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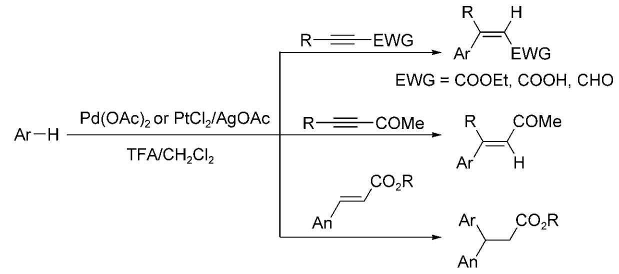
[$PdCl_2(MeCN)_2$]-Catalyzed Highly Regio- and Stereoselective Allylation of Electron-Rich Arenes with 2,3-Allenoates

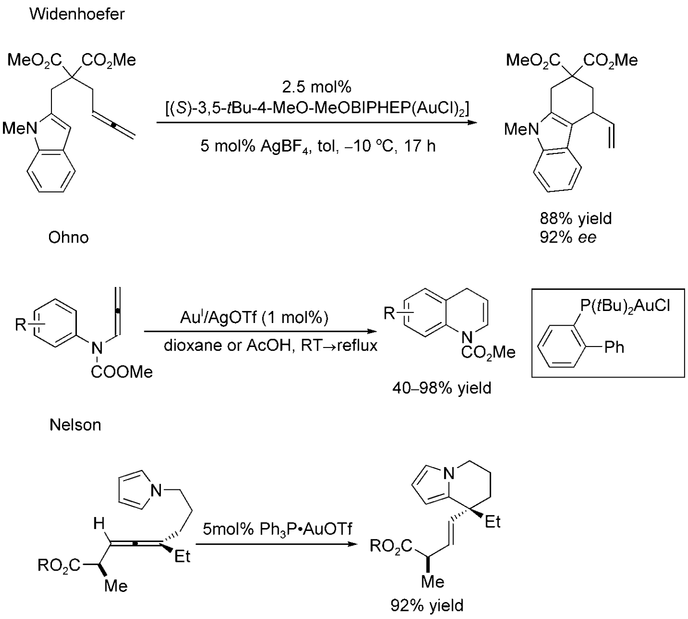
Zhao Fang, Chunling Fu, and Shengming Ma*[a]

Noticeable progress has been observed in the area of transition-metal-catalyzed functionalization of aromatic C–H bonds followed by C–C, C–O and C–N coupling reactions, which has became one of the most convenient access for the synthesis of organic intermediates bearing an aryl group.[1] In addition to these reports, examples have been reported for the reactions of arenes with unsaturated bonds such as alkenes,[2] alkynes,[3] and allenes:[4] Fujiwara et al. reported selective hydroarylation reactions of various electron-rich arenes with activated alkenes and alkynes including acrylates,[2c,d] propiolates,[2c,d,3] propiolic acids[2c,d] and propiolaldehydes[2c,d] at room temperature affording addition products in which $Pd(OAc)_2$ or $PtCl_2$ served as the catalyst in a mixed solvent containing trifluoroacetic acid (Scheme 1).



Scheme 1. Pd-catalyzed addition of aromatic C–H bonds to C–C unsaturated bonds reported by Fujiwara.

For the reaction with allenes, gold(I)-catalyzed intermolecular or intramolecular hydroarylations of allenes have been developed.[4] Widenhoefer et al. reported a cyclization of 3,4-allenoates with an intramolecular indole nucleophile.[4g] Hydroarylation of *N*-(1,2-allenyl)anilines and phenols affording dihydroquinoline and chromene derivatives were achieved by Ohno in 2007.[4c] Nelson et al. developed a gold-catalyzed intramolecular annulation of enantioenriched allenes with pyrrole, which was applied in the total synthesis of (−)-rhazinilam (Scheme 2).[4b] However, the corresponding intermolecular variants are rare except for a recent result by Gagné,[4j] in which it was found that unsubstituted 3-methylbuta-1,2-diene worked best with electron-rich arenes such as 1,3,5-trimethoxybenzene (Scheme 3). We have been studying the functionalization of electron-rich arene with allene for long time with very limited success.[5] In this paper, we wish to report a palladium-catalyzed hydroarylation reaction of 2,3-allenoates with high regio-and stereoselectivity.



Scheme 2. Previously reported gold(I)-catalyzed intermolecular or intramolecular hydroarylations of allenes.

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[a] Z. Fang, Prof. Dr. C. Fu, Prof. Dr. S. Ma
Department of Chemistry, Zhejiang University
Hangzhou 310027 (PR China)
Fax: (+86) 021-62609305
E-mail: masm@mail.sioc.ac.cn

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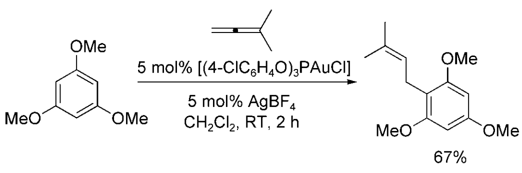
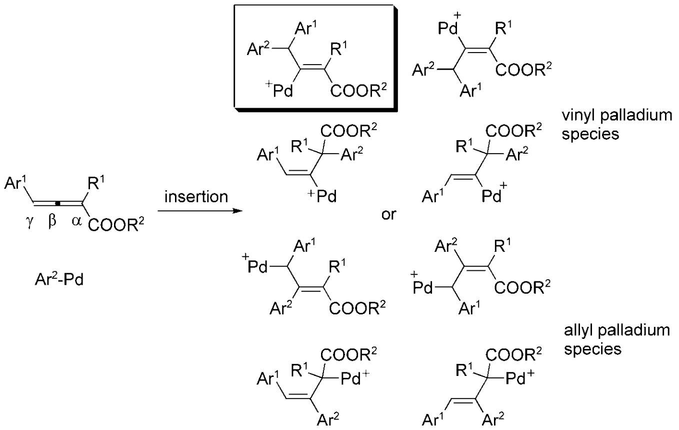


Scheme 3. Gold(I)-catalyzed intermolecular hydroarylation of allenes with electron-rich arenes.

2,3-Allenoates are a class of compounds with two C–C double bonds and one electron-withdrawing group, which could be inserted into the aryl–Pd species resulting in the formation of eight types of intermediates depending on the regio- and stereoselectivity (Scheme 4). As far as we know, the insertion of the C–C double bonds in allene moiety with C–Pd bond usually led to π-allylic type intermediates,[6] however, vinylpalladium intermediate with aryl transferred to the terminal carbon was also observed in some cases.[7] Thus, control of the regioselectivity and the stereoselectivity referring to configuration of the remaining double bond is challenging. Herein we wish to disclose our recent observation on the Pd-catalyzed high regio- and stereoselective allylation of electron-rich arenes, with the aryl group connecting at the γ position most likely through a vinylpalladium intermediate.



Scheme 4. Different carbopalladation of 2,3-allenoates.

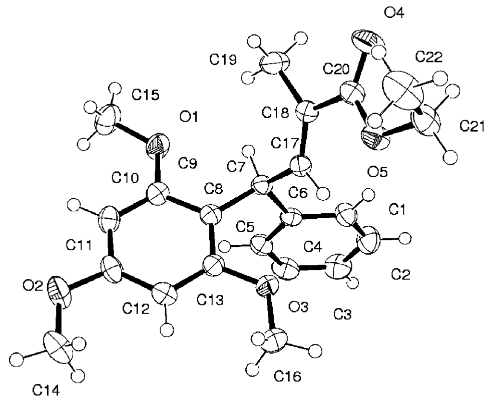


Figure 1. ORTEP Representation of (*E*)-**3a**.

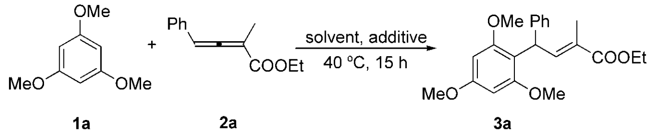
Firstly, we used 1,3,5-trimethoxybenzene (**1a**) and ethyl 2-methyl-4-phenylbuta-2,3-dienoate (**2a**) as the model substrates to screen a series of different conditions. As a first try, the reaction in a mixture of dichloromethane and TFA gave the product **3a** in 31 % yield as the only product indicating the high regio- and stereoselectivity (entry 1, Table 1). The structure of **3a** was unambiguously established by the X-ray diffraction study indicating the *E* selectivity of the double bond and attachment of the aryl group at the γ position(Figure 1).[8] The reaction in pure TFA gave better result (entry 3, Table 1). It should be noted that addition of dimethylacetamide (DMA) to TFA as the co-solvent afforded the product in higher yield (entry 4, Table 1). Replacement of TFA in the mixed solvent with trichloroacetic acid led to a decreased yield (entry 5, Table 1). The reaction in more acidic trifluoromethanesufonic acid became complicated probably due to the decomposition of the 2,3-allenoate **2a** (entry 6, Table 1). Addition of both metal and non-metal Lewis acid slightly decreased the yield (compare entries 7 and 8 with entry 4, Table 1). Interestingly, addition of [$PdCl_2(MeCN)_2$] increased the yield to 64 % isolated yield. Thus, the reaction in DMA/TFA (1:4 by volume) with [$PdCl_2(MeCN)_2$] as the catalyst at 40 °C is defined as the standard conditions (entry 9, Table 1).

With the optimized reaction conditions in hand, some typical results of Pd-catalyzed reaction of different buta-2,3-dienoates and arene **1a** are listed in Table 2. Reactions proceeded smoothly under the standard conditions affording differently substituted ethyl 4,4-diarylbut-2(*E*)-enoate (**3**) in moderate to good yields. When 1,3,5-trimethoxybenzene (**1a**) was used as the arene, R^2 could be methyl, ethyl, benzyl or allyl group while the yield dropped as the group became larger probably due to the steric effect (entries 1–4, Table 2). R^1 could be substituted phenyl groups with either electron-donating groups or electron-withdrawing groups (entries 5–10, Table 2). As to *para*-bromo substrate **2j**, high temperature and prolonged reaction time were necessary for complete conversion of the arene (entry 10, Table 1). Unfortunately, when R^1 was n-C_4H_9, no reaction occurred with recovery of the arene and decomposition of the allenoates (entry 11, Table 1).

In addition to **1a**, we also tried other types of arenes. To our delight, the reaction of anisole, a less electron-rich arene, afforded the *para* C–H bond activation based product ethyl 4,4-diaryl-2-methylbut-2(*E*)-enoates **3k**, **3l**, and **3m** in moderate yields exclusively (Scheme 5). Interestingly, even phenol also underwent this type of highly regioselective transformation (Scheme 5). This was very different from the gallium chloride catalyzed hydroarylation of arylacetylene with phenols reported recently in which the *otho* C–H bond was functionalized.[9]

A rationale for this reaction is proposed in Scheme 6. Activated Pd^{II} species was formed from [$PdCl_2(MeCN)_2$] in TFA[2c,d] which served as an electrophile to proceed electrophilic palladation reaction generating the aryl-palladium

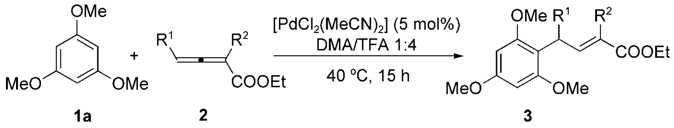
Table 1. Optimization of reaction conditions for the hydroarylation of 1,3,5-trimethoxybenzene **1a** with ethyl 2-methyl-4-phenylbuta-2,3-dienoate **2a**.[a]



Entry	Solvent	Additive	Recovery of **1a** (% by NMR)	NMR yield of **3a** [%]
1	CH_2Cl_2/TFA	–	30	31
2	toluene/TFA	–	47	29
3	TFA	–	35	40
4	DMA/TFA	–	32	53
5	DMA/TCA[b]	–	36	34
6	DMA/TfOH	–	29	complex mixture
7	DMA/TFA	$BF_3 \cdot Et_2O$[c]	30	43
8	DMA/TFA	$Sc(OTf)_3$	27	41
9	DMA/TFA	$[PdCl_2(MeCN)_2]$	0	61 (64)[d]
10	DMA/TFA	$[Pd(OCOCF_3)_2]$	28	46

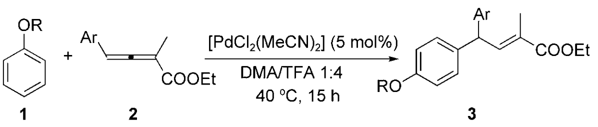
[a] The reaction was carried out using 0.3 mmol of **1a**, 1.2 equiv of **2a**, 5 % mmol of additive in 1.2 mL of acid and 0.3 mL of co-solvent and the yields and recovery were determined by ^{1}H NMR analysis with CH_2Br_2 as the internal standard. (TFA = trifluoroacetic acid) [b] The reaction was conducted at 60 °C because the melting point of TCA is 57.5 °C (TCA = trichloroacetic acid). [c] 1.0 equiv of $BF_3 \cdot Et_2O$ was added as the additive. [d] Isolated yield.

Table 2. Reactions of different 2,3-allenoates with 1,3,5-trimethoxybenzene **1a**.[a]



Entry	R^1	R^2	Yield of **3**
1	Ph	Me (**2a**)	64 [(*E*)-**3a**]
2	Ph	Et (**2b**)	40 [(*E*)-**3b**]
3	Ph	Bn (**2c**)	50 [(*E*)-**3c**]
4	Ph	allyl (**2d**)	37 [(*E*)-**3d**]
5	α-naphthyl	Me (**2e**)	69 [(*E*)-**3e**]
6	*p*-MeC_6H_4	Me (**2f**)	61 [(*E*)-**3f**]
7	*p*-$MeOC_6H_4$	Me (**2g**)	38 [(*E*)-**3g**]
8	*p*-FC_6H_4	Me (**2h**)	70 [(*E*)-**3h**]
9	*p*-ClC_6H_4	Me (**2i**)	52 [(*E*)-**3i**]
10	*p*-BrC_6H_4	Me (**2j**)	51[b] [(*E*)-**3j**]
11	*n*-C_4H_9	Me (**2k**)	–[c]

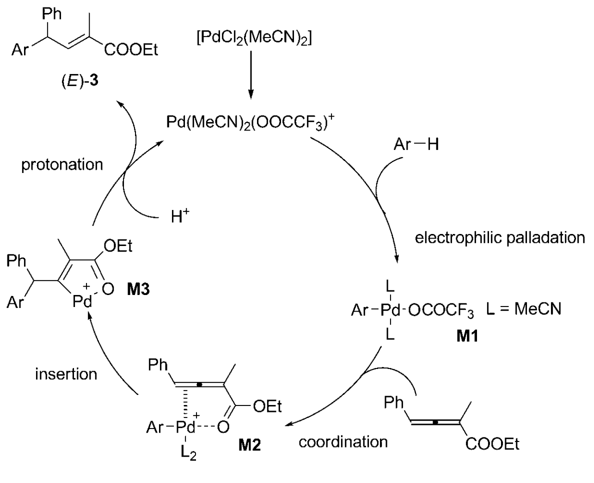
[a] The reaction was carried out using 0.3 mmol of **1** and 1.2 equiv of **2** in 0.3 mL of DMA and 1.2 mL of TFA at 40 °C for 15 h. [b] The reaction was conducted at 60 °C for 24 h until 100 % conversion of **1a** as monitored by TLC. [c] **1a** was recovered in 96 % NMR yield while **2k** decomposed under the reaction condition.



1b: R = Me	**2a**:	Ar = Ph	52% [(*E*)-**3k**]
	2e:	Ar = α-naphthyl	58% [(*E*)-**3l**]
	2h:	Ar = *p*-FC_6H_4	50% [(*E*)-**3m**]
1c: R = H	**2a**:	Ar = Ph	40% [(*E*)-**3n**]
	2e:	Ar = α-naphthyl	58% [(*E*)-**3o**]

Scheme 5. Reactions of different 2,3-allenoates with anisole or phenol.

species **M1**.[1] Subsequently, coordination of allene moiety and the ethoxycarbonyl group with the palladium atom forms the coordination complex **M2**. The *syn*-insertion of the relatively electron-rich C-C double bond to the σ-aryl–Pd bond results in the formation of intermediate **M3**. The coordination of carbonyl group with Pd explains the stereoselectivity. Upon protonation under acidic condition, **M3** affords the final product (*E*)-**3** and regenerates the catalytically active Pd^{II}.[2c,d,3]



Scheme 6. Proposed mechanism.

In conclusion, we have developed a palladium-catalyzed highly selective allylation of 1,3,5-trimethoxybenzene, anisole, or phenol in TFA under mild conditions with 2,3-allenoate affording 4,4-diarylbut-2(*E*)-enoate in moderate yields. Considering the complexity of this type of products and their potentials as structural units and building block in organic synthesis, this highly regio- and stereoselective transformation will be useful in organic synthesis and medicinal chemistry. Further study on expansion of the substrate scope and improvement of the yield was carried out in our laboratory.

Experimental Section

To a reaction tube were added sequentially **1a** (49.4 mg, 0.29 mmol), $[PdCl_2(MeCN)_2]$ (3.5 mg, 0.013 mmol), and DMA (0.3 mL). Then ethyl 2-methyl-4-phenylbuta-2,3-dienoate (**2a**) (72.9 mg, 0.36 mmol) was added followed by rinsing with TFA (1.2 mL). After being stirred at 40 °C for 15 h as monitored by TLC, the resulting mixture was quenched with 10 mL of an aqueous saturated solution of $NaHCO_3$, extracted with diethyl ether (15 mL × 3), washed with an aqueous saturated solution of

NaHCO$_3$, and dried over anhydrous Na$_2$SO$_4$. Filtration, evaporation, and chromatography on silica gel (petroleum ether/ethyl acetate 7.5:1) afforded (*E*)-**3a** (69.6 mg, 64 %). White solid; m.p. 90–92 °C (*n*-hexane/diethyl ether); ^{1}H NMR (300 MHz, CDCl$_3$, 20 °C, TMS): δ = 7.50 (d, ^3J = 9.3 Hz, 1H; C=CH), 7.27–7.18 (m, 2H; C=CH), 7.18–7.09 (m, 3H; C=CH), 6.14 (s, 2H; C=CH), 5.59 (d, ^3J = 9.3 Hz, 1H; CH), 4.18 (q, ^3J = 7.4 Hz, 2H; CH$_2$), 3.79 (s, 3H; CH$_3$), 3.71 (s, 6H; CH$_3$), 1.88 (s, 3H; CH$_3$), 1.28 ppm (t, ^3J = 7.4 Hz, 3H; CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$, 20 °C, TMS) δ = 168.6, 160.1, 158.8, 144.1, 143.3, 127.9, 127.4, 127.1, 125.5, 111.3, 91.2, 60.3, 55.7, 55.2, 38.4, 14.3, 12.4 ppm; IR (KBr): $\tilde{\nu}$ = 3059, 2938, 2838, 1706 (C=O), 1642, 1605, 1493, 1465, 1455, 1418, 1367, 1331, 1280, 1220, 1205, 1151, 1112, 1057, 1037 cm^{-1}; MS (70 eV): *m/z* (%): 370 (10) [M^+], 324 (100) [$M^+ -$OEt$-$H]; elemental analysis calcd (%) for C$_{22}$H$_{26}$O$_5$: C 71.33, H 7.07; found: C 71.28, H 7.06.

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Keywords: allenoates · arenes · C–H functionalization · palladium

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[8] Crystal data for compound (*E*)-**3a**: C$_{22}$H$_{26}$O$_5$, M_W = 370.43, triclinic, space group $P\bar{1}$, final R indices [$I > 2\sigma(I)$], $R1$ = 0.0383, $wR2$ = 0.1015, R indices (all data) $R1$ = 0.0416, $wR2$ = 0.1051, a = 8.7423(3), b = 9.0396(3), c = 14.5905(7) Å, α = 93.5940(10), β = 102.7960(10), γ = 116.4640(10)°, V = 989.23(7) Å^3, T = 173 (2) K, Z = 2, reflections collected/unique: 11 506/3472 (R_{int} = 0.0172), number of observations [$I > 2\sigma(I)$] 3163, parameters: 244. CCDC-752421 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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