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Authors: Karu Ramesh and Gedu Satyanarayana

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COMMUNICATION

Transition-Metal Catalyzed Stereoselective γ-Arylation and Friedel-Crafts Alkylation: A Concise Synthesis of Indenes

Karu Rameshᵃ and Gedu Satyanarayana*ᵃ

[a] Prof. G. Satyanarayana, Department of Chemistry
Indian Institute of Technology (IIT) Hyderabad, Kandi – 502 285, Sangareddy District, Telangana, INDIA
Fax: +91(40) 2301 6032
E-mail: gvsatya@iith.ac.in
Home page: https://sites.google.com/site/gsresearchgrouphomepage/home

Abstract: A highly stereoselective [Pd]-catalyzed arylation of *tert*-alkenols, is presented. Further, applied to the synthesis of indenes using intramolecular Friedel-Crafts alkylation sequence. The initial Heck reaction is performed by using water as the green solvent. A simple acid triggers intramolecular alkylation in short reaction times at room temperature. Notably, indenes have been accomplished using a single column chromatography technique.

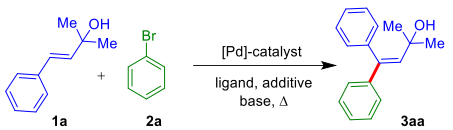
Establishing new carbon-carbon bond-forming processes are vital in organic chemistry. An innumerable number of examples have developed towards C–C bond-forming reactions.[1] Notably, various acids have been employed to construct the C–C bond.[2] Also, transition-metals[3] attained much interest in constructing diverse C–C bonds through coupling reactions, few of them are Fujiwara-Moritani,[4] Mizoroki-Heck,[5] Suzuki,[6] Sonogashira,[7] and Glaser couplings.[8] Amongst, Fujiwara-Moritani and Mizoroki-Heck reactions are a class of reactions, in which synthesis of substituted olefins are accomplished. Specifically, these two named reactions are differentiated in terms of aryl ring couples with the olefin moiety. In the Fujiwara-Moritani reaction, the simple arene couples with olefin double bond, while aryl halide is the coupling partner in Mizoroki-Heck reaction. Later, numerous transition metal-mediated Heck type coupling reactions are reported on different functional group-containing olefins.[9] To the best of our knowledge, there are very few reports of arylation on a double bond of unprotected hydroxyl group-containing olefins, that too with poor selectivity.[10] This may be attributed to the fact that the hydroxyl group is Lewis basic in nature and competent enough to engage the metal catalyst. This sort of alcohol reactivity is well known from the degradative coupling of propargylic alcohols with haloarenes, under [Pd]-catalysis.[11] Also, hydroxyl functionality is known to be reactive toward oxidative couplings that are facilitated by a transition-metal catalyst.[12] With this viewpoint, we still believed that, under suitable conditions, it would be feasible to touch the double bond stereoselectively without effecting the hydroxyl group. So that it becomes possible to perform some useful subsequent transformations on the arylated *tert*-alkenols centered at a free hydroxyl group. Therefore, we aimed at stereoselective [Pd]-catalyzed γ-arylation (Mizoroki-Heck) on *tert*-alkenols. Intramolecular Friedel-Crafts alkylation of the resulted arylated *tert*-alkenols would lead to indenes efficiently. Due to the presence of unprotected OH group, γ-arylated/Mizoroki-Heck tertiary alcohol would rather reactive towards the cyclization (Friedel-Crafts alkylation). Indenes are an essential class of compounds as they are of significant structural motifs found as core structures in natural as well as products of biological significance.[13] Hence, many research groups have been attracted towards the synthesis of indenes in different paths using transition metal catalysis[14] and acid-mediated transformations.[15] In continuation of our interest in developing transition-metal catalysis[16] as well as acid-mediated cyclizations,[17] herein, we report the synthesis of indenes. The strategy involves intermolecular Heck and intramolecular Friedel-Crafts alkylation of *tert*-alkenols. Significantly, the entire process is achieved by a single column chromatography technique.

To initiate the optimization study, the reaction was carried out with cinnamyl tertiary alcohol **1a** and bromobenzene **2a** by taking 5 mol% of $Pd(OAc)_2$, 10 mol% of BINAP, 1 equiv of TBAI (tetrabutylammonium iodide), 4 equiv of K_2CO_3, and toluene (0.5 mL) as a solvent, at 100 °C for 24 h. However, there was no progress in the reaction; only the starting material **1a** (88%) was recovered (entry 1, Table 1). More or less, the same result was noted when the temperature was increased to 120 °C (entry 2, Table 1). Thus, the reaction was conducted at a relatively higher temperature and longer reaction times, i.e., 140 °C for 36 h (entry 3, Table 1). To our delight, the reaction was progressed well and delivered the desired product **3aa** in 60% of yield. When 10 mol% of Xantphos was employed as the ligand, afforded the product **3aa** in moderate yields (entry 4, Table 1). On the other hand, with 10 mol% of $P(Cy)_3$ ligand, under similar conditions, furnished **3aa** in 65% yield (entry 5, Table 1). Notably, switching the ligand to L-proline improved the yield of **3aa** to 73% (entry 6, Table 1). Besides, when the reaction was screened with other solvents like xylene and DMF, the product **3aa** was formed in 72% and 75% yields, respectively (entry 7 & 8, Table 1). Based on the above outcomes, it was believed that water, the green solvent, may also promote the reaction, under similar conditions. Gratifyingly, 80% of the requisite product **3aa** was obtained by employing water as the sole solvent, under similar reaction conditions (entry 9, Table 1). In the similar context, other additives like BTEAC (benzyl triethylammonium chloride), TBAB (tetrabutylammonium bromide), TBAC (tetrabutylammonium chloride) were also afforded the desired product **3aa**, but in 78%, 70% and 61% of yields, respectively (entries 10, 11 & 12, Table 1). When the temperature was decreased to 130 °C, parallelly, the yield was also reduced to 55% (entry 13, Table 1). Likewise, further decreasing the temperature to 120 °C, the starting material was not consumed completely and recovered the starting material **1a** in 70% (entry 14, Table 1). On the other hand, the reaction was also screened with regards to time scale; i.e., the reaction was conducted for 24

10.1002/ejoc.202000030

and 30 h (entries 15 & 16, Table 1). However, there was no complete conversion, despite recovered the starting material **1a** 61% and 46% respectively. While the reaction for prolonged time 48 h, led to the formation of **3aa**, in 60% yield only (entry 17, Table 1), which may be due to the decomposition of the starting materials or product. Whereas, the reaction with $Pd(TFA)_2$ (5 mol%), TBAI (1 equiv), L-proline (10 mol%), K_2CO_3 (4 equiv), and solvent water at 140 °C for 36 h, furnished **3aa**, in 64% yield (entry 18, Table 1). When a relatively strong base Cs_2CO_3 was used, the yield of **3aa** was dropped to 58% (entry 19, Table 1). While the reaction with a weaker base Na_2CO_3, the starting material **1a** was not consumed completely, 68% of **1a** was recovered back (entry 20, Table 1).

Table 1: Optimization studies to generate arylated *tert*-alkenol **3aa**.[a-g]



1a 2a 3aa

entry	additive (1 equiv)	ligand (10 mol%)	solvent (0.5 mL)	temp (°C) & time (h)	yield **3aa** [b](%)
1	TBAI	BINAP	toluene	100, 24	-[c]
2	TBAI	BINAP	toluene	120, 24	-[c]
3	TBAI	BINAP	toluene	140, 36	60
4	TBAI	Xantphos	toluene	140, 36	40
5	TBAI	$P(cy)_3$	toluene	140, 36	65
6	TBAI	L-proline	toluene	140, 36	73
7	TBAI	L-proline	xylene	140, 36	72
8	TBAI	L-proline	DMF	140, 36	75
9	**TBAI**	**L-proline**	**H_2O**	**140, 36**	**80**
10	BTEAC	L-proline	H_2O	140, 36	78
11	TBAB	L-proline	H_2O	140, 36	70
12	TBAC	L-proline	H_2O	140, 36	61
13	TBAI	L-proline	H_2O	130, 36	55
14	TBAI	L-proline	H_2O	120, 36	20 + -[c]
15	TBAI	L-proline	H_2O	140, 24	25 + -[c]
16	TBAI	L-proline	H_2O	140, 30	40 + -[c]
17	TBAI	L-proline	H_2O	140, 48	60
18[d]	TBAI	L-proline	H_2O	140, 36	64
19[e]	TBAI	L-proline	H_2O	140, 36	58
20[f]	TBAI	L-proline	H_2O	140, 36	28 + -[c]

[a]Reaction conditions: 0.25 mmol of cinnamyl tertiary alcohol **1a**, 0.62 mmol of bromobenzene **2a**, $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), additive (1 equiv), Base = K_2CO_3 (4 equiv), solvent (0.5 mL). [b]Isolated yields of product **3aa**. [c]Starting material was recovered. [d][Pd]-catalyst is $Pd(TFA)_2$ (5 mol%). [e]Base is Cs_2CO_3. [f]Base is Na_2CO_3. [g]TBAI: tetrabutylammonium iodide; TBAB: tetrabutylammonium bromide; BTEAC: Benzyltriethylammonium chloride and TBAC: tetrabutylammonium chloride.

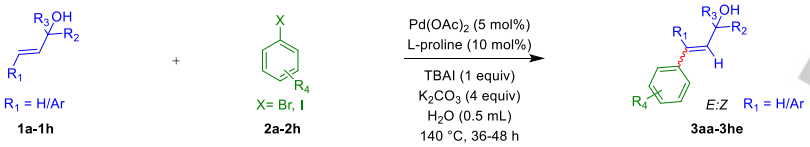
The above optimization studies reveal that entry 9 of Table 1 is the best-optimized conditions to deliver the desired product **3aa**. Thus, by implementing these optimal conditions (entry 9, Table 1), it was further aimed to exemplify with the other cinnamyl tertiary alcohols. Hence, the arylation was carried out on cinnamyl tertiary alcohols, under standard conditions. When iodobenzene, as the arylating agent, gave the product **3aa** in more or less same yield (Table 2). As expected, the reaction was smooth with aryl halides flanked to moderately as well as strongly electron-donating substituents, such as 3-/4-bromotoluenes (**2b** & **2c**) and 3-/4-bromoanisoles (**2d** & **2e**). Hence, γ-arylated products were isolated as *E*/*Z* stereoisomers in good yields **3ab**+**3ab'** (72%), **3ac**+**3ac'** (70%), **3ad**+**3ad'** (68%), and **3ae**+**3ae'** (65%) respectively (Table 2). While the reaction with bromoveratrole **2f** was also amenable and afforded as *E*/*Z* stereoisomers **3af**+**3af'** (63%) in good yields (Table 2). Further, the reaction with other cinnamyl tertiary alcohols like (3*E*)-4-(4-ethylphenyl)-2-methylbut-3-en-2-ol **1e** and (1*E*)-1-phenyl-3-propylhex-1-en-3-ol **1f** was rather smooth and yielded the products **3ea**+**3ea'** and **3fa**, in 70% and 59% of yields, respectively (Table 2). Moreover, arylation on vinyl tertiary alcohols **1h** was also successful and resulted the products **3ha** (70%), **3hd** (72%) and **3he** (75%) as exclusive *E*-isomers (Table 2). Further, the stereochemistry of compound **3ha** was confirmed based on the NMR data analysis. In the ^{1}H-NMR spectrum, olefinic protons resonate at δ 6.63 (1H, J = 16.1 Hz) and δ 6.35 (1H, J = 16.1 Hz). Thus, the large coupling constant (J = 16.1 Hz) for both olefinic protons reveals the *E*-geometry of the double bond. Moreover, the spectral data of the synthetic compound **3ha** was in good agreement with the reported data, thus confirmed the stereochemistry of **3ha** as *E*-stereoisomer.[18] Based on this observation, the stereochemistry of other related products such as, **3hd** and **3he** was also predicted as *E* isomer.

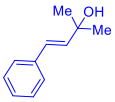
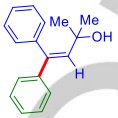
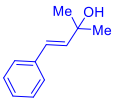
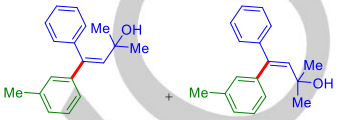
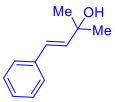
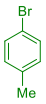
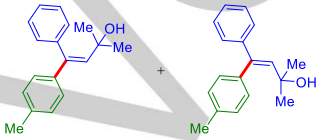
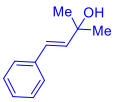
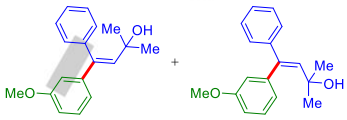
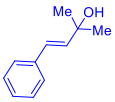
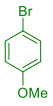
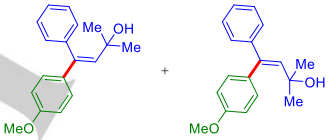
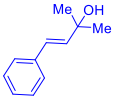
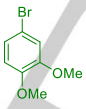
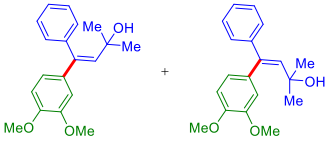
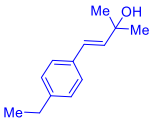
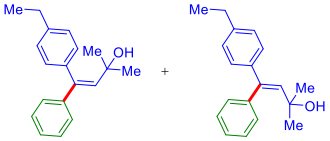
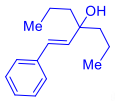
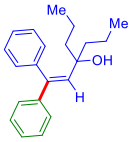
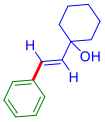
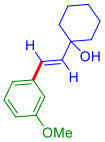
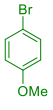
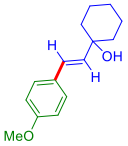
After achieving [Pd]-catalyzed selective γ-arylated *tert*-alkenols, it was decided to implement acid-mediated intramolecular Friedel-Crafts alkylation, to accomplish indene products. Thus, the workup concentrated crude reaction mixture of **3aa**, was treated with triflic acid, under neat conditions at room temperature, for 5 minutes. However, it led to the decomposition (entry 1, Table 3). While with conc. H_2SO_4 at room temperature, for 5 minutes, to our delight, furnished the cyclized indene product **4aa**, in 78% of yield (entry 2, Table 3). Gratifyingly, the yield of **4aa** was raised to 85% upon dropping the reaction time to 2 minutes (entry 3, Table 3). However, further decreasing the reaction time (1 minute), dropped the yield of **4aa** to 52% (entry 4, Table 3). Further, to improve the yield of the product **4aa**, it was also checked with conc. H_2SO_4, solvent DCE (1 mL), at room temperature, for 2 minutes. Nevertheless, no improvement in the yield was observed, and afforded **4aa**, in 60% yield (entry 5, Table 3).

On the other hand, the attempts to achieve indene in a one-pot pathway without making workup were unsuccessful and ended up in generating multiple spots on a TLC plate. Therefore, it was concluded that the workup and concentration were necessary after completion of the γ-arylation step and before subjecting to acid-induced cyclization. Thus the entire process was carried out using a single column chromatography technique.

The stereoselectivity in the arylation step (i.e., γ-selectivity) is confirmed from NMR spectral analysis of indene product **4aa** as well as by comparing it with that reported in the literature. The analysis is in support that the arylation has happened at γ-position of the double bond of *tert*-alkenol **1a**. Further, it can be ascertained that in the present indene product **4aa**, the chemical shift of olefinic proton appeared at δ 6.41 (^{1}H-NMR), which falls in the deshielding zone of the phenyl ring. If it were the olefinic proton of indene olefin formed *via* the β-arylation path, it appears at further deshielding position (around δ 7.00 in its ^{1}H-NMR spectra), as it falls in the deshielding region of both the aromatic rings.[19]

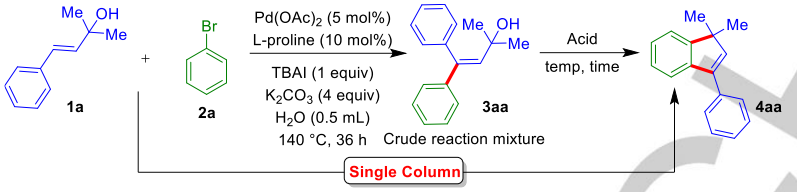
Table 2: Synthesis of γ-arylated products **3aa**-**3he**.[a-d]



Entry	Substrates 1		Substrates 2		Product	Yield (*E*:*Z*)
1		**1a**		**2a**		**3aa** X = Br (80%) **I** (82%)
2		**1a**		**2b**		**3ab** + **3ab′** (1.8:1)[c] (72%)
3		**1a**		**2c**		**3ac** + **3ac′** (1.9:1)[c] (70%)
4		**1a**		**2d**		**3ad** + **3ad′** (3.8:1)[c] (68%)
5		**1a**		**2e**		**3ae** + **3ae′** (4.5:1)[c] (65%)
6		**1a**		**2f**		**3af** + **3af′** (1.7:1)[c] (63%)
7		**1e**		**2a**		**3ea** + **3ea′** (2.6:1)[c] (70%)
8		**1f**		**2a**		**3fa** (59%)
9		**1h**		**2a**		**3ha** (70%)[d]
10		**1h**		**2d**		**3hd** (72%)[d]
11		**1h**		**2e**		**3he** (75%)[d]

[a]Reaction conditions: 0.25 mmol of cinnamyl/vinyl tertiary alcohols **1a-1h**, 0.62 mmol of aryl halides **2a-2j**, $Pd(OAc)_2$ (5 mol%), TBAI (tetrabutylammonium iodide) (1 equiv), L-proline (10 mol%), K_2CO_3 (4 equiv), solvent water (0.5 mL), 140 °C, 36-48 h. [b]Isolated yields of products **3aa-3he.** [c]The ratio of *E/Z* stereoisomers was determined by ^{1}H-NMR analysis. [d]0.25 mmol of aryl halides used.

Table 3: Optimization study for Friedel-Crafts alkylation to give **4aa**.[a-d]



entry	acid (mL)	solvent (mL)	temp (°C) & time (min)	yield (**4aa%**)[c]
1	triflic acid	-	rt & 5	-[d]
2	conc. H_2SO_4	-	rt & 5	78
3	**conc. H_2SO_4**	**-**	**rt & 2**	**85**
4	conc. H_2SO_4	-	rt & 1	52
5	conc. H_2SO_4	DCE (1 mL)	rt & 2	60

[a]Reaction conditions for γ-aryalation: 0.25 mmol of cinnamyl tertiary alcohol **1a**, 0.62 mmol of aryl halide **2a**, $Pd(OAc)_2$ (5 mol%), L-proline (10 mol%), TBAI (tetrabutylammonium iodide) (1 equiv), K_2CO_3 (4 equiv), water (0.5 mL), 140 °C, 36-48 h. [b]Reaction conditions for Friedel-Crafts alkylation: conc. H_2SO_4 (0.5 mL), DCE (1 mL), rt, 2 to 5 min. [c]Isolated yields of product **4aa**. [d]**3aa** decomposed.

With the above-optimized conditions, for the single column based protocol to give indene **4aa** (entry 3, Table 3), further to showcase the efficacy of the strategy, it was aimed at the synthesis of various indenes. Hence, after a γ-arylation reaction of **1a** with 3-bromotoluene **2b**, the concentrated crude reaction mixture of **3ab** was treated with conc. H_2SO_4. As anticipated, resulted a mixture of two indene products **4ab**+**4ab'** (1.2:1) in 70% yield (Table 4). Similar results were obtained in the case of 4-bromotoluene **2c** as well (**4ac**+**4ac'**, 2.1:1, 68%, Table 4). This may be due to the reason that phenyl and tolyl groups are more or less exert the same sort of electronic effects toward electrophile (due to the small electron-donating ability of alkyl substituents *via* +ve inductive effect). At the same time, 3-bromoanisole **2d** gave **4ad** as an exclusive product in 62% yield (Table 4). Since the *para*-position to electron releasing OMe group is free, electron-rich, and is in the right proximity to be captured by the internal electrophile. However, the reaction of **1a** with 4-bromoanisole **2e** afforded a mixture of two products **4ae**+**4ae'** (1.1:1) in 64% yield (Table 4). This can be rationalized based on the fact that the electrophile can only react at the *meta*-position to the electron releasing OMe group of anisyl moiety, which is not much electron-rich site when compared to the reactive *ortho*-*para*-sites to OMe group. Thus, simple phenyl and *para*-anisyl moieties may compete with each other toward aromatic electrophilic substitution. As a result, it led to the formation of a mixture of two products. To our delight, in all other examples, when one out of the two aromatic rings, is sufficiently electron-rich nature, prevailed in participating in cyclization step selectively and furnished the corresponding indene products **4af-4ga** (Table 4).

In addition to the spectroscopic evidence toward the chemical structures **4aa**-**4ga**, the stereoselectivity of arylation was further confirmed with the single-crystal X-ray of **4af**.[20] (Figure 1, for details, see: supporting information).

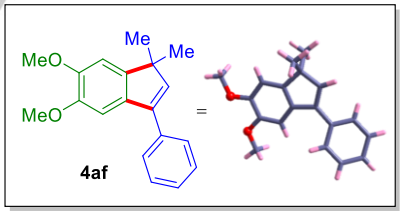


Figure 1: Single-crystal X-ray structure of indene **4af**.

In conclusion, an efficient single column chromatography based protocol was established for the synthesis of indenes. A [Pd]-catalyzed stereoselective γ-arylation and intramolecular Friedel-Crafts alkylation reactions were employed as key steps. It is worth mentioning that the solvent water was utilized as the green solvent.

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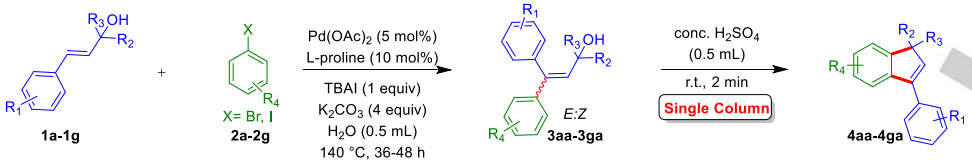
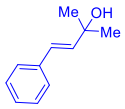
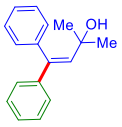
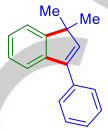
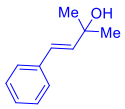
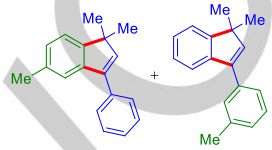
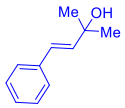
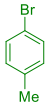
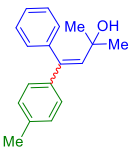
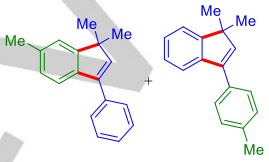
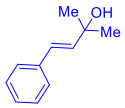
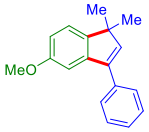
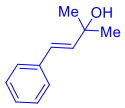
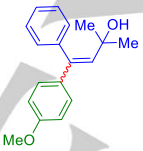
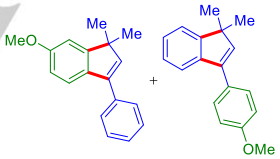
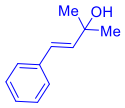
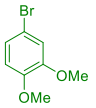
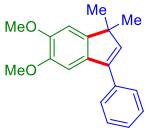
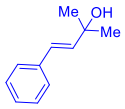
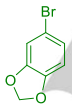
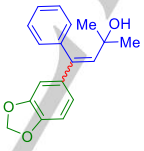
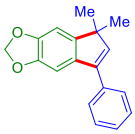
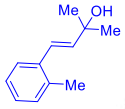
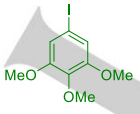
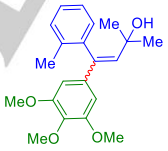
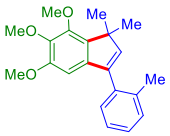
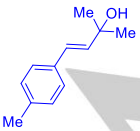
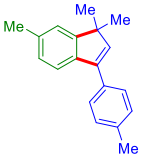
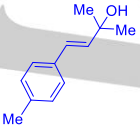
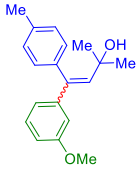
Table 4: Substrate scope for indenes **4aa**-**4ga**.[a-d]



Entry	Substrates		Intermediate	Product	Yield
1		**1a**  **2a**		**3aa** 	**4aa** (81%)
2		**1a**  **2b**		**3ab** 	**4ab** + **4ab'** (1.2:1)[d] (70%)
3		**1a**  **2c**		**3ac** 	**4ac** + **4ac'** (2.1:1)[d] (68%)
4		**1a**  **2d**		**3ad** 	**4ad** (62%)
5		**1a**  **2e**		**3ae** 	**4ae** + **4ae'** (1.1:1)[d] (64%)
6		**1a**  **2f**		**3af** 	**4af** (61%)
7		**1a**  **2h**		**3ah** 	**4ah** (63%)
8		**1b**  **2g**		**3bg** 	**4bg** (51%)
9		**1c**  **2c**		**3cc** 	**4cc** (74%)
10		**1c**  **2d**		**3cd**	**4cd** (71%)

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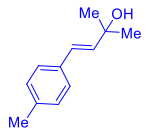
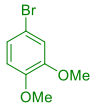
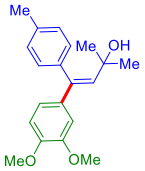
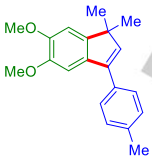
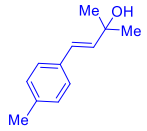
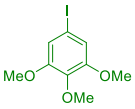
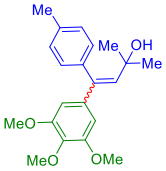
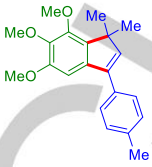
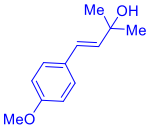
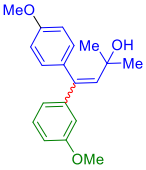
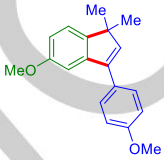
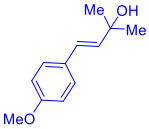
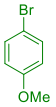
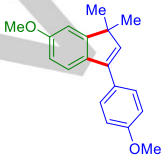
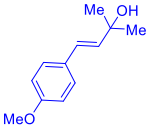
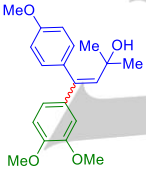
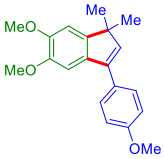
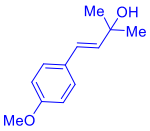
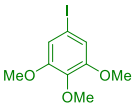
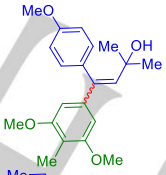
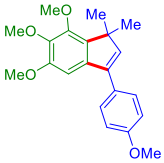
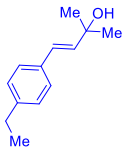
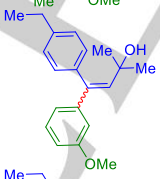
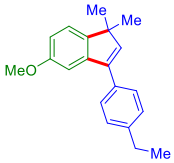
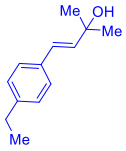
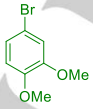
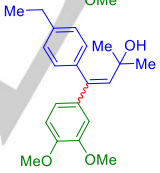
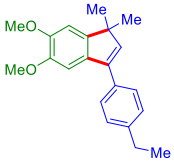
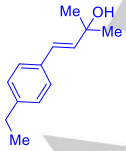
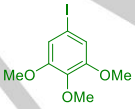
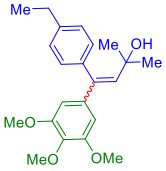
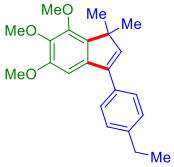
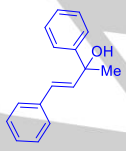
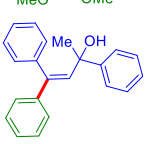
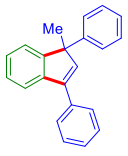
Entry	Substrates		Intermediate	Product	Yield
11		**1c** 	**2f** 	**3cf** 	**4cf** (62%)
12		**1c** 	**2g** 	**3cg** 	**4cg** (60%)
13		**1d** 	**2d** 	**3dd** 	**4dd** (75%)
14		**1d** 	**2e** 	**3de** 	**4de** (64%)
15		**1d** 	**2f** 	**3df** 	**4df** (78%)
16		**1d** 	**2g** 	**3dg** 	**4dg** (63%)
17		**1e** 	**2d** 	**3ed** 	**4ed** (67%)
18		**1e** 	**2f** 	**3ef** 	**4ef** (65%)
19		**1e** 	**2g** 	**3eg** 	**4eg** (62%)
20		**1g** 	**2a** 	**3ga** 	**4ga** (62%)

[a]Reaction conditions for γ-arylation: 0.25 mmol of cinnamyl tertiary alcohols **1a**-**1g**, 0.62 mmol of aryl halides **2a**-**2g**, $Pd(OAc)_2$ (5 mol%), TBAI (tetrabutylammonium iodide) (1 equiv), L-proline (10 mol%), K_2CO_3 (4 equiv), solvent water (0.5 mL), 140 °C, 36-48 h. [b]Reaction conditions for Friedel-Crafts alkylation: conc. H_2SO_4 (0.5 mL), rt, 2 min. [c]Isolated yields of products **4aa**-**4ga**. [d]The ratio of *E/Z* stereoisomers was determined by ^{1}H-NMR analysis.

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20. CCDC number for the compound **4af**: CCDC1975434.

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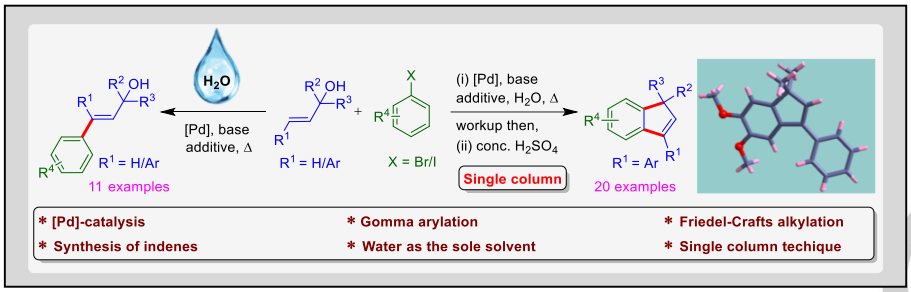

A concise synthesis of Mizoroki-Heck products and corresponding indenes starting with simple *tert*-alkenols and aryl halides is presented. Notably, the γ-arylation was done under [Pd]-catalysis by using water as the sole green solvent and the synthesis of indenes *via* acid-mediated intramolecular Friedel-Crafts cyclization.