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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.6b06438 • Publication Date (Web): 12 Sep 2016

Pd-Catalyzed Site-Selective Mono Allylic Substitution and Bis-Arylation by Directed Allylic C-H Activation: Synthesis of *anti*-γ-(Aryl,Styryl)-β-Hydroxy Acids and Highly Substituted Tetrahydrofurans

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Key words: Catalysis, palladium, boronic acids, π-allylpalladium, arylation, tetrahydrofurans, lactones

ABSTRACT: An efficient palladium-catalyzed site-selective arylation of γ-vinyl-γ-lactone by aryl boronic acid has been developed. The γ-vinyl-γ-lactone **1a** has been contemplated as allyl electrophile donor for allylic arylation *via* π-allyl palladium intermediate using 1.5 equiv. of aryl boronic acid **2**. Use of 3.0 equiv. of the latter resulted in monoarylation by allylic substitution and subsequent site-selective second arylation by directed allylic C-H activation giving stereoselectively *anti*-γ-(aryl,styryl)-β-hydroxy acids. Presence of O_2 was crucial for the second arylation *via* Pd(II) catalysis. Thus a good synergy of dual catalysis by Pd(0) and Pd(II) was observed. This methodology has been elaborated to synthesize highly substituted tetrahydrofurans including aryl-Hagen's gland lactone analogues *via* intramolecular iodoetherification.

INTRODUCTION

Transition metal catalyzed cross-coupling reaction between allylic electrophiles with various nucleophiles constitutes a powerful tool for C-C bond formation.[1] This method has been elaborated for various transformations and synthesis of complex natural products *via* π-allyl palladium complexes.[1,2] After the first report in 1979 by Trost and Klun[3] on allylic alkylation, π-allyl palladium complexes have been reacted with a wide spectrum of nucleophiles to afford highly diversified and synthetically useful olefinic compounds.[4] In the past decades, electrophilic π-allyl palladium species are derived from allyl halides, esters, carbonates, phosphonates, etc., through leaving group ionization.[5] The recent pioneering work by Trost *et al.* has enabled the synthesis of π-allyl palladium species through allylic C-H activation.[6] Subsequently they reported an elegant unprecedented tandem Pd(0) and Pd(II) catalysis for allylic alkylation[7] wherein Pd(0) was oxidized *in-situ* to Pd(II) (Figure 1, a). While the electrophile donors are centered mostly on activated aliphatic allyl substrates, the cyclic systems are less explored.[8] The γ-vinyl-γ-lactones can be contemplated as electrophile donors similar to allylic acetates. Hence leaving group ionization mediated by Pd(0) is possible to generate π-allyl palladium species to be trapped by soft nucleophiles. For such cyclic systems, attempts are made through Cu-catalyzed S_N2' type substitutions.[9] With strategic similarity of cyclic γ-vinyl-γ-lactone **1a**[10] to allyl acetates, we visualized arylation of the former under Pd-catalysis as this process would be *traceless and atom economical* unlike the case of allyl acetates (Figure 1, b). While monoarylation was anticipated to occur through Pd(0) *via* π-allyl palladium intermediate **A** formed by leaving group ionization, a slight excess of nucleophile triggered a site-selective second arylation by directed allylic C-H activation that was unprecedented in literature. It is remarkable that the allyl alcohol system does not participate in leaving group ionization.[11] The reaction would occur through allylic C-H activation (**B**) and would preferentially require Pd(II) catalysis. White *et al.*[12] have explored extensively allylic activation based substitution, however our strategy is different and has some resemblance to Trost's work[7] based on dual catalysis. Similarly, the presence of oxygen has been crucial in this work as an oxidant for Pd(0) to Pd(II) conversion (Figure 1). Thus, this is dual catalysis by Pd(0) and the *in-situ* generated Pd(II) catalyst. The monoarylated system **3** is present in lobatamide A[13] and constitutes an important building block for further modifications. A simple iodocyclization, elimination and iodoetherification of monoarylated compound would lead to aryl-Hagen's gland lactone[14] analogues. The bis-arylated compound **4** can be iodoetherified *via* the β-hydroxy group to deliver highly substituted tetrahydrofurans with 2,4-bisaryl units. This motif is present in calyxolanes A, B[15] and magnosalicin[16] (Figure 1).

RESULTS AND DISCUSSION

The optimization study commenced with the reaction of **1a** (0.5 mmol) with phenylboronic acid **2a** (0.75 mmol) and $Pd_2(dba)_3$ catalyst (5 mol%) with TMEDA (10 mol%) as ligand in dioxane at room temperature. However even after 72 h we did not get the desired product **5a** (the esterification to methyl ester was considered for easy isolation). The reaction resulted in the isomerized lactone **1b** (**1a**:**1b** = 1:1, 68%, Table 1, entry 1). The same reaction at 110 °C provided a mixture of isomerized compound **1b** (**1a**:**1b** = 2:1, 48%) and **3a**. The latter being isolated as methyl ester **5a** in 37% yield (entry 2). The addition occurred at the less hindered terminus of the π-allylpalladium intermediate. A switch in solvent to *t*AmOH improved the yield to 58% with no side reactions (entry 3).

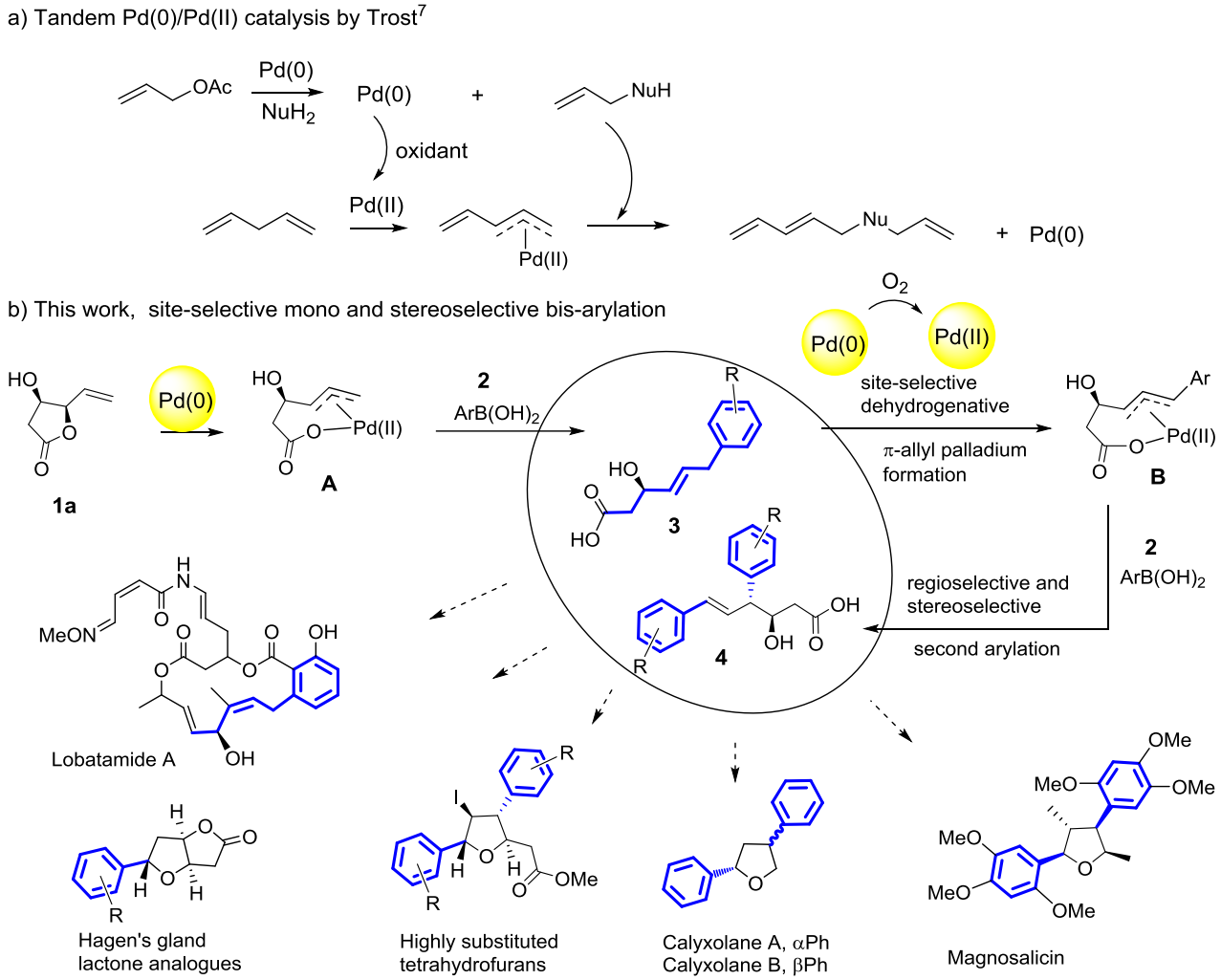
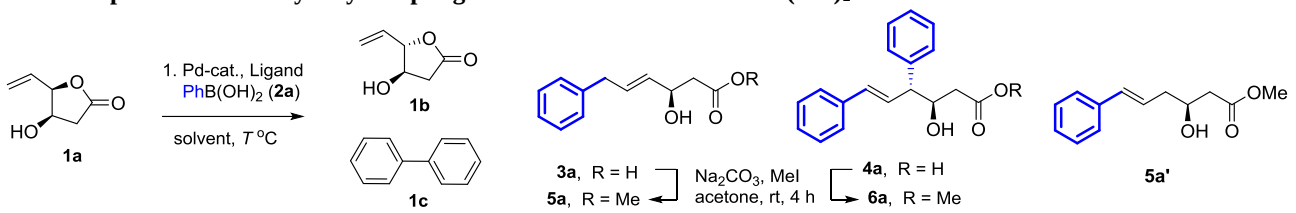


Figure 1. Tandem catalysis by Pd(0) and Pd(II). Allylic arylation of γ-vinyl-γ-lactone **1a** and further modifications.

Other solvents like DMA and toluene were not successful to increase the yields of **5a**.[17] Addition of phosphine ligand (or that present in catalyst) did not favor arylation but promoted isomerization of **1a** and undesired self-coupling of boronic acid to **1c** (entries 4-7). A variation in Pd-catalyst (entries 8-10) showed $Pd(OAc)_2$ to be better giving **5a** in 68% yield (entry 10). Change of solvent to dioxane, toluene or THF did not prove better.[17] Fortunately a switch to combination of solvents (dioxane and *t*AmOH, 1:1) improved the yield of **5a** to acceptable level of 80% (entry 11). With this solvent combination we back-checked the ligands: bipyridine, PPh_3 and BINAP (entries 12-14). While bipyridine worked well, others gave isomerized product **1b** and biaryl **1c**. Keeping other conditions same, we changed $Pd(OAc)_2$ to $Pd_2(dba)_3$, which resulted in **5a** in 73% yield (entry 15). The variation in Pd-catalyst loading suggested that 5 mol% was the optimum requirement.[17] The reaction without the ligand TMEDA resulted in only isomerized product **1b** (**1a**:**1b** = 1:1.5, 61%, entry 16). A decrease in TMEDA concentration to 5 mol% lowered the yield of **5a**.[17] In all cases above, **5a** was obtained as *E*/*Z* mixture with *E*-isomer as the major product (ratio of >6:1). An increase in arylboronic acid concentration to 2.0 equiv. resulted in the formation of mixture of mono- and bis-arylated products, **5a** and **6a** (after esterification) in 38% and 25% isolated yields respectively (entry 17) with the recovery of unreacted **1a** in 9% yield. We believe the amount of boronic acid was not sufficient to drive the reaction to higher yields of **5a** or **6a**. It is also possible that the mono and bis-arylation occurs simultaneously. The site-selective second arylation is remarkable and unprecedented in literature. After monoarylation this can arise via directed π-allyl palladium formation through C-H activation probably facilitated by internal carboxylate anion, followed by second arylation. It is remarkable to note that the allyl alcohol system did not participate in leaving group ionization. We anticipated that a further increase in concentration of aryl boronic acid would give predominantly the bis-arylated product. To our delight, 3.0 equiv. of **2a** indeed delivered **6a** (36%) and **5a** was obtained in 15% yield (entry 18). We realized that the second arylation involving dehydrogenative *π*-allyl palladium formation requires Pd(II) catalyst, which could be generated from Pd(0) by traces of oxygen present. Hence we speculated that addition of external oxidant would benefit the reaction. When the reaction was carried out under O_2 (balloon), indeed the bis-arylated compound **6a** was obtained in 62% yield (entry 19). Use of benzoquinone[7] or silver acetate as oxidants (3.0 equiv.)[17] gave comparable results to those with O_2 as oxidant (entry 19). However considering cost and greener use of O_2 we further optimized the conditions using

Table 1.Optimization of allyl-aryl coupling reaction between 1a and $PhB(OH)_2$ 2a.[a]

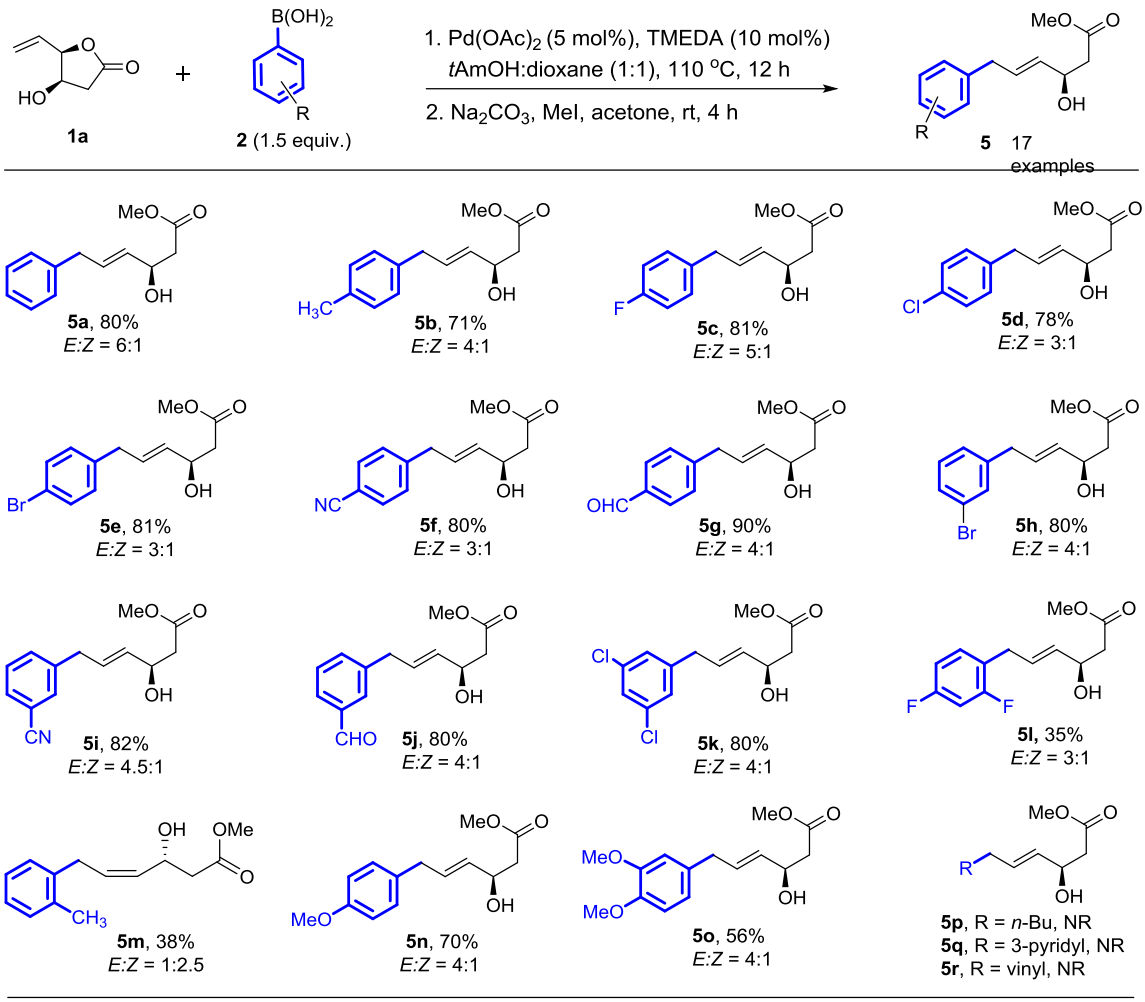


entry	catalyst (mol %)	ligand (mol %)	solvent	*T* (°C)	time(h)	yield of **1a**:**1b** (%)	**1c** (%)	yield of **5a** (%)	yield of **6a** (%)
1	$Pd_2(dba)_3$ (5)	TMEDA (10)	Dioxane	rt	72	1:1 (68)	-	-	-
2	$Pd_2(dba)_3$ (5)	TMEDA (10)	Dioxane	110	48	2:1 (48)	-	37	-
3	$Pd_2(dba)_3$ (5)	TMEDA (10)	*t*AmOH	110	12	-	-	58	-
4	$Pd_2(dba)_3$ (5)	PPh_3 (10)	*t*AmOH	110	12	2:1 (72)	32	-	-
5	$Pd(PPh_3)_4$(5)	TMEDA (10)	*t*AmOH	110	72	1:1.5 (69)	40	-	-
6	$Pd(PPh_3)_4$ (5)	PPh_3 (10)	*t*AmOH	110	72	1:2 (66)	38	-	-
7	$PdCl_2(dppf)_2$(5)	PPh_3 (10)	*t*AmOH	110	72	1:1.5 (58)	38	-	-
8	Pd-C (5)	TMEDA (10)	*t*AmOH	110	72	1:1 (62)	-	-	-
9	$Pd(CO_2CF_3)_2$ (5)	TMEDA (10)	*t*AmOH	110	12	1:2.5 (68)	-	33	-
10	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*AmOH	110	12	-	-	68	-
11	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*AmOH:Dioxane	110	12		-	80	-
12	$Pd(OAc)_2$(5)	Bpy (10)	*t*AmOH:Dioxane	110	24	-	-	68	-
13	$Pd(OAc)_2$ (5)	PPh_3 (10)	*t*AmOH:Dioxane	110	24	1:2.5 (78)	41	-	-
14	$Pd(OAc)_2$ (5)	BINAP (10)	*t*AmOH:Dioxane	110	24	1:1 (63)	29	-	-
15	$Pd_2(dba)_3$ (5)	TMEDA (10)	*t*AmOH:Dioxane	110	12	-	-	73	-
16	$Pd(OAc)_2$ (5)	-	*t*AmOH:Dioxane	110	12	1:1.5 (61)	-	-	-
17[b]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*AmOH:Dioxane	110	24	**1a** (9)	-	38	25
18[c]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*AmOH:Dioxane	110	24	-	-	15	36
19[c,d]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*AmOH:Dioxane	110	24	-	-	-	62
20[c,d]	$Pd(OAc)_2$ (10)	TMEDA (20)	*t*AmOH:Dioxane	110	24	-	-	-	72
21[c,d]	$Pd(OAc)_2$ (20)	TMEDA (20)	*t*AmOH:Dioxane	110	24	-	-	-	73
22[a,d]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*AmOH:Dioxane	110	24	**1a** (16)	-	-	35
23[c,e]	$Pd(OAc)_2$ (10)	TMEDA (20)	*t*AmOH:Dioxane	110	24	-	6	63	-
24[a,d,f]	$Pd(OAc)_2$ (5)	TMEDA (10)	*t*AmOH:Dioxane	110	24	-	-	10	36[g]

[a]reaction condition: **1a** (0.5 mmol), $PhB(OH)_2$ (0.75 mmol), Pd-source (5-20 mol%), ligand (10-20 mol%), dioxane:*t*AmOH (1:1, 2 mL), rt-110 °C.[b]2.0 equiv. of **2a** used. [c]3.0 equiv. of **2a** used. [d]O_2 used. [e] No oxidant (in glove box). [f]Reaction on separated crude **3a**. [g]**5a'** (12%).

$Pd(OAc)_2$ (10 and 20 mol%) and TMEDA (20 mol%) with O_2 as oxidant to give **6a** in 72% and 73% yields respectively (entries 20 and 21). Lowering of boronic acid **2a** to 1.5 equiv. and under O_2 atmosphere delivered **6a** in only 35% yield (entry 22) with the recovery of **1a** (16%) indicating the need of excess **2a**. A reaction carried out in absence of O_2 or any other oxidants in a glove box with 3.0 equiv. of boronic acid **2a** resulted in only monoarylation giving **5a** in 63% yield (entry 23) along with 6% of biphenyl **1c** isolated. This indicated the need of external oxidant for Pd(0) to Pd(II) conversion for the success of the second arylation. We also attempted the second arylation on the crude **3a** (obtained after monoarylation) with **2a** (1.5 equiv.), $Pd(OAc)_2$ (5 mol%) and TMEDA (10 mol%) under O_2 atmosphere (entry 24). This reaction delivered indeed **6a** in 36% overall yield from **1a** along with 12% of double bond isomerized product **5a'** isolated as methyl ester and recovered **5a** in 10% yield. The compound **5a'** was earlier detected in few cases but was in traces. Thus a one-pot reaction with excess boronic acid **2a** gave better results than the step-wise reaction. Possibly the presence of free carboxylate in the one-pot reaction might facilitate the second arylation. The reaction on **5a** (with OMe group) for second arylation delivered mostly the double bond isomerized compound **5a'** (32%) with some recovery of **5a** (24%) substantiating the earlier statement. When the OH group in **1a** was protected as TBS group (compound **1a'**), the attempted mono-arylation was not observed, but the lactone **1a'** was isomerized to **1b'** (**1a'**:**1b'** = 2:1). This indicated that the presence of free OH was desirable for the success of this reaction.

Scheme 1. Allyl-aryl cross coupling of various boronic acids 2 (1.5 equiv.) with 1a. (NR = No reaction)

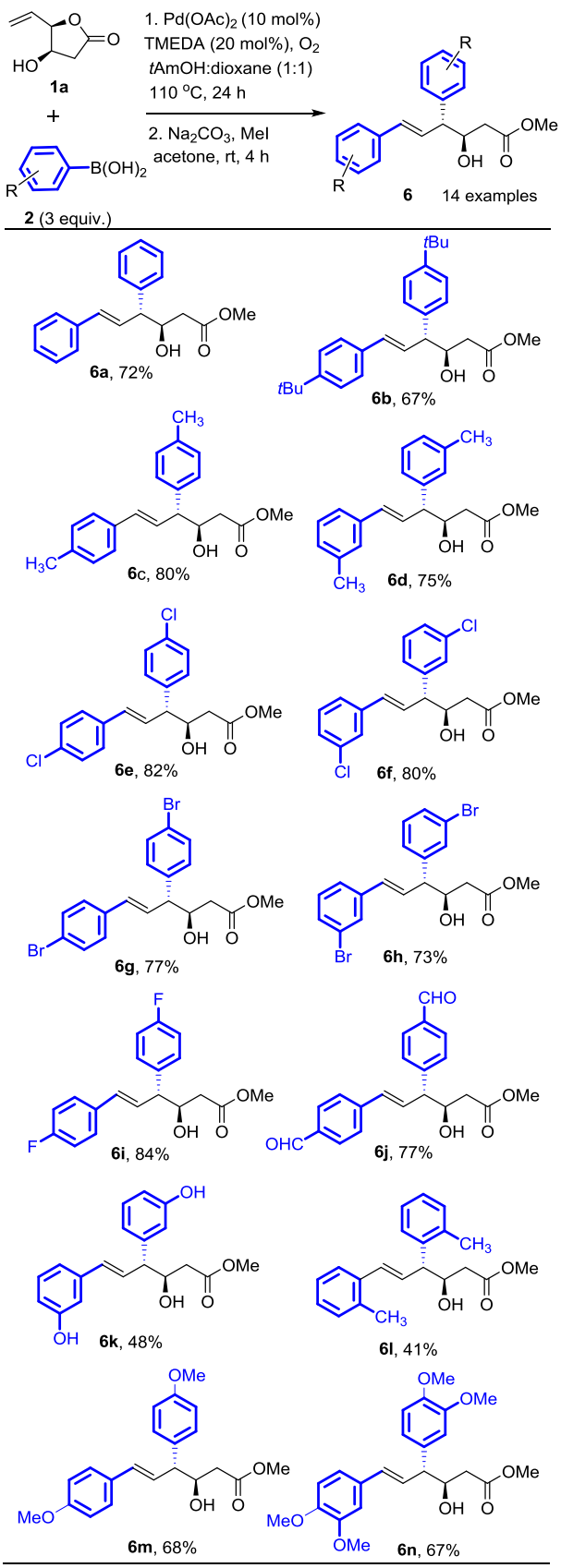


With the optimized conditions, the scope and limitations of the allyl-aryl coupling reaction with various substituted arylboronic acids **2** was investigated. As shown in Scheme 1, the coupling of **1a** with various substituted arylboronic acids **2** (1.5 equiv.) of varying electronic or steric nature proceeded to give the corresponding allyl-aryl coupled products **5a-o** in moderate to high isolated yields (isolated as esters) with complete regioselectivity for linear systems and good *E*/*Z* ratio of up to 6:1. Halogenated aryl boronic acids were well tolerated giving the products **5c**, **d**, **e**, **h**, **k** and **l** in good yields. The latter with bis-fluoride was an exception to be obtained in lower yield (35%). Similarly the formyl and cyano substituted boronic acids gave best results delivering **5f**, **g**, **i** and **j** in high yields. The ortho-methyl substituted arylboronic acid produced exceptionally the *Z*-isomer **5m** as major product (*E*/*Z* = 1:2.5). The *Z*-selectivity may be anticipated due to the prolonged reaction time which accounts for isomerization of π-allyl palladium intermediate while incorporating sterically crowded boronic acids. *n*Butylboronic acids **2p**, heteroarylboronic acid **2q** and vinylboronic acid **2r** failed under the present protocol to give the corresponding products **5p**, **5q** and **5r** respectively.

The bis-arylation of **1a** with 3.0 equiv. of various aryl boronic acids **2** was also investigated for scope and limitations. Based on optimized conditions we employed $Pd(OAc)_2$ (10 mol%) and TMEDA (20 mol%) under O_2 atmosphere (balloon). As shown in Scheme 2, diversely substituted bis-arylated products **6a-n** (after esterification) were obtained in good to high yields with complete regioselectivity towards styryl olefinic bond and with exclusive *E*-selectivity. No trace of 1,1-bis-aryl compound was obtained in any of the cases. The halogenated aryl boronic acids were well tolerated in the Pd-catalyzed bis-coupling reaction to produce **6e-i** in good yields. The formyl and free phenolic boronic acids delivered the products **6j** and **6k** respectively in good to moderate yields. The ortho-methyl substituted product **6l** was obtained in moderate yield with exclusive (*E*)-olefinic bond unlike the (*Z*) obtained in mono arylation (**5m**, Scheme 1). This could be attributed to the difference in substrates for mono and bis-arylation with different steric environment. The allylic-OH group appeared to be a spectator group and did not participate in leaving group ionization.[11]

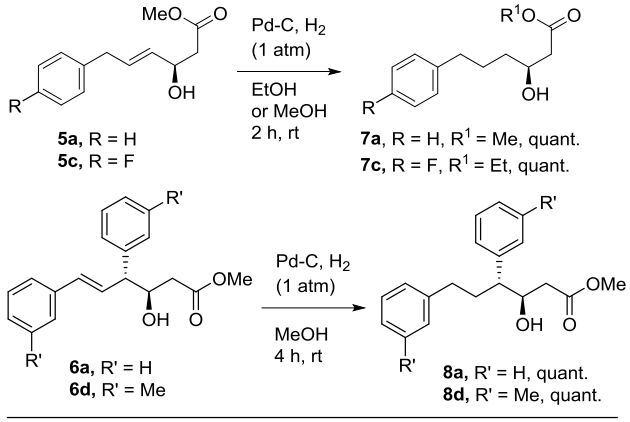
We further considered synthetic modifications of mono and bis-arylated compounds of Schemes 1 and 2. The β-hydroxy acid/ester is an important intermediate for β-lactams and pheromones synthesis and this motif is present in many natural products.[18] A catalytic hydrogenation of **5a**, **5c**, **6a**, and **6d** gave the β-hydroxy esters **7a**, **7c**, **8a** and **8d** respectively in quantitative yields (Scheme 3). For **5c**, since the reaction was carried out in EtOH, the *trans*-esterified product **7c** was obtained.

Scheme 2. Bis-arylation of 1a with various arylboronic acids 2 (3.0 equiv.) under Pd(II) and Pd(0) dual catalysis



While the monoarylated compounds **5** were obtained as *E*/*Z* mixtures, the hydrogenation of double bond gave single enantiomer. The HPLC performed on **7a** and **7c** for example indicated enantiopure compounds (100% ee, see supporting information). Similarly, the hydrogenation of **6a** and **6d** gave **8a** and **8d** as single diastereomers. No *syn*-isomer was detected within the limits of ^{1}H and ^{13}C NMR.

Scheme 3. Synthesis of saturated *ω*-aryl-*β*-hydroxy- and *γ,ω*-bisaryl-*β*-hydroxyesters

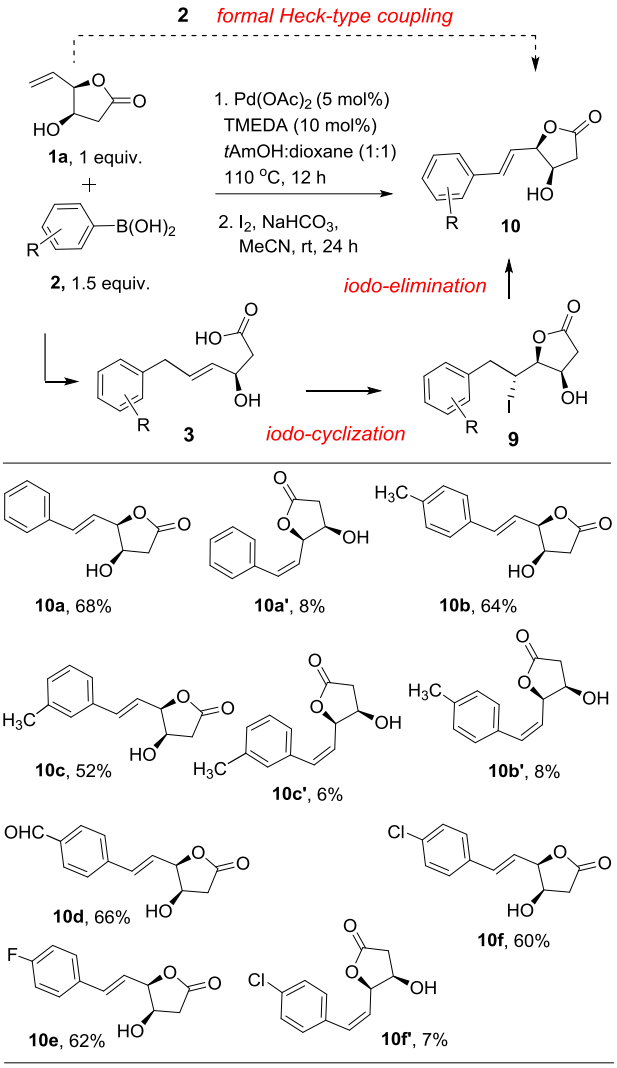


The intermediate γ,δ-unsaturated acids **3** were visualized further for a possible iodolactonization. Thus, the crude acids **3** obtained upon monoarylation were treated with iodine and $NaHCO_3$ in CH_3CN solvent to deliver the intermediate iodo-γ-lactones **9**, that underwent efficient iodo-elimination *in-situ* furnishing γ-styryl-γ-lactones **10** in good yields (Scheme 4). The ring closure was highly *syn*-selective. This constitutes a formal Heck-type coupling of **1a** with arylboronic acids **2**. In few cases the minor *Z*-olefin isomers **10a′**, **10b′**, **10c′** and **10f'** were isolated in 6-8% yields (Scheme 4). A direct coupling of lactone **1a** with iodobenzene was attempted earlier in our laboratory for Heck reaction.[10d] However, this resulted in only isomerization of **1a** to **1b**.

The γ-styryl-γ-lactones **10** were further available for iodocyclization *via* the β-hydroxy group and the styryl olefin. We had earlier employed a similar strategy in the protecting-group-free synthesis of Hagen's gland lactones.[10a,c] The diastereoselectivity in ring closure was quite high towards C-2/C-5 *anti*-tetrahydrofuran isomer. Thus, the compounds **10** were considered for synthesis of aryl analogues of Hagen's gland lactones.[14] As shown in Scheme 5, the γ-styryl-γ-lactones **10a**, **b**, **e** and **f** upon iodo-etherification delivered the compounds **11a**, **b**, **e** and **f** respectively in good yields and high diastereoselectivity toward the 2,5-*anti*-tetrahydrofuran ring. The *syn*-isomer if formed, could be in traces as is not detected in the ^{1}H NMR. These upon de-iodination provided the aryl-Hagen's gland lactone analogues[14] **12a**, **b**, **e** and **f** in high yields (Scheme 5). Since the iodo-lactonization, iodo-elimination (from **3** to **10**) and subsequent iodo-etherification (from **10** to **11**) requires $I_2/NaHCO_3$, we planned these two reactions in one-pot with excess of these reagents. Thus, after monoarylation of **1a**, the crude acids **3a** or **f** were taken up in CH_3CN and treated with I_2 (2.0 equiv.) and $NaHCO_3$ (3.0 equiv.) for 24 h followed by addition of another 2.0 and 3.0 equiv. respectively of both the reagents in the same flask and stirring for further

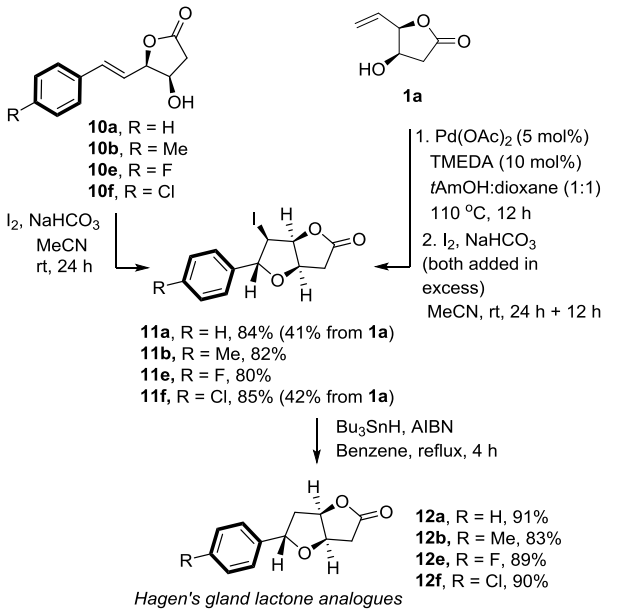
12 h. From this we could isolate compounds **11a** (41%) and **11f** (42%) directly (Scheme 5) from **1a**. This displayed an excellent compatibility of sequential carboxylic acid mediated iodo-cylization, iodo-elimination and iodo-etherification reactions occurring in one-pot.

Scheme 4. Tandem iodo-lactonization and iodo-elimination (formal Heck-type coupling)

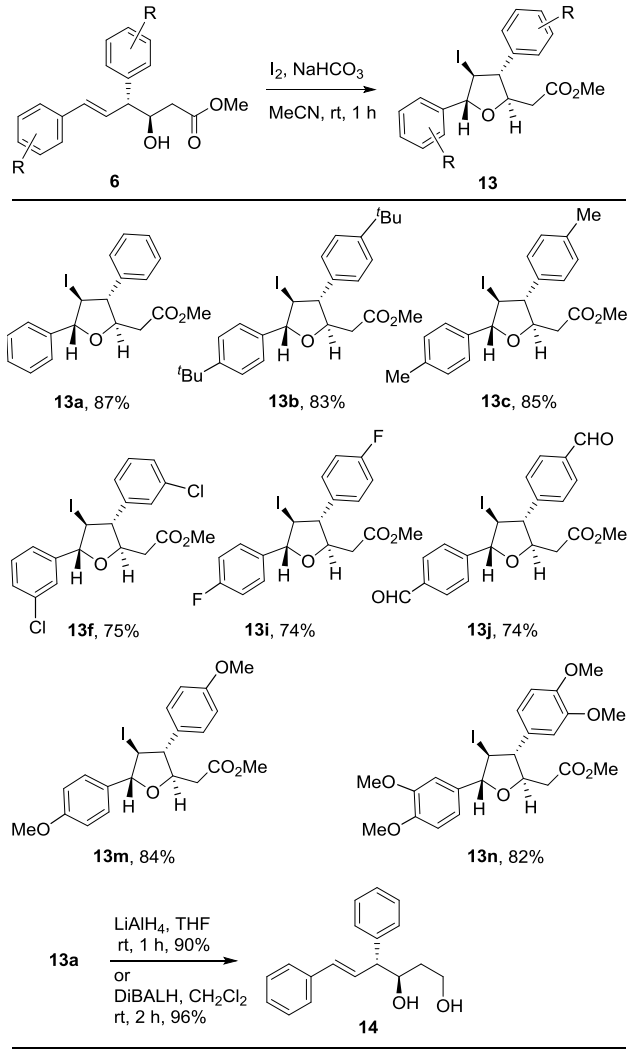


The bis-arylated compounds **6** appeared appealing candidates for iodo-etherification using the pendant β-OH group and the styryl olefin bond to obtain densely substituted tetrahydrofurans. Thus, when compounds **6a-c**, **f**, **i**, **j**, **m** and **n** were treated with iodine and $NaHCO_3$ in CH_3CN solvent, they delivered the densely substituted tetrahydrofurans **13a-c**, **f**, **i**, **j**, **m** and **n** respectively in good yields (74-87%) and high diastereoselectivity toward the 2,5-*anti*-tetrahydrofuran ring (Scheme 6). The iodo and ester groups in **13** can be elaborated further. The 2,4-biaryl tetrahydrofuran moiety is present in calyxolanes A, B and magnosalicin natural products (Figure 1). In an attempt to de-iodinate and reduce the ester group, the compound **13a** was treated with $LiAlH_4$. This delivered the olefin-diol **14** (90%) with the iodo group eliminated to olefin rather than reduced. A similar reaction occurred with DiBAL-H giving **14** in 96% yield.

Scheme 5. Synthesis of aryl-Hagen's Gland lactone analogues.



Scheme 6. Synthesis of densely substituted tetrahydrofurans



The double bond geometry in the bis-arylated product **6** has been determined as (*E*) based on the coupling constant (J = 15.5−16.0 Hz). The relative stereochemical relationship in **6**, between γ-aryl and β-OH groups is ascertained by the $J_{H\text{-}H}$ coupling constant, ^{1}H-^{1}H-COSY, ^{1}H-^{1}H-NOESY and NOE study of tetrahydrofuran **13c** (Figure 2). The ^{1}H-^{1}H-COSY and ^{1}H-^{1}H-NOESY indicated no NOE correlation between H_a and H_b protons (^{1}H-^{1}H-COSY and ^{1}H-^{1}H-NOESY and NOE spectral details are available in supporting information). The ^{1}H-^{1}H coupling constant data of tetrahydrofuran **13c** (J_{Ha} = 9.2 Hz, J_{Hb} = 17.0, 10.8, 4.5 Hz, J_{Hc} = 10.4, 9.6 Hz and J_{Hd} = 10.4, 9.2 Hz) indicates the γ-aryl and β-OH are not in same face. In NOE experiment, irradiation of H_a shows an enhancement with H_d (3%) and H_b (0%). Irradiation of H_b shows an enhancement with H_c (2%) and H_a (0%). Therefore, H_a and H_d are in same face (similarly, H_b and H_c). With the NOE data we concluded that H_a and H_b are not in the same face orientation (similarly, H_c and H_d). Based on NOE experimental study of **13c**, the relative stereochemical relationship between γ-aryl and β-OH in **6** is confirmed as *anti*-relative configuration (Scheme 2)

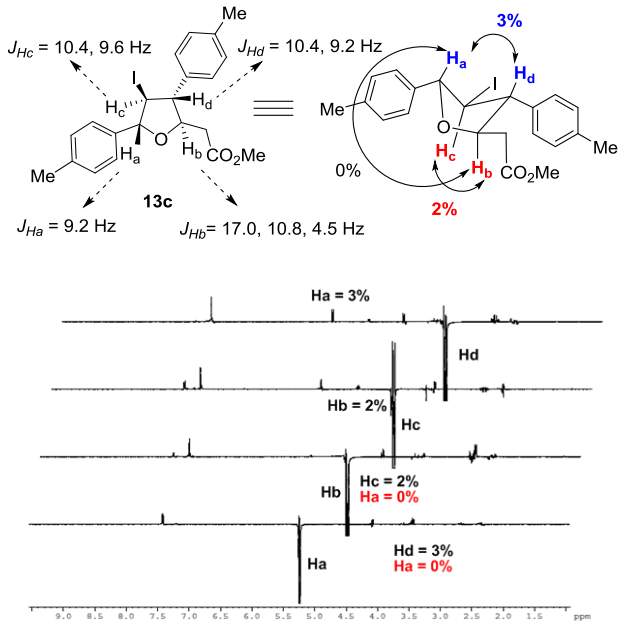
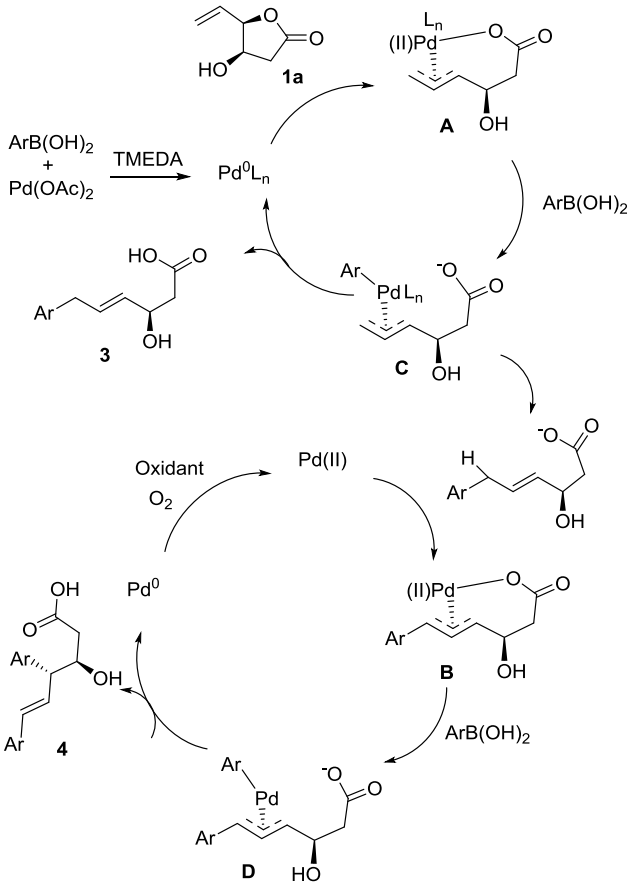


Figure 2. NOE correlation and coupling constants

The mechanistic considerations could be similar to allylic alkylation of allyl acetates. The opening of γ-vinyl-γ-lactone by Pd(0) (generated from $Pd(OAc)_2$ by boronic acid or ligand)[19] is expected to deliver the π-allyl palladium intermediate **A** stabilized by carboxylate co-ion. Transmetalation with boronic acid would generate intermediate **C**. Subsequent reductive elimination would lead to linear aryl substituted product **3** (that is esterified to **5** for easy isolation). Similar to acetate ligand acting as hydrogen abstracter, the carboxylate anion can assist the abstraction of allylic hydrogen as proton leading to second π-allyl palladium intermediate **B** in presence of Pd(II) which is generated by oxidation of Pd(0) by O_2. Subsequent transmetallation with the excess boronic acid **2** will result in **D**. The next reductive elimination gives the branched bis-arylated product **4** (that is esterified to **6** for easy isolation). Thus the regeneration of Pd(II) species from Pd(0) has been achieved by using the oxidant O_2.[20] One would expect that the second π-allylpalladium intermediate formation would occur involving the allyl alcohol system *via* the leaving group ionization. This has been reported in literature.[11] However, this was not observed and the final compound **6** has the OH group intact. This represents a good example of site-selective π-allyl palladium formation by allylic C-H activation over allylic OH-based leaving group ionization that is unprecedented in literature. The presence of OH group also adds to the atom economy and availability of additional functional group.

Scheme 7. Plausible mechanism



CONCLUSION

In conclusion, we have developed a method for ring opening of γ-vinyl-γ-lactone via electrophilic π-allyl palladium formation to deliver monoarylated products and an unprecedented regio- and stereoselective directed bis-arylation using excess boronic acid. The method developed is a good example of site-selective directed allylic arylation involving C-H activation verses the allylic OH-based leaving group ionization that is unprecedented in literature. The retention of OH group adds to the diversity in functional groups in the product and displays an efficient atom economy. A good synergistic dual catalysis occurred involving oxidation of Pd(0) to Pd(II) by O_2 as oxidant. The monoarylated products of this method have been efficiently converted into the Hagen's gland lactone analogues, while the bis-arylated compounds are converted into highly substituted tetrahydrofurans. The 2,4-biaryltetrahydrofuran unit synthesized is present in natural

products like calyxolanes and magnosalicin. A shift from boronic acids to other nucleophiles may generate new intermediates/products with applications in natural products synthesis.

ASSOCIATED CONTENT

Supporting Information.
Experimental details, compound data and NMR spectra. This material is available free of charge *via* the Internet at http:/pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the Department of Science and Technology, New Delhi, (Grant No. SB/S1/OC-42/2013) and Board of Research in Nuclear Sciences (BRNS), Government of India (Basic Sciences, Grant No. 2013/37C/59/BRNS/2443) for financial support. J.L.N thanks Council of Scientific and Industrial Research (CSIR), New Delhi for research fellowship.

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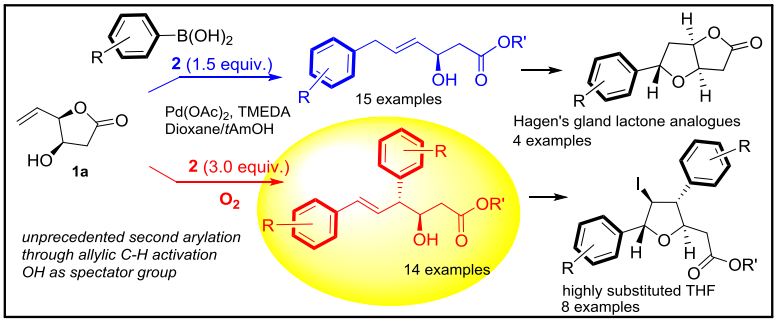
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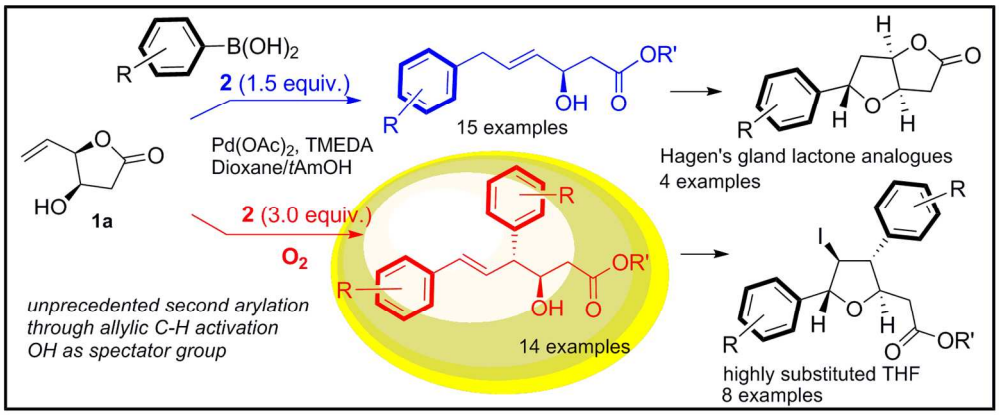

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