Further studies regarding the redox-relay process involving other functional groups are ongoing and should be reported in due course.[21]

4. EXPERIMENTAL SECTION

General Experimental Methods. All the Heck-Matsuda reactions were carried out in 4 mL vessel under air atmosphere (open-vessel), unless stated otherwise. Reaction temperatures are reported as the temperature of the heat transfer medium surrounding the vessel. The other reactions were carried out under an atmosphere of nitrogen with dry solvents under anhydrous conditions unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. Triethylamine (Et_3N), dichloromethane (DCM), hexane, and toluene (PhMe) were distilled from CaH_2 prior to use. *N*-bromosuccinimide (NBS) was recrystallized from water. Triphenylphosphine (PPh_3) was recrystallized from hexane. Carbon tetrachloride (CCl_4) was distilled prior to use. Propionaldehyde was distilled from hydroquinone prior to use. Oxalyl chloride was distilled prior to use. Benzene anhydrous 99.8% was purchased and used as received. The other reagents were used without further purification, unless otherwise stated. The purification of reaction products was performed by flash chromatography using silica gel (220-440 mesh) and EtOAc/hexane as the eluent. Solvents used for chromatography were technical grade and were distilled before use. Analytical thin layer chromatography (TLC) was performed

employing silica gel 60 F_{254} plates. Visualization was accomplished with UV light and vanillin staining solutions followed by heating. NMR analyses were acquired at 250 MHz for ^{1}H NMR and 62.5 MHz for ^{13}C NMR, at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR, or at 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR. Chemical shifts (δ) are reported in ppm using residual non-deuterated solvent as an internal standard ($CHCl_3$ at 7.26 ppm, DMSO at 2.50 ppm, MeOH at 3.31 ppm, and TMS at 0.00 ppm for ^{1}H NMR spectra and $CDCl_3$ at 77.16 ppm, DMSO-d_6 at 39.52 ppm, and MeOH-d_4 at 49.0 ppm for ^{13}C NMR spectra). Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (*J*) in Hertz, and integrated intensity. The multiplicities of the signals are denoted by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), bs (broad singlet), dd (double doublet), dt (doublet of triplet), dq (doublet of quartet), td (triplet of doublet), dqd (doublet of quartet of doublet), and m (multiplet). 1,3-bis(trifluoromethyl)-5-bromobenzene was used as internal standard for the determination of chemical yields by ^{1}H NMR. High-resolution mass spectrometry (HRMS) were measured using electrospray ionization (ESI) (Q-TOF) or electron impact (EI) (Q-TOF). Melting points were measured in melting apparatus and the values are uncorrected. When applicable, diastereomeric ratios (*dr*) were calculated through ^{1}H NMR of the crude reaction.

4.1. Synthesis of substrates

4.1.1. Arenediazonium salts

The tetrafluoroborate arenediazonium salts **2a-2l** were prepared according to the literature procedure.[22]

4-chloroarenediazonium tosylate (2m). The title salt was obtained as previously reported.[22a] IR-ATR (cm^{-1}): 2296 (N≡N). ^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 7.7 Hz, 2H), 2.37 (s, 3H).; ^{13}C NMR (100 MHz, CD_3OD) δ 149.9, 143.6, 141.7, 135.2, 133.2, 129.8, 126.9, 115.0, 21.3.

4.1.2. Preparation of olefins 1a, 1b, 1c, 1d, 1e, 4a, 4b, 10a, 10b, 2-*d*-10a, 2-*d*-10b, 2-*d*-10c.

(*E*)-3-methylhex-3-en-2-ol (1a). To a solution of (*E*)-2-methyl-2-pentenal (3.5 mL, 30.5 mmol, 1 equiv) in THF (300 mL) at 0 °C, it was added MeLi (1.6 M in ether, 21.0 mL 33.6 mmol, 1.1 equiv), dropwise. The reaction mixture was stirred at 0 °C for 5 h and then the reaction was quenched with aqueous saturated solution of NH_4Cl (50 mL) and H_2O (50 mL). Then, the mixture was allowed to warm to room temperature, the layers were separated,

and the aqueous layer was extracted with Et_2O (2 × 150 mL). The organic layers were combined, washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (95:5) as eluent to provide the (*E*)-3-methylhex-3-en-2-ol (**1a**) (55%, 1.9 g, 17 mmol). Note: volatile product. Physical state: light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (t, *J* = 7.0 Hz, 1H), 4.19 (q, *J* = 6.4 Hz, 1H), 2.10–1.94 (m, 2H), 1.61 (s, 3H), 1.46 (s, 1H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 7.6 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 127.1, 73.5, 21.7, 20.9, 14.2, 11.4.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_7H_{14}ONa$ 137.0937; Found 137.0953.

(*E*)-*tert*-butyldimethyl((3-methylhex-3-en-2-yl)oxy)silane (1b).[23] To a solution of **1a** (0.5 g, 4.4 mmol, 1 equiv) in DCM (50 mL), were added imidazole (0.45 g, 6.6 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl chloride (0.80 g, 5.3 mmol, 1.2 equiv). The mixture was stirred overnight at room temperature. Water was then added, and the layers were separated. The aqueous layer was extracted with DCM (3 × 150 mL). The organic layers were combined, washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexanes as eluent to provide the compound **1b** (quantitative, 1.0 g, 4.4 mmol). Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (t, *J* = 7.1 Hz, 1H), 4.14 (q, *J* = 6.3 Hz, 1H), 2.11−1.87 (m, 2H), 1.56 (s, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 125.8, 74.2, 26.0, 23.4, 20.8, 18.4, 14.2, 11.3, −4.6, −4.8.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{28}OSiNa$ 251.1801; Found 251.1809.

(*E*)-triisopropyl((3-methylhex-3-en-2-yl)oxy)silane (1c). To a solution of **1a** (0.5 g, 4.4 mmol, 1 equiv) in DCM (50 mL), were added imidazole (0.45 g, 6.6 mmol, 1.5 equiv) and triisopropylsilyl chloride (1.02 g, 5.4 mmol, 1.2 equiv). The mixture was stirred overnight at room temperature. Water was then added, and the layers were separated. The aqueous layer was extracted with DCM (3 × 150 mL). The organic layers were combined, washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexanes as eluent to provide the compound **1c** (quantitative, 1.2 g, 4.4 mmol). Physical state: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.30 (t, *J* = 7.1 Hz, 1H), 4.25 (q, *J* = 6.3 Hz, 1H), 2.20–1.87 (m, 2H), 1.58 (s, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.02–1.06 (m, 21H), 0.94 (t, *J* = 7.5 Hz, 3H).;

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 125.8, 74.3, 23.8, 20.9, 18.24, 18.22, 14.2, 12.5, 11.0.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{34}OSiNa$ 293.2271; Found 293.2281.

(*E*)-*tert*-butyl((3-methylhex-3-en-2-yl)oxy)diphenylsilane (1d). A 50-mL round-bottomed flask was charged with alcohol **1a** (0.348 g, 3 mmol, 1 equiv) and imidazole (0.449 mg, 6.6 mmol, 2.2 equiv). Next, DMF (30 mL) and *tert*-butyldiphenylsilyl chloride (1.02 mL, 1.08 g, 3.93 mmol, 1.3 equiv) were added. The reaction was magnetically stirred for over 24 h, followed by addition of 200 mL of water. The mixture was then extracted with ethyl ether (3 × 50 mL) and the combined organic layers was washed with water (3 × 75 mL), dried over $NaSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes as eluent to provide the compound **1d** (91%, 0.963 g, 2.73 mmol). Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.76 (m, 4H), 7.54−7.42 (m, 6H), 5.25 (t, *J* = 7.1 Hz, 1H), 4.31 (q, *J* = 6.2 Hz, 1H), 2.14−1.96 (m, 2H), 1.72 (s, 3H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.18 (s, 9H), 0.99 (t, *J* = 7.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 136.1, 136.0, 135.0, 134.6, 129.6, 129.5, 128.9, 127.6, 127.5, 127.3, 126.6, 75.2, 27.2, 23.3, 20.8, 19.5, 14.1, 11.1.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{32}OSiNa$ 375.2114; Found 375.2108.

(*E*)-2-methoxy-3-methylhex-3-ene (1e). A 50-mL round-bottomed flask was charged with NaH (60% wt. suspension in mineral oil, 4.19 g, 124 mmol, 9 equiv) and the solid was washed with hexane (7 × 5 mL) and anhydrous Et_2O (2 × 5 mL) using a syringe until no mineral oil was detected in TLC analysis. Then, Et_2O (15 mL) was added and the suspension was cooled to 0 °C. A solution of **1a** (1.59 g, 13.9 mmol, 1 equiv) in Et_2O (10 mL) was added and the mixture was allowed to warm to room temperature. After 3 hours (hydrogen evolution was finished at that time), the mixture was cooled to 0°C and MeI (3.7 mL, 11 g, 60 mmol, 4.3 equiv) was added. The reaction was then magnetically stirred at room temperature overnight. The resulting suspension was filtered through a sintered glass filter and the inorganic residue was washed with Et_2O (5 × 5 mL). The solvent was removed by careful distillation and the residue was purified by flash chromatography on silica gel using pentane. The fractions containing the product were combined and carefully distilled to provide the product **1e** as an 80% wt. solution in pentane. (38%, 851 mg, 5.31 mmol). Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (t, *J* = 7.0 Hz, 1H), 3.59 (q, *J* = 6.4 Hz, 1H), 3.14 (s, 3H), 2.19−1.88 (m, 2H), 1.52 (s, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 0.95 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 129.6, 82.9, 55.6, 20.9, 20.1, 14.2, 10.1.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_8H_{16}ONa$ 151.1093; Found 151.1087.

(*E*)-3-phenylhex-3-en-2-ol (4a). To a solution of phenylmagnesium bromide (1.0 M in THF, 51.5 mL, 51.5 mmol, 5 equiv) at −72 °C in THF (60 mL) it was added CuI (30 mol%, 0.6 g, 3.09 mmol) followed by addition of a solution of 3-hexyn-2-ol (1.02 g, 10.3 mmol, 1 equiv) in THF (25 mL) dropwise. Then, the reaction mixture was stirred at room temperature for 1 h, followed by reflux overnight (until complete conversion by TLC). The reaction was cooled to 0 ºC, quenched with saturated aqueous solution of NH_4Cl (60 mL) and filtered through a pad of Celite. Then, the mixture was allowed to warm to room temperature and the layers were separated. The aqueous layer was next extracted with Et_2O (3 × 50 mL). The organic layers were combined and washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (90:10) as eluent to provide compound **4a** (57%, 1.0 g, 5.7 mmol). Physical state: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.36 (m, 2H), 7.32−7.29 (m, 1H), 7.19–7.17 (m, 2H), 5.73 (t, *J* = 7.3 Hz, 1H), 4.53 (q, *J* = 5.4 Hz, 1H), 1.93 (quint, *J* = 7.4 Hz, 2H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 138.6, 129.3, 129.1, 128.2, 127.0, 72.3, 22.4, 22.0, 14.5.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{12}H_{16}ONa$ 199.1093; Found 199.1080.

(*E*)-*tert*-butyldimethyl((3-phenylhex-3-en-2-yl)oxy)silane (4b). To a solution of **4a** (0.18 g, 1.0 mmol, 1 equiv) in DCM (15 mL) were added imidazole (0.136 g, 2.0 mmol, 2 equiv) and *tert*-butyldimethylsilyl chloride (0.301 g, 2.0 mmol, 2 equiv), and the mixture stirred overnight at room temperature. Water was then added, and the layers were separated. The aqueous layer was extracted with DCM (3 × 150 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (90:10) as eluent to provide the compound **4b** (quantitative, 2.9 g, 1.0 mmol). Physical state: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.4 Hz, 2H), 7.29–7.26 (m, 1H), 7.16–7.15 (m, 2H), 5.73 (t, *J* = 7.1 Hz, 1H), 4.48 (q, *J* = 6.1 Hz, 1H), 1.92 (quint, *J* = 7.5 Hz, 2H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.96 (s, 9H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.13 (s, 3H), 0.11 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 139.6, 129.4, 128.1, 128.0, 126.7, 72.8, 26.1, 23.7, 21.9, 18.5, 14.6, −4.6, −4.8.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{30}OSiNa$ 313.1958; Found 313.1943.

Ethyl-2-(4-methoxyphenyl)acetate (S1). The compound **S1** was prepared from 4-methoxyphenylacetic acid (**5**) according to the literature procedure.[12] Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H),

4.14 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.55 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 158.8, 130.4, 126.4, 114.1, 60.9, 55.4, 40.7, 14.3.

(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)triphenylphosphonium bromide (6). To a solution of ethyl-2-(4-methoxyphenyl)acetate (**S1**) (5.77 g, 29.7 mmol) in CCl_4 (66 mL) it was added AIBN (0.243 g, 1.48 mmol, 0.05 equiv) and NBS (5.82 g, 32.7 mmol, 1.1 equiv). The mixture was refluxed for 5 h. After this period, the reaction mixture was cooled to room temperature and 150 mL of hexane was added. The mixture was filtered through a pad of Celite and the cake was washed with hexane. The 2-bromo ester product was then concentrated under reduced pressure and used in the next step without further purification.

To a solution of PPh_3 (8.58 g, 32.7 mmol, 1.1 equiv) in PhMe (51 mL) it was added the bromo ester intermediate prepared above and the reaction mixture was stirred for 12 h at 70 °C (oil bath temperature). After this period, the mixture was cooled to room temperature and filtered. The cake was then washed with PhMe (20 mL) and Et_2O (2 × 15 mL). The resulting phosphonium salt **6** was dried in vacuo (84% over 2 steps, 13.4 g, 25.1 mmol). Physical state: pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 14.0 Hz, 1H), 7.92–7.88 (m, 6H), 7.77–7.74 (m, 3H), 7.64–7.60 (m, 6H), 7.30–7.28 (m, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 4.18–4.09 (m, 2H), 3.75 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 160.5 (d, *J* = 2.8 Hz), 135.1 (d, *J* = 9.8 Hz), 134.9 (d, *J* = 2.8 Hz), 133.1 (d, *J* = 5.3 Hz), 129.9 (d, *J* = 12.6 Hz), 119.0 (d, *J* = 6.0 Hz), 118.3, 117.6, 114.2 (d, *J* = 2.0 Hz), 63.2, 55.4, 48.1 (d, *J* = 52.4 Hz), 13.8.; HRMS (ESI/Q-TOF) *m/z*: $[M-Br^-]^+$ Calcd for $C_{29}H_{28}O_3P$ 455.1771; Found 455.1772.

(*E*)-ethyl 2-(4-methoxyphenyl)pent-2-enoate (*E*-8). To a solution of phosphonium salt **6** (13.4 g, 25.1 mmol) in MeOH (110 mL) it was added an aqueous solution of NaOH (30% w/v) until pH 10, followed by addition of 170 mL of water. The MeOH was then removed under reduced pressure (rotavapor water bath about 25 °C), and EtOAc (100 mL) was added to the flask. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the phosphorane **7** (96% yield, 10.9 g, 24.0 mmol), which was used immediately.

To a solution of phosphorane **7** (8.63 g, 19.0 mmol) in anhydrous benzene (80 mL) it was added propionaldehyde (4.2 mL, 57 mmol, 3.0 equiv). The reaction mixture was stirred for 5 days at 90 °C (oil bath temperature). After this period, the reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography using a

gradient of hexane/EtOAc (95:5) → hexane/EtOAc (90:10) as eluent to provide ester ***E*-8** (71% yield, 3.17 g, 13.5 mmol, *E*:*Z*= 10:1). **(*E*)-ethyl 2-(4-methoxyphenyl)pent-2-enoate (*E*-8):** Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.06 (m, 2H), 7.00 (t, *J* = 7.7 Hz, 1H), 6.94–6.85 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.11 (quint, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 158.9, 146.1, 133.1, 131.0, 127.8, 113.5, 60.9, 55.4, 23.1 14.4, 13.5.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{18}O_3Na$ 257.1148; Found 257.1151. **(*Z*)-ethyl 2-(4-methoxyphenyl)pent-2-enoate (*Z*-8):** Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.24 (m, 2H), 6.87–6.84 (m, 2H), 6.07 (t, *J* = 7.6 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.40 (quint, *J* = 7.5 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 159.2, 139.4, 133.8, 130.5, 128.3, 113.8, 60.8, 55.4, 23.6, 14.4, 14.1.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{18}O_3Na$ 257.1148; Found 257.1161.

(*E*)-3-(4-methoxyphenyl)hex-3-en-2-ol (10a). To a solution of ester ***E*-8** (1.24 g, 5.29 mmol) in DCM (30 mL) at −78 °C, it was added a solution of DIBAL-H (1.0 M in toluene, 13.2 mL, 13.2 mmol, 2.5 equiv) dropwise over 1 h via syringe pump. The mixture was stirred at −78 °C for 1 h. After this period, the reaction was warmed to 0 °C, quenched by the addition of aqueous saturated solution of Rochelle's salt (50 mL), and stirred overnight. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the alcohol **9**, which was used in the next step without further purification.

To a solution of oxalyl chloride (0.54 mL, 6.35 mmol, 1.2 equiv) in DCM (30 mL), at −78 °C, it was added DMSO (0.90 mL, 12.7 mmol, 2.4 equiv) dropwise. The mixture was stirred for 30 min, followed by the dropwise addition of a solution of alcohol **9** in DCM (15 mL). After 30 min, Et_3N (3.7 mL, 26.4 mmol, 5 equiv) was added dropwise, and the resulting slurry was warmed to 0 °C and stirred for 1 h. The mixture was diluted with Et_2O (35 mL) and saturated aqueous solution of NH_4Cl (10 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phase was washed with H_2O (3 × 50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the aldehyde, which was used in the next step without further purification.

To a solution of aldehyde prepared as described above in anhydrous THF (30 mL), under nitrogen and at 0 °C, it was added a solution of MeLi (1.6 M in Et_2O, 3.6 mL, 5.82 mmol, 1.1 equiv) dropwise. The mixture was stirred for 30 min in this temperature. Then, aqueous saturated solution of NH_4Cl (20 mL) and water (10 mL) were added. The phases were separated, and the aqueous phase was extracted with Et_2O (3×80 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/EtOAc (80:20) as eluent to provide the alcohol **10a** (77% over 3 steps, 0.836 g, 4.05 mmol). Physical state: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.04 (m, 2H), 6.94–6.84 (m, 2H), 5.67 (t, *J* = 7.3 Hz, 1H), 4.57–4.38 (m, 1H), 3.82 (s, 3H), 1.91 (quint, *J* = 7.4 Hz, 2H), 1.52 (d, *J* = 4.5 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 143.9, 130.7, 130.4, 129.2, 113.7, 72.5, 55.4, 22.4, 22.0, 14.5.; HRMS (ESI/Q-TOF) *m/z*: $[M-H_2O]^+$ Calcd for $C_{13}H_{16}O$ 188.1274; Found 188.1262.

(*E*)-tert-butyl((3-(4-methoxyphenyl)hex-3-en-2-yl)oxy)dimethylsilane (10b). To a solution of **10a** (0.206 g, 0.1 mmol, 1 equiv) in DCM (20 mL), were added imidazole (0.10 g, 0.15 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl chloride (0.18 g, 0.12 mmol, 1.2 equiv). The mixture was stirred overnight at room temperature. Water was then added, and the layers were separated. The aqueous layer was extracted with DCM (3 × 25 mL). The organic layers were combined, washed with brine (30 mL), dried over MgSO4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (90:10) as eluent to provide compound **10b** (60%, 0.192 g, 0.6 mmol). Physical state: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07–7.04 (m, 2H), 6.88–6.85 (m, 2H), 5.68 (td, *J* = 7.4, 0.8 Hz, 1H), 4.43 (q, *J* = 6.2 Hz, 1H), 3.81 (s, 3H), 1.95–1.86 (m, 2H), 1.10 (d, *J* = 6.3 Hz, 3H), 0.93 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 143.7, 131.8, 130.4, 128.1, 113.4, 72.9, 55.3, 26.1, 23.7, 21.9, 18.5, 14.6, −4.5, −4.8.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{32}O_2SiNa$ 343.2064; Found 343.2050.

2-*d*-(*E*)-3-(4-methoxyphenyl)hex-3-en-2-ol (2-*d*-10a). To a solution of oxalyl chloride (0.2 mL, 2.3 mmol, 1.2 equiv) in CH_2Cl_2 (2.5 mL) at −78 °C it was added DMSO (0.4 mL, 5.6 mmol, 2.4 equiv) dropwise. The mixture was stirred for 30 min, followed by the dropwise addition of a solution of alcohol **10a** (0.109 g, 0.53 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL). After 30 min, Et_3N (0.70 mL, 5.0 mmol, 5 equiv) was added dropwise, and the resulting slurry was left to warm up to 0 ºC (ice bath) for over 2 hours. The resulting mixture was extracted

with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the corresponding ketone **S2** (25%, 28 mg, 0.137 mmol). Next, to a 10-ml round-bottomed flask charged with a solution of ketone **S2** (28 mg, 0.137 mmol, 1 equiv) in CD_3OD (1.0 mL) at –48 ºC it was added sodium borodeuteride (12 mg, 0.28 mmol, 1.02 equiv). The reaction was stirred until complete consumption of the starting material (ca. 1.0 h) and quenched with H_2O (0.5 mL), at –48 ºC, for over 15 minutes. Then, water (5 mL) was added and the mixture was extracted with EtOAc (3 × 2 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using a gradient of hexane/EtOAc (95:5) → hexane/EtOAc (80:20) as eluent to provide compound **2-*d*-10a** (84%, 24 mg, 0.116 mmol, >98% 2-*d*). **(*E*)-3-(4-methoxyphenyl)hex-3-en-2-one (S2):** Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03−7.00 (m, 2H); 6.93−6.89 (m, 2H), 6.83 (t, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 2.28 (s, 3H), 2.10 (quint, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H).;^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 159.0, 145.7, 142.2, 130.8, 128.3, 113.8, 55.3, 27.4, 23.3, 13.5.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{16}O_2Na$ 227.1042; Found 227.1047. **2-*d*-(*E*)-3-(4-methoxyphenyl)hex-3-en-2-ol (2-*d*-10a):** Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.06 (m, 2H), 6.91−6.87 (m, 2H), 5.67 (t, *J* = 7.3 Hz, 1H), 3.82 (s, 3H), 1.91 (quint, *J* = 7.5 Hz, 2H), 1.54 (s, 1H), 1.20 (s, 3H), 0.92 (t, *J* = 7.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 143.8, 130.7, 130.4, 129.2, 113.7, 72.1 (three lines, *J* = 22 Hz), 55.3, 22.3, 22.0, 14.5.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{17}DO_2Na$ 230.1262; Found 230.1262.

2-*d*-(*E*)-*tert*-butyl((3-(4-methoxyphenyl)hex-3-en-2-yl)oxy)dimethylsilane (2-*d*-10b). To a 5-mL round-bottomed flask charged with **2-*d*-10a** (35 mg, 0.17 mmol) and imidazole (25 mg, 0.37 mmol, 2.2 equiv) at 0 °C was added DCM (2 mL). Then, *tert*-butyldimethylsilyl chloride (28 mg, 0.19 mmol, 1.1 equiv) was added and the reaction was allowed to warm up to room temperature. The starting material was monitored by TLC until its complete consumption. The resulting mixture was filtered throw a pad of silica, and the cake was washed with DCM and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexanes as eluent to provide the silyl ether **2-*d*-10b** (95%, 52 mg, 0.16 mmol, >98% 2-*d*). Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07−7.04 (m, 2H), 6.88−6.85 (m, 2H), 5.67 (t, *J* = 7.4 Hz, 1H), 3.81 (s, 3H), 1.90 (quint, *J* = 7.4 Hz, 2H), 1.09 (s, 3H), 0.93 (s, 9H),

0.91 (t, *J* = 7.4 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 143.7, 131.7, 130.4, 128.2, 113.4, 72.6 (three lines, *J* = 21.0 Hz), 55.3, 26.1, 23.6, 21.9, 18.5, 14.6, −4.5, −4.8.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{31}DO_2SiNa$ 344.2126; Found 344.2125.

2-*d*-(*E*)-1-methoxy-4-(2-methoxyhex-3-en-3-yl)benzene (2-*d*-10c). To a 5-mL round-bottomed flask charged with NaH (60% in mineral oil, 16 mg, 0.34 mmol, 1.8 equiv) at 0 °C, a solution of **2-*d*-10a** (39 mg, 0.19 mmol) in THF (2 mL) was quickly added. The suspension was stirred at this temperature for over 1 h and MeI (32 µL, 72 mg, 0.51 mmol) was then added. The reaction was allowed to warm up to room temperature. The starting material was monitored by TLC until its complete consumption. The resulting mixture was filtered throw a silica pad, and the cake was washed with THF, and the resulting solution was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexane/EtOAc (95:5) as eluent to provide the methyl ether **2-*d*-10c** (74%, 31 mg, 0.14 mmol, >98% 2-*d*). Physical state: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07−7.04 (m, 2H), 6.89−6.85 (m, 2H), 5.61 (t, *J* = 7.3 Hz, 1H), 3.81 (s, 3H), 3.37 (s, 3H), 1.96 (quint, *J* = 7.4 Hz, 2H), 1.12 (s, 3H), 0.94 (t, *J* = 7.5 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 139.7,132.0, 130.8, 130.3, 113.5, 82.1 (three lines, *J* = 21.6 Hz), 55.9, 55.3, 22.0, 20.6,14.7.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{19}DO_2Na$ 244.1418; Found 244.1419.

4.2. General procedure for the synthesis of aryl methyl ketones 3a-3r

A 4 mL vial equipped with a magnetic stir bar was charged with $Pd(TFA)_2$ (2.0 mol%, 0.004 mmol, 1.33 mg), olefin **1a-1b** or **4a-4b** (1 equiv, 0.2 mmol), $ZnCO_3$ (0.5 equiv, 0.1 mmol, 12.5 mg), the appropriate arenediazonium salt **2** (2.0 equiv, 0.4 mmol) and MeOH (0.2 M, 1.0 mL). The vial was then closed and allowed to stir at 40 °C for **1a-1b** or 60 °C for **4a-4b** until total consumption of the olefin (TLC). After completion, the solvent was removed under reduced pressure. The crude material was dissolved in EtOAc (3 mL), filtered through a short pad of silica gel and the cake was washed with EtOAc (3 × 5 mL). The crude material was concentrated under reduced pressure and purified by flash column chromatography on silica gel using hexane/EtOAc (90:10) as eluent to afford the corresponding Heck-Matsuda products **3a-3r**.

(3*R,4*R**)-3-methyl-4-(4-(trifluoromethyl)phenyl)hexan-2-one (3a)** was obtained in 80% isolated yield (0.16 mmol; 40 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 2.88–2.78 (m, 2H), 1.87 (s, 3H), 1.90–1.80 (m,

1H), 1.59–1.48 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H), 0.70 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 147.6, 128.8 (q, *J* = 32.4 Hz), 128.7, 125.4 (q, *J* = 3.5 Hz), 124.4 (q, *J* = 271.5 Hz), 52.9, 49.6, 29.5, 24.8, 14.7, 11.8.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{14}H_{17}F_3O$ 258.1231; Found 258.1236.

(3*R,4*R**)-4-(4-bromophenyl)-3-methylhexan-2-one (3b)** was obtained in 85% isolated yield (0.17 mmol, 45 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.36 (m, 2H), 7.03−7.00 (d, *J* = 8.4 Hz, 2H), 2.78 (dq, *J* = 9.1, 6.8 Hz, 1H), 2.71–2.65 (m, 1H), 1.86 (s, 3H), 1.84–1.76 (m, 1H), 1.53–1.41 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.69 (t, *J* = 7.4 Hz, 3H).;^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 142.3, 131.6, 130.1, 120.2, 53.0, 49.3, 29.6, 24,8, 14.7, 11.8.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{13}H_{17}BrO$ 268.0463; Found 268.0475.

(3*R,4*R**)-4-(4-chlorophenyl)-3-methylhexan-2-one (3c)** was obtained in 88% isolated yield (0.17 mmol, 39 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.23 (m, 2H), 7.09−7.05 (m, 2H), 2.78 (dq, *J* = 9.1, 6.8 Hz, 1H), 2.72–2.66 (m, 1H), 1.86 (s, 3H), 1.86–1.77 (m, 1H), 1.54−1.42 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.69 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 141.8, 132.2, 129.7, 128.7, 53.1, 49.3, 29.6, 24.8, 14.7, 11.8.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{13}H_{17}ClO$ 224.0968; Found 224.0952.

(3*R,4*R**)-3-methyl-4-(4-nitrophenyl)hexan-2-one (3d)** was obtained in 95% isolated yield (0.19 mmol, 44.2 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.12 (m, 2H), 7.33−7.29 (m, 2H), 2.91–2.81 (m, 2H), 1.89 (s, 3H), 1.93–1.83 (m, 1H), 1.60–1.48 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.69 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 151.6, 146.8, 129.2, 123.8, 52.8, 49.5, 29.6, 24.8, 14.8, 11.8.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{18}NO_3$ 236.1281; Found 236.1289.

(3*R,4*R**)-4-(4-methoxyphenyl)-3-methylhexan-2-one (3e)** was obtained in 87% isolated yield (0.17 mmol, 38 mg) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 2.77 (dq, *J* = 13.2, 6.7 Hz, 1H), 2.68–2.59 (m, 1H), 1.83 (s, 3H), 1.83–1.72 (m, 1H), 1.54–1.41 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.70 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 158.2, 135.1, 129.2, 113.9, 55.3, 53.4, 49.3, 29.5, 25.0, 14.7, 11.9.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{14}H_{20}O_2$ 220.1463; Found 220.1433.

methyl (4-((3*R,4*R**)-4-methyl-5-oxohexan-3-yl)phenyl)carbamate (3f)** was obtained in 60% isolated yield (0.12 mmol, 31 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.08–7.05 (m, 2H), 6.64 (s, 1H), 3.76 (s, 3H), 2.78 (dq, *J* = 9.0, 6.8 Hz, 1H), 2.69–2.63 (m, 1H), 1.84 (s, 3H), 1.84–1.75 (m, 1H), 1.54–1.42 (m, 1H), 1.13 (d, *J* =

6.8 Hz, 3H), 0.69 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 154.2, 138.2, 136.3, 128.9, 118.8, 53.2, 52.4, 49.4, 29.5, 24.9, 14.6, 11.8.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{15}H_{21}NO_3$ 263.1521; Found 263.1543.

(3*R,4*R**)-3-methyl-4-phenylhexan-2-one (3g)** was obtained in 45% isolated yield (0.09 mmol, 17 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2H), 7.20–7.16 (m, 1H), 7.15–7.13 (m, 2H), 2.82 (dq, *J* = 9.0, 6.8 Hz, 1H), 2.73–2.67 (m, 1H), 1.87–1.77 (m, 1H), 1.83 (s, 3H), 1.59–1.48 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.71 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 143.2, 128.5, 128.3, 126.5, 53.2, 50.1, 29.5, 24.8, 14.6, 11.9.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{13}H_{18}O$ 190.1358; Found 190.1329.

(3*R,4*R**)-4-(2-methoxyphenyl)-3-methylhexan-2-one (3h)** was obtained in 55% isolated yield (0.11 mmol, 24 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.15 (m, 1H), 7.09 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.91 (td, *J* = 7.5, 0.9 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 3.84 (s, 3H), 3.35–3.29 (m, 1H), 2.88 (quint, *J* = 7.0 Hz, 1H), 2.00 (s, 3H), 1.68–1.58 (m, 2H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.72 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 157.5, 131.0, 128.4, 127.3, 120.6, 110.7, 55.5, 51.5, 41.8, 28.2, 22.7, 13.0, 11.9.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{14}H_{20}O_2$ 220.1463; Found 220.1433.

(3*R,4*R**)-3-methyl-4-(2-nitrophenyl)hexan-2-one (3i)** was obtained in 45% isolated yield (0.09 mmol, 21 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.55–7.51 (m, 1H), 7.38–7.30 (m, 2H), 3.53–3.47 (m, 1H), 2.90 (quint, *J* = 7.1 Hz, 1H), 2.01 (s, 3H), 1.86–1.76 (m, 1H), 1.68–1.57 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 137.3, 133.5, 132.3, 128.9, 127.3, 124.4, 52.5, 42.2, 28.3, 24.1, 13.5, 11.5.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{18}NO_3$ 236.1281; Found 236.1287.

(3*R,4*R**)-4-(3-methoxyphenyl)-3-methylhexan-2-one (3j)** was obtained in 77% isolated yield (0.15 mmol, 32 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.9 Hz, 1H), 6.75–6.68 (m, 3H), 3.79 (s, 3H), 2.81 (dq, *J* = 9.0, 6.9 Hz, 1H), 2.67 (ddd, *J* = 11.0, 9.3, 3.6 Hz, 1H), 1.86 (s, 3H), 1.86–1.75 (m, 1H), 1.58–1.44 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.72 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 159.7, 144.9, 129.4, 120.8, 114.4, 111.5, 55.3, 53.1, 50.0, 29.5, 24.8, 14.6, 11.9.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{21}O_2$ 221.1536; Found 221.1536.

(3*R,4*R**)-3-methyl-4-(3-(trifluoromethyl)phenyl)hexan-2-one (3k)** was obtained in 80% isolated yield (0.16 mmol, 41 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–

7.32 (m, 4H), 2.88–2.78 (m, 2H), 1.87 (s, 3H), 1.80–1.80 (m, 1H), 1.58–1.48 (m, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.70 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 144.4, 132.0, 130.8 (q, *J* = 32.1 Hz), 129.0, 124.7 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 272.3 Hz), 123.5 (q, *J* = 3.8 Hz), 52.9, 49.6, 29.6, 24.7, 14.6, 11.8.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{14}H_{17}F_3O$ 258.1231; Found 258.1257.

(3*R,4*R**)-3-methyl-4-(3,4,5-trimethoxyphenyl)hexan-2-one (3l)** was obtained in 75% isolated yield (0.15 mmol, 41.7 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 2H), 3.82 (s, 6H), 3.80 (s, 3H), 2.79 (dq, *J* = 9.1, 6.9 Hz, 1H), 2.64–2.58 (m, 1H), 1.86 (s, 3H), 1.79 (dqd, *J* = 14.7, 7.4, 3.7 Hz, 1H), 1.47 (ddq, *J* = 14.4, 11.0, 7.2 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.73 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 153.2, 139.0, 136.6, 105.3, 61.0, 56.2, 53.0, 50.4, 29.6, 25.0, 14.8, 11.9.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{25}O_4$ 281.1747; Found 281.1765.

(3*S,4*R**)-4-(4-methoxyphenyl)-3-phenylhexan-2-one (3m)** was obtained in 70% isolated yield (0.14 mmol, 39 mg) as a white solid. mp: 125-128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 7.19–7.15 (m, 2H), 6.87–6.83 (m, 2H), 3.96 (d, *J* = 11.2 Hz, 1H), 3.79 (s, 3H), 3.20 (td, *J* = 11.2, 3.6 Hz, 1H), 1.82 (s, 3H), 1.41–1.20 (m, 2H), 0.57 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 158.2, 137.5, 135.1, 129.3, 129.0, 127.6, 113.9, 66.3, 55.3, 48.8, 30.8, 26.4, 11.7.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{23}O_2$ 283.1693; Found 283,1688.

(3*S,4*R**)-4-(4-bromophenyl)-3-phenylhexan-2-one (3n)** was obtained in 75% isolated yield (0.15 mmol, 47 mg) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.37–7.28 (m, 5H), 7.14 (d, *J* = 8.3 Hz, 2H), 3.94 (d, *J* = 11.2 Hz, 1H), 3.23 (td, *J* = 11.2, 3.4 Hz, 1H), 1.84 (s, 3H), 1.39–1.30 (m, 1H), 1.30–1.21 (m, 1H), 0.55 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4, 142.5, 137.0, 131.6, 130.2, 129.1, 129.0, 127.8, 120.2, 65.9, 48.9, 30.7, 26.2, 11.7.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{20}BrO$ 331.0692; Found 331.0677.

(3*S,4*R**)-3-phenyl-4-(4-(trifluoromethyl)phenyl)hexan-2-one (3o)** was obtained in 77% isolated yield (0.154 mmol, 47 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.32–7.22 (m, 7H), 3.93 (d, *J* = 11.2 Hz, 1H), 3.26 (td, *J* = 11.1, 3.7 Hz, 1H), 1.77 (s, 3H), 1.36–1.13 (m, 2H), 0.48 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 147.8, 136.8, 129.2, 129.0, 128.8, 128.8 (q, *J* = 32.1 Hz), 127.9, 125.4 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 272.0 Hz), 65.7, 49.2, 30.6, 26.3, 11.6.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{20}F_3O$ 321.1461; Found 321.1458.

(3*S,4*R**)-3-phenyl-4-(3-(trifluoromethyl)phenyl)hexan-2-one (3p)** was obtained in 60% isolated yield (0.12 mmol, 33 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.22 (m, 9H), 3.93 (d, *J* = 11.1 Hz, 1H), 3.26 (td, *J* = 11.1, 3.7 Hz, 1H), 1.77 (s, 3H), 1.37–1.16 (m, 2H), 0.48 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.2, 144.6, 136.8, 132.4, 130.8 (q, *J* = 31.8 Hz), 129.2, 129.0, 128.9, 127.9, 124.6 (q, *J* = 3.6 Hz), 124.4 (q, *J* = 272.3 Hz), 123.5 (q, *J* = 3.7 Hz), 65.7, 49.2, 30.6, 26.3, 11.6.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{20}F_3O$ 321.1461; Found 321.1437.

(3*S,4*R**)-4-(2-methoxyphenyl)-3-phenylhexan-2-one (3q)** was obtained in 50% isolated yield (0.10 mmol, 27 mg) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 7.19–7.15 (m, 2H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 4.23 (d, *J* = 11.1 Hz, 1H), 3.88 (s, 3H), 3.74 (dd, *J* = 12.9, 5.2 Hz, 1H), 1.86 (s, 3H), 1.41–1.35 (m, 2H), 0.57 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 157.9, 137.8, 131.1, 129.2, 128.8, 127.4, 120.7, 111.1, 64.3, 55.7, 29.7, 25.3, 11.5.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{23}O_2$ 283.1693; Found 283.1688.

(3*S,4*R**)-3,4-diphenylhexan-2-one (3r)** was obtained in 60% isolated yield (0.12 mmol, 28 mg) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.18 (m, 10H), 4.01 (d, *J* = 11.2 Hz, 1H), 3.25 (td, *J* = 11.1, 3.6 Hz, 1H), 1.82 (s, 3H), 1.41–1.26 (m, 2H), 0.57 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 143.2, 137.4, 129.0, 128.5, 128.4, 127.6, 126.5, 66.0, 49.6, 30.7, 26.4, 11.7.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{18}H_{20}O$ 252.1514; Found 252.1532.

4.3. Total synthesis of *meso*-hexestrol (14) from olefin 10a

(3*S,4*R**)-3,4-bis(4-methoxyphenyl)hexan-2-one (11a) – gram scale.** A 50-mL round-bottomed flask equipped with a magnetic stir bar was charged with $Pd(TFA)_2$ (2.0 mol%, 0.1 mmol, 32.2 mg), olefin **10a** (1.0 g, 4.85 mmol, 1 equiv), $ZnCO_3$ (304 mg, 2.42 mmol, 0.5 equiv), the appropriate arenediazonium salt **2e** (9.70 mmol, 2.0 equiv) and MeOH (0.2 M, 25.5 mL). The flask was then closed and allowed to stir at 60 °C until total consumption of olefin (TLC). After completion, the solvent was removed under reduced pressure. The crude material was solubilized with EtOAc (30 mL), filtered through a short pad of silica gel and the cake was washed with EtOAc (3 × 50 mL). The crude material was concentrated under reduced pressure and purified by flash column chromatography on silica gel using hexane/EtOAc (90:10) as eluent to afford the product **11a** (65%, 0.98 g, 3.14 mmol). Physical state: white solid. mp: 125-128 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.89 (d,

J = 11.2 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.15 (td, *J* = 11.2, 3.4 Hz, 1H), 1.81 (s, 3H), 1.42−1.34 (m, 1H), 1.30–1.21 (m, 1H), 0.57 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.4, 159.1, 158.1, 135.2, 130.0, 129.5, 129.3, 114.4, 113.9, 65.3, 55.4, 55.3, 48.8, 30.6, 26.4, 11.7.; HRMS (EI/Q-TOF) *m/z*: $[M]^{+\cdot}$ Calcd for $C_{20}H_{24}O_3$ 312.1725; Found 312.1752.

(3*S,4*R**)-3,4-bis(4-methoxyphenyl)hexan-2-one (11a) – 0.2 mmol scale.** A 4 mL vial equipped with a magnetic stir bar was charged with $Pd(TFA)_2$ (2.0 mol%, 0.004 mmol, 1.33 mg), olefin **10a** or **10b** (1 equiv, 0.2 mmol), $ZnCO_3$ (0.5 equiv, 0.1 mmol, 12.5 mg), the appropriate arenediazonium salt **2e** (2.0 equiv, 0.4 mmol) and MeOH (0.2 M, 1.0 mL). The vial was then closed and allowed to stir at 60 °C until total consumption of olefin (TLC). After completion, the solvent was removed under reduced pressure. The crude material was solubilized with EtOAc (3 mL), filtered through a short pad of silica gel and the cake was washed with EtOAc (3 × 5 mL). The crude material was concentrated under reduced pressure and purified by flash column chromatography on silica gel using hexane/EtOAc (90:10) as eluent to afford the product **11a** (78%, 46 mg, 0.15 mmol).

2-((1*S,2*R**)-1,2-bis(4-methoxyphenyl)butyl)-2-methyl-1,3-dithiolane (12).** To a stirred solution of ketone **11a** (0.031 g, 0.1 mmol) in DCM (0.25 mL), at −5 °C, was added 1,2-ethanedithiol (0.017 mL, 0.2 mmol, 2.5 equiv) followed by $BF_3.OEt_2$ (0.09 mL, 0.07 mmol). The reaction mixture was maintained at −5 °C for 2 h. After this time more $BF_3.OEt_2$ (0.09 mL, 0.07 mmol) was added. The mixture was allowed to warm room temperature and maintained under magnetic stirring for 12 h. After completion, the reaction mixture was filtered through a short pad of silica gel and the cake was washed with EtOAc (3 × 5 mL). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel using hexane/EtOAc (90:10) as eluent to provide the dithiane **12** (quantitative, 0.038 g, 0.1 mmol). Physical state: viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2H), 7.18–7.14 (m, 2H), 6.85 (d, *J* = 8.7 Hz, 4H), 3.82 (s, 3H), 3.81 (s, 3H), 3.42 (d, *J* = 8.8 Hz, 1H), 3.22–3.01 (m, 5H), 1.75 (s, 3H), 1.64–1.53 (m, 1H), 1.27–1.15 (m, 1H), 0.51 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 158.5, 135.7, 134.5, 130.5, 113.5, 113.2, 72.0, 62.6, 55.31, 55.28, 49.6, 40.9, 37.3, 32.2, 28.0, 12.4.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{28}O_2S_2Na$ 411.1423; Found 411.1445.

4,4'-((3*RS*,4*SR*)-hexane-3,4-diyl)bis(methoxybenzene) (13).[18] A solution of dithiane **12** (0.038 g, 0.1 mmol) in MeOH (5 mL) was stirred under hydrogen with activated Raney

nickel (570 mg, 15 equiv. in mass). The reaction mixture was stirred at room temperature for 24 h. After completion, the reaction mixture was carefully filtered through a short pad of silica gel and the cake was washed with EtOAc (3 × 5 mL). The combined filtrate was taken to dryness under vacuum and the residue was purified by flash chromatography on silica gel using hexane/EtOAc (90:10) as eluent to provide the compound **13** (77%, 0.023 g, 0.077 mmol). Physical state: white solid. mp: 140-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.5 Hz, 4H), 6.87 (d, *J* = 8.5 Hz, 4H), 3.82 (s, 6H), 2.52–2.45 (m, 2H), 1.45–1.19 (m, 4H), 0.54 (t, *J* = 7.3 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 136.8, 129.3, 113.7, 55.3, 53.7, 27.5, 12.4.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{26}O_2Na$ 321.1825; Found 321.1801.

4,4'-((3*R,4*S**)-hexane-3,4-diyl)diphenol (14).**[24] To a solution of compound **13** (0.029 g, 0.1 mmol) in DCM (20 mL) was added a solution of BBr_3 (0.9 M in DCM, 0.54 mL, 0.5 mmol), at −72 °C. The solution was allowed to warm to room temperature and stirred for 3.5 h, poured onto 20 mL of ice-water, and extracted with Et_2O (3 × 15 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using hexane/EtOAc (50:50) as the eluent to provide the *meso*-hexestrol (**14**) (82%, 0.022 g, 0.082 mmol). Physical state: white solid. mp: 184-186 °C. ^{1}H NMR (500 MHz, DMSO/$CDCl_3$) δ 8.88 (bs, 2H), 6.88 (d, *J* = 8.1 Hz, 4H), 6.66 (d, *J* = 8.0 Hz, 4H), 2.34−2.32 (m, 2H), 1.32 – 1.10 (m, 4H), 0.43 (t, *J* = 7.2 Hz, 6H).; ^{13}C NMR (126 MHz, DMSO/$CDCl_3$) δ 155.0, 134.2, 128.5, 114.7, 52.7, 26.7, 11.8.

4.4. Experimental procedure for mechanistic studies

General procedure for Heck-Matsuda arylations (Table 3 and Scheme 4). A 4-mL vial containing a stir bar was charged with the olefin **1d−e** (1 equiv, 0.2 mmol) or **2-*d*-10a−c** (1 equiv, 0.1 mmol), the arenediazonium salt (2 equiv) and base (0.5 equiv for $ZnCO_3$, 1.0 equiv for proton-sponge, and 0.5 equiv for $ZnCO_3$ + 1.0 equiv for DTBMP). A solution of $Pd(TFA)_2$ (5 mol%) in HPLC-grade methanol or toluene (0.2 M) was prepared and immediately added to the former mixture. The vial was sealed with a polypropylene screw top hole cap and heated at 40 °C in a heating block. A needle was kept pierce into the vial top to release N_2 pressure. The reaction was monitored by TLC analysis until complete consumption of the starting material (1-2 h). The crude reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate (5 mL) and filtered through a silica gel (2-3 g) pad with ethyl acetate (20 mL). The solution was concentrated under reduced

pressure and the residue was purified by flash chromatography on silica gel using hexane/EtOAc (95:5) as eluent to afford the Heck-Matsuda products **3c** and **3-*d*-11a**.

3-*d*-(3*R,4*S**)-3,4-bis(4-methoxyphenyl)hexan-2-one (3-*d*-11a)** was obtained in 45% isolated yield (0.045 mmol, >98% 3-*d*) from **2-*d*-10a**, 71% isolated yield (0.071 mmol, >98% 3-*d*) from **2-*d*-10b**, and 58% isolated yield (0.058 mmol, >98% 3-*d*) from **2-*d*-10c** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.25 (m, 2H), 7.17−7.14 (m, 2H), 6.91−6.87 (m, 2H), 6.86−6.82 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.14 (dd, *J* = 11.1 Hz, 3.2 Hz, 1H), 1.81 (s, 3H), 1.43−1.19 (m, 2H), 0.57 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 159.1, 158.1, 135.2, 129.9, 129.4, 129.3, 114.4, 113.9, 64.8 (three lines, *J* = 19.4 Hz), 55.4, 55.3, 48.7, 30.5, 26.4, 11.7.; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{23}DO_3Na$ 336.1680; Found 336.1678.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystallographic data of compound **3m** (CIF).

^{1}H and ^{13}C NMR spectra of all compounds are provided (PDF).

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) a) Noda, H.; Amemiya, F.; Weidner, K.; Kumugai, N.; Shibasaki, M. *Chem. Sci.* **2017**, *8*, 3260–3269. b) Han, B.; Huang, W.; Ren, W.; He, G.; Wang, J-.H.; Peng, C. *Adv. Synth. Catal.* **2015**, *357*, 561–568. c) Gati, W.; Yamamoto, H. *Acc. Chem. Res.* **2016**, *49*, 1757–1768.

(2) a) Ozeki, M.; Hayama, N.; Fukutome, S.; Egawa, H.; Arimitsu, K.; Kajimoto, T.; Hosoi, S.; Iwasaki, H.; Kojima, N.; Node, M.; Masayuki, M. *ChemistrySelect.* **2016**, *1*, 2565–2569. b) Gurubrahamam, R. Cheng, Y-.S.; Chen, K. *Org. Lett.* **2015**, *17*, 430−433.

(3) a) Kitamura, K.; Shimada, N.; Stewart, C.; Atesin, A. C.; Ateşin, T. A.; Tius, M. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 1–5. b) Li, J.; Lin, L.; Hu, B.; Zhou, P.; Huang, T.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2016**, *55*, 1–5.

(4) Zhang, C.; Tutkowski, B.; DeLuca, R. J.; Joyce, L. A.; Wiest, O.; Sigman, M. S. *Chem. Sci.* **2017**, *8*, 2277–2282.

(5) For recent references see: a) Carmona, R. C.; Correia, C. R. D. *Adv. Synth. Cat.* **2015**, *357*, 2639–2643. b) Oliveira, C. C.; Pfaltz, A.; Correia, C. R. D. *Angew. Chem. Int. Ed.* **2015**, *54*, 14036–14039. c) Silva, J. O.; Angnes, R.A.; Silva, V. H. M.; Servilha, B. M.; Adeel, M.; Braga, A. A. C.; Aponick, A.; Correia, C. R. D. *J. Org. Chem.* **2016**, *81*, 2010–2018. d) de Azambuja, F.; Carmona, R. C.; Chorro, T.; Heerdt, G.; Correia, C. R. D. *Chem. Eur. J.* **2016**, *22*, 11205–11209. e) Khan, I. U.; Kattela, S.; Hassan, A.; Correia, C. R. D. *Org. Biomol. Chem.* **2016**, *14*, 9476–9480. f) Kattela, S.; Heerdt, G.; Correia, C. R. D. *Adv. Synth. Cat.* **2017**, *359*, 260–267. g) Silva, A. R.; Polo, E. C.; Martins, N. C; Correia, C. R. D. *Adv. Synth. Cat.* **2018**, *360*, 346–365.

(6) For latest references see: a) Zhang, C.; Santiago, C. B.; Kou, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 7290–7293. b) Hilton, M. J.; Cheng, B.; Buckley, B. R.; Xu, L.; Wiest, O.; Sigman, M. S. *Tetrahedron* **2015**, *71,* 6513–6518. c) Eiji, Y.; Hilton, M. J.; Orlandi, M.; Saini, V.; Toste, F.D.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 15877–15880. d) Chen, Z.-M.; Hilton, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 11461–11464. e) Thornbury, R. T.; Saini, V.; Fernandes, T. d. A.; Santiago, C. B.; Talbot, E. P. A.; Sigman, M. S.; McKenna, J. M.; Toste, F. D. *Chem. Sci.* **2017**, *8*, 2890–2897. f) Avila, C. M.; Patel, J. S.; Reddi, Y.; Saito, M.; Nelson, H. M.; Shunatona, H. P.; Sigman, M. S.; Sunoj, R. B.; Toste, F. D. *Angew. Chem. Int. Ed.* **2017**, *56*, 5806–5811.

(7) For synthesis of hexestrol see: a) Campbell, N. R.; Dodds, C.; Lawson, W. *Proc. Roy. Soc.* **1940**, *128*, 253–268. b) Solmssen, U. V. *Chem. Rev.* **1945**, *37*, 481–598. c) Grundy, J.

Chem. Rev. **1957**, *57*, 281–415. d) Murakami, K.; Yorimitsui, H.; Oshima, K. *Org. Lett.* **2009**, 11, 2373–2375.

(8) For references about the pharmacological activities of hexestrol and its isomers, see: a) Martinez-Azorin, F.; Teruel, J. A.; Fernandez-Belda, F.; Gomez-Fernandez, J. C. *J. Biol. Chem.* **1992**, *267*, 11923–11929. b) Wiseman, H.; Halliwell, B. *FEBS Lett.* **1993**, *332*, 159–163. c) Ohishi, H.; Ogawa, M. *Chem. Pharm. Bull.* **1993**, *41*, 1157–1159. d) Kuiper, G. G.; Carlsson, B.; Grandien, K.; Enmark, E.; Haggblad, J.; Nilsson, S.; Gustafsson, J. A. *Endocrinology*. **1997**, *138*, 863–870. e) Syasina; I. G.; Shved; N. A. *Environ*. *Toxicol*. *Phar*. **2015**, 39, 597–605.

(9) a) Sato, Y.; Murai, T.; Oda; T.; Saito, H.; Kodama, M.; Hirata, A.; *J. Biochem.* **1987**, *101*, 1247–1252. b) Sakakibara, Y.; Hasegawa, K.; Oda, T.; Saito, H.; Kodama, M.; Hirata, A.; Matsuhashi, M.; Sato; Y. *Biochem. Pharmacol.* **1990**, *39*, 167–170. c) Oda, T.; Watanuki, M.; Sakakibara, Y.; Sato, Y.; *Biol. Pharm. Bull.* **1995**, *18*, 1435–1438.

(10) Oliveira, C. C.; Angnes, R. A.; Correia, C. R. D. *J. Org. Chem.* **2013**, *78*, 4373–4385.

(11) CCDC 1588573 contains the supplementary crystallographic data for **3m**. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

(12) Davis, O. A.; Croft, R. A.; Bull, J. A. *Chem. Commun.* **2015**, *51*, 15446–15449.

(13) Lill, A. P.; Rödl, C. B.; Steinhilber, D.; Stark, H.; Hofmann, B. *Eur. J. Med. Chem.* **2015**, *89*, 503-523.

(14) Tang, C.; Li, Z.; Wang, Y.; Xu, J.; Kong, L.; Yao, H.; Wu, X. *Tetrahedron Lett.* **2011**, *52*, 3275-3278.

(15) Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 1222–1225.

(16) Dias, L. C.; de Lucca, Jr., E. C. *Org. Lett.* **2015**, *17*, 6278–6281.

(17) Tang, Z.; Mathieu, B.; Tinant, B.; Dive, G.; Ghosez, L. *Tetrahedron* **2007**, *63*, 8449–8462.

(18) Landvatter, S. W.; Katzenellenbogen, J. A. *J. Med. Chem*. **1982**, *25*, 1300–1307.

(19) Kocen, A. L.; Brookhart, M.; Daugulis, O. *Chem. Commun*. **2017**, *53*, 10010–10013.

(20) a) Xu, L.-X; Hilton, M.J.; Zhang, X.; Norrby, P.-O.; Wu, Y.-D.; Sigman, M.; Wiest, O. *J. Am. Chem. Soc*. **2014**, *136*, 1960–1967. b) Hilton, M. J.; Xu, L.-X; Norrby, P.-O.; Wu, Y.-D.; Wiest, O.; Sigman, M. *J. Org. Chem.* **2014**, *79*, 11841–11850.

(21) The enantioselective version of these new redox Heck arylations is under investigation, with preliminary results indicating that *N*,*N*-bisoxazoline ligands can provide the

corresponding α,β-diarylated methyl ketones **3** in good yields and enantiomeric ratios up to 83:17. Further experiments are ongoing and should be reported in due course.

(22) a) Filimonov, V. D.; Trusova, M.; Postnikov, P.; Krasnokutskaya, E. A.; Lee, Y. M.; Hwang, H. Y.; Kim, H.; Chi, K.-W. *Org. Lett.* **2008**, *10*, 3961–3964. b) Kutonova, K. V.; Trusova, M. E.; Postnikov, P.; Filimonov, V. D.; Parello, J. *Synth.* **2013**, *45*, 2706–2710. c) Kolar, G. F. Z. *Naturforsch. B* **1972**, *27*, 1183–1185.

(23) Jacolot, M.; Jean, M.; Levoin, N; Wegh, P. V. *Org. Lett.* **2012**, *14*, 58–61.

(24) Sigma-Aldrich homepage.
https://www.sigmaaldrich.com/spectra/fnmr/FNMR003232.PDF (accessed Jan 17, 2018).