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Palladium-Catalyzed, Chelation-Assisted Stereo- and Regioselective Synthesis of Tetrasubstituted Olefins by Oxidative Heck Arylation

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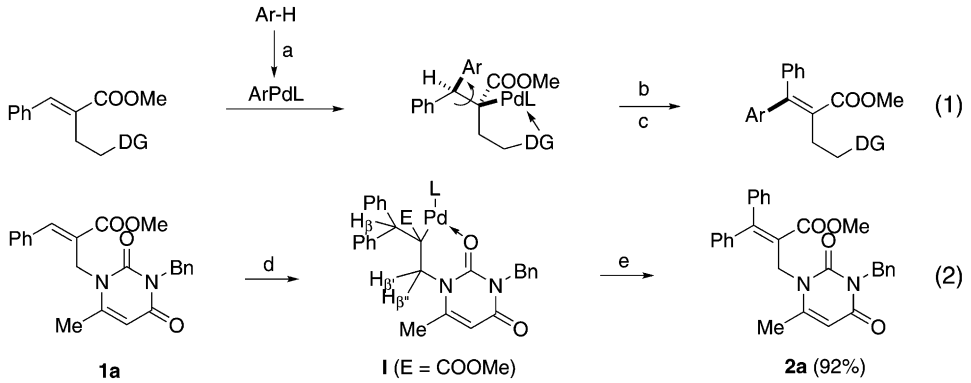
Abstract: An efficient synthesis of tetrasubstituted olefins was achieved *via* a palladium-catalyzed, chelation-assisted oxidative Heck arylation protocol from trisubstituted olefins bearing a tether with a directing group in a completely stereo- and regioselective manner. The stereo- and regioselectivity as well as excellent yields of tetrasubstituted olefins originated from the stabilization of a palladium intermediate by chelation between the palladium center and a directing group.

Keywords: chelation; Morita–Baylis–Hillman adducts; oxidative Heck arylation; palladium

The Pd-catalyzed Mizoroki–Heck arylation of olefins with aryl halides has become a well-established synthetic method for C–C bond formation.[1] However, the normal intermolecular Heck reaction did not work well for the synthesis of tetrasubstituted olefins due to the reluctance of trisubstituted olefins to participate in the carbopalladation process.[1] Increased steric crowdedness during the insertion of the ArPdL species to the hindered olefin might be an important reason for the failure. As a powerful variant of the normal Heck reaction, the Pd(II)-catalyzed oxidative arylation of olefins with arenes has attracted much attention.[2] The oxidative cross-coupling between olefins and arenes, commonly known as the Fujiwara–Moritani reaction or simply dehydrogenative Heck reaction, circumvents the use of preformed or less readily accessible aryl halides. However, the reaction also did not work well for the synthesis of highly-substituted olefins.[2] Thus, the stereo- and regioselective synthesis of highly-substituted olefins is still very challenging, and a very limited number of papers has been published.[3]

In this report, we describe an effective stereo- and regioselective synthesis of tetrasubstituted olefins by a Pd(II)-catalyzed oxidative cross-coupling reaction between an arene and a trisubstituted olefin bearing a tether with a directing group (DG), as shown in Scheme 1, conceptually [Eq. (1)] and with an example [Eq. (2)]. The DG can assist the carbopalladation of



Scheme 1. Eq. (1): Basic concept of arylation: a) C-H activation; b) rotation; c) β-H elimination. Eq. (2): Arylation example: d) benzene, $Pd(TFA)_2$, AgOAc, PivOH; e) $-H_\beta L$, –Pd(0).

ArPdL species to the C=C double bond and control the regiochemistry of the β-H elimination. Although such a chelation-assisted reaction has been studied extensively for the purpose of stereo- and regiocontrol, and multiple arylations;[4,5] however, most of the reactions involved the use of aryl halides or arylboronic acids instead of arenes.[4,5] Very recently, Pd-catalyzed oxidative Heck reactions of allyl esters have been reported with arenes and heteroarenes.[5d–g]

During our recent studies on Pd(II)-catalyzed oxidative couplings, we found that a C–H bond activation of an arene occurs very effectively under the influence of PivOH and AgOAc.[6] The conditions employing PivOH as a proton shuttle during the aryl C–H bond activation were originally developed by Fagnou[7a] and applied extensively for the C–H bond activation of arenes.[7b–j] Moreover, a carbopalladation of ArPdOPiv species onto the C=C double bond would occur readily by a chelation-assisted stabilization of the palladium center with a suitable DG.[4,5] With these points in mind, the reaction of methyl cinnamate derivative **1a** (DG = carbonyl group of a uracil moiety) and benzene was examined in the presence of $Pd(TFA)_2$, AgOAc, and PivOH. As shown in Scheme 1, tetrasubstituted olefin **2a** was obtained in an excellent yield (92%). The reaction of **1a** and PhPdOPiv gave the palladium intermediate **I**, and the palladium center of **I** was stabilized by the oxygen atom at the 2-position of a uracil moiety. The formation of this stabilized intermediate made the β-H_β a readily removable elimination partner among the three β-hydrogen atoms. The two remaining β-hydrogens inside the cycle are somewhat difficult to adapt the required *syn*-relationships with the palladium center.

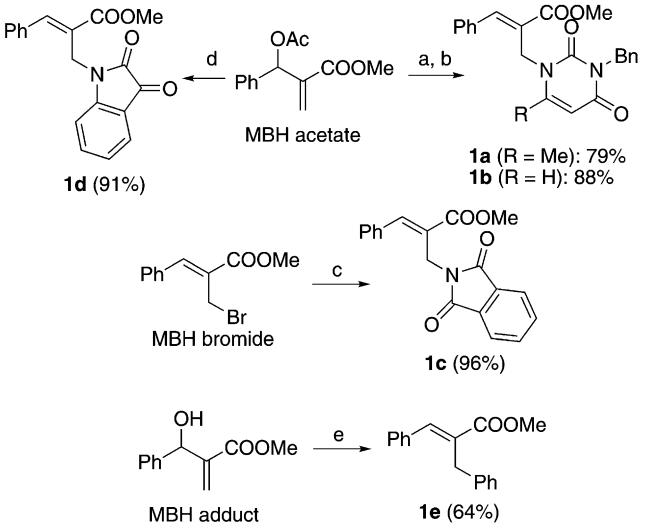
Although the initial result was quite satisfactory we examined the other reaction conditions including the use of other oxidants, and the results are summarized in Table 1. The use of $Pd(OAc)_2$ was less efficient (entry 2) than $Pd(TFA)_2$. The reaction without PivOH (entry 3) and the use of AcOH (entry 4) or CF_3COOH (entry 5) were not better. Replacement of AgOAc with other oxidants such as $Cu(OAc)_2$ or $K_2S_2O_8$ decreased the yield of **2a** (entries 6 and 7). Ag_2CO_3 was less efficient than AgOAc (entry 8). Based on the screening results, the original conditions (entry 1) were selected as an optimum ones.

The required starting materials **1a–e**, α-substituted methyl cinnamates, could be prepared readily from Morita–Baylis–Hillman (MBH) adducts.[8,9] Compounds **1a** and **1b** were prepared from the MBH acetate and 6-methyluracil or uracil, by an S_N2' type displacement reaction and a subsequent protection of NH with a benzyl group, as shown in Scheme 2.[9a,b] Phthalimide and isatin-bearing starting materials **1c** and **1d** were prepared similarly from the MBH bromide and acetate, respectively.[9b–e] Phenyl derivative **1e** was prepared by a Friedel–Crafts reaction with benzene from MBH adduct as reported.[9f]

Table 1. Optimization of reaction conditions for the conversion of **1a** to **2a**.[a]

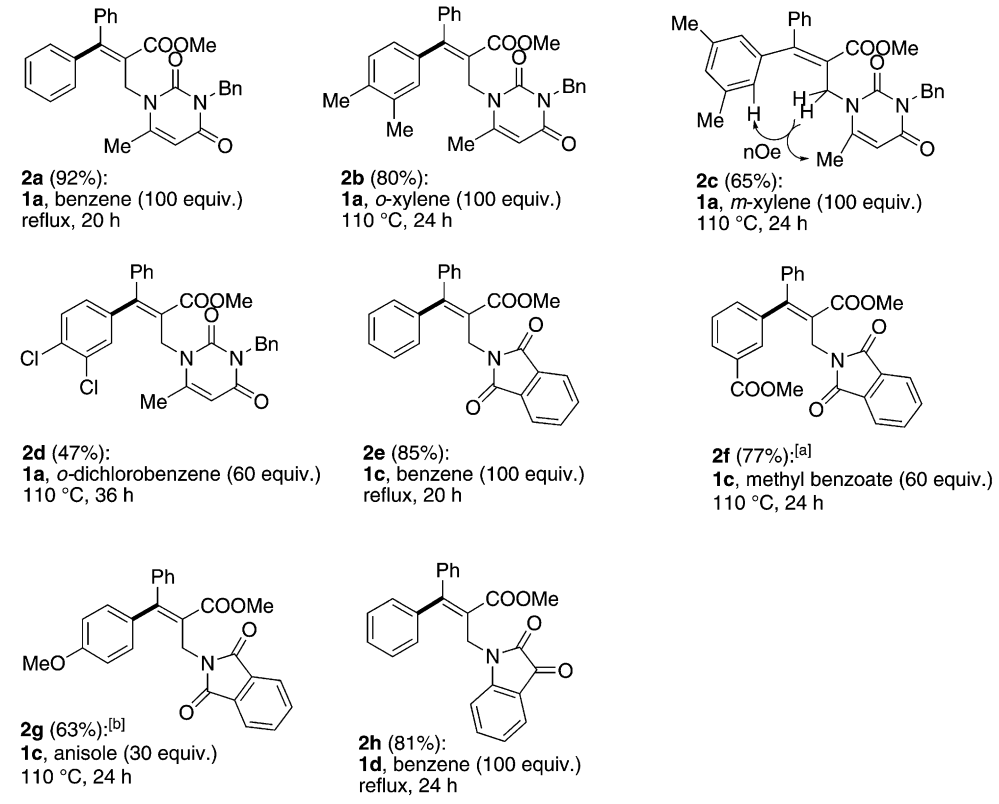
Entry	Catalyst[b]	Oxidant[c]	Additive[d]	Time [h]	Yield [%]
1	$Pd(TFA)_2$	AgOAc	PivOH	20	92
2	$Pd(OAc)_2$	AgOAc	PivOH	32	78
3	$Pd(TFA)_2$	AgOAc	none	24	75
4	$Pd(TFA)_2$	AgOAc	AcOH	24	81
5	$Pd(TFA)_2$	AgOAc	TFA	24	<5[e]
6	$Pd(TFA)_2$	$Cu(OAc)_2$	PivOH	32	32[e]
7	$Pd(TFA)_2$	$K_2S_2O_8$	PivOH	32	6[e]
8	$Pd(TFA)_2$	Ag_2CO_3	PivOH	32	68

[a] *Conditions:* benzene (100 equiv.), reflux.
[b] 5 mol%.
[c] 3.0 equiv.
[d] 6.0 equiv.
[e] Starting material **1a** was recovered in 62–87%.



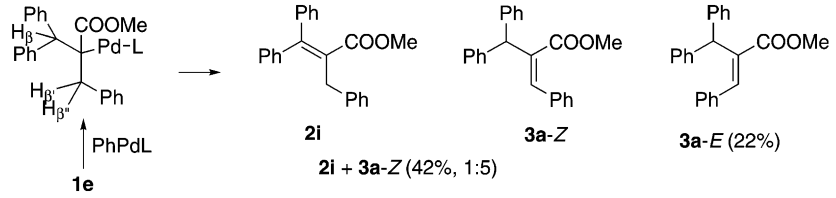
Scheme 2. Preparation of starting materials: a) 6-methyluracil, K_2CO_3, TBAB, DMF, 50 °C, 4 h, 56%; uracil, K_2CO_3, DMF, room temperature, 3 h, 81%; b) $PhCH_2Br$, K_2CO_3, DMF, room temperature, 3 h; c) potassium phthalimide, DMF, room temperature, 4 h; d) isatin, K_2CO_3, CH_3CN, room temperature, 24 h; e) benzene, H_2SO_4, reflux, 5 h.

With these starting materials, we examined the palladium-catalyzed oxidative arylations under the optimized reaction conditions, and the results are summarized in Figure 1, Scheme 3 and Scheme 4. Figure 1 shows the results obtained from the reactions of **1a**, **1c** and **1d**. Scheme 3 demonstrates the results obtained from the reaction of **1e**, and Scheme 4 describes the reaction of a uracil derivative **1b**. As shown in Figure 1, arylations of 6-methyluracil derivative **1a** with *ortho*-xylene and *meta*-xylene afforded **2b** and **2c** in good yields. It is interesting to note that the

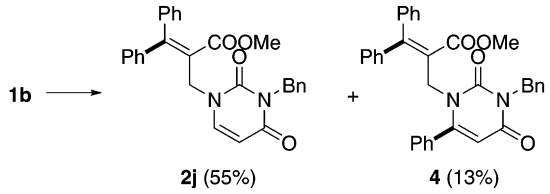


[a] Combined yield of *meta*-COOMe (54%) and *para*-COOMe (23%).
[b] Combined yield of *para*-OMe (50%) and *meta*-OMe (13%).

Figure 1. Palladium-catalyzed oxidative arylation. *Conditions:* substrate **1** (0.5 mmol), arene (30–100 equiv.), $Pd(TFA)_2$ (5 mol%), AgOAc (3.0 equiv.), PivOH (6.0 equiv.).



Scheme 3. *Conditions:* benzene, $Pd(TFA)_2$, AgOAc, PivOH, reflux, 20 h.



Scheme 4. *Conditions:* benzene, $Pd(TFA)_2$, AgOAc, PivOH, reflux, 20 h.

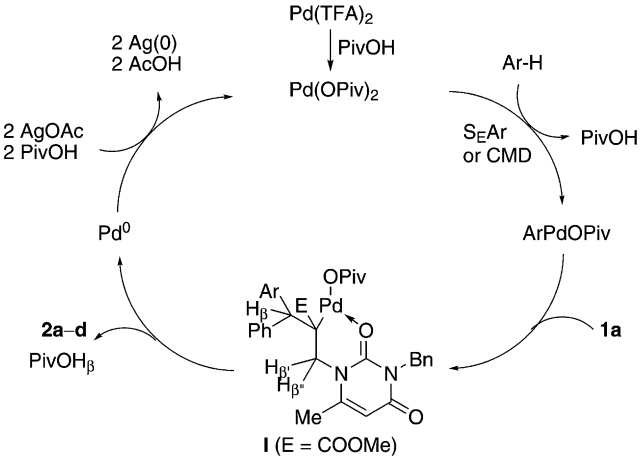
reaction of **1a** and *para*-xylene failed presumably due to the steric hindrance of the methyl group of *para*-xylene. A trace amount of the product was observed on TLC at the right position; however, we failed to isolate the compound in appreciable amounts. The reaction of **1a** and *ortho*-dichlorobenzene afforded **2d** in moderate yield (47%). During the synthesis of **2b–d** we did not observe the formation of any regioisomers. The reactions of phthalimide derivative **1c** with benzene, methyl benzoate, and anisole produced corresponding products **2e–g** in moderate to good yields (63–85%). The *meta*-isomer was formed as a major product (54%) along with a minor *para*-isomer (23%) with methyl benzoate, while *para*-isomer was formed as a major product with anisole. The observed regioselectivity with methyl benzoate and anisole suggested that aryl C–H activation might involve an electrophilic palladation (S_EAr) mechanism (*vide infra*).[2f–i,5d] The reaction of isatin derivative **1d** and benzene gave **2h** in good yield (81%).

In order to clarify the chelation effect of a DG in **1a**, **1c** and **1d**, we examined the reaction of phenyl derivative **1e** which does not have such a DG. As expected, three types of products were formed together, as shown in Scheme 3, due to three possible β-H eliminations. Actually, compound **3a**-*E* (22%) and a mixture of **2i**/**3a**-*Z* (42%, 1:5) were isolated. In addition, the combined yields (64%) of all products were lower than the case of **2a** (92%). The results stated that the formation of a stabilized palladium intermediate **I** (Scheme 1, *vide supra*) certainly controls the regiochemistry of the β-H elimination and facilitates the carbopalladation step of an arylpalladium intermediate at the same time.

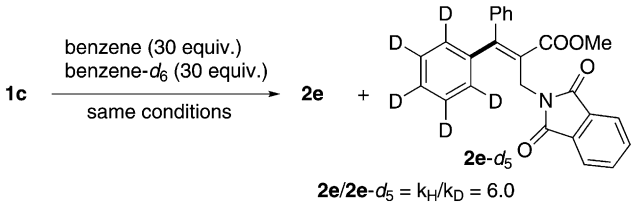
When we used uracil derivative **1b** as a starting material (Scheme 4), the phenylation occurred in moderate yield (68%, **2j**+**4**) at the benzylic position; however, further arylation at the 6-position of a uracil moiety occurred to some extent to give compound **4** (13%), as in our previous paper.[6a]

In order to check the possibility of a direct C–H activation of the vinyl hydrogen,[10] benzazepine derivative **5** was prepared as in our previous paper[9a] and examined in the reaction with benzene under the same reaction conditions, as shown in Scheme 5. No arylation product **6** was observed, and the result strongly suggested that the arylation of substituted methyl cinnamates might involve a typical oxidative Heck-type reaction involving a carbopalladation, rotation around C–C bond, and a β-H elimination process.

Thus, a plausible reaction mechanism could be suggested as shown in Scheme 6. An arylpalladium intermediate could be generated from arene and $Pd(OPiv)_2$ most likely *via* an electrophilic palladation (S_EAr) process.[2f–i,5d] However, a partial contribution of a concerted metalation-deprotonation (CMD) process cannot be ruled out completely at this stage based on the formations of **2c** and *meta*-**2g**.[2e,11] A subsequent carbopalladation of the arylpalladium intermediate to **1a** might produce the stabilized palladium intermediate **I**. As described above (Scheme 1, *vide supra*), selective β-H_β elimination would produce **2a**–**d**. The reduced Pd(0) was oxidized to Pd(II) by AgOAc and the Pd(II) carry out the catalytic cycle. Under the reaction conditions, no stereochemical mutation is observed, and the stereochemistry of the product obeyed that of the typical *syn* elimination process. As an example, the stereochemistry of **2c** was unequivocally confirmed with NOE experiments, as shown in Figure 1 (*vide supra*).



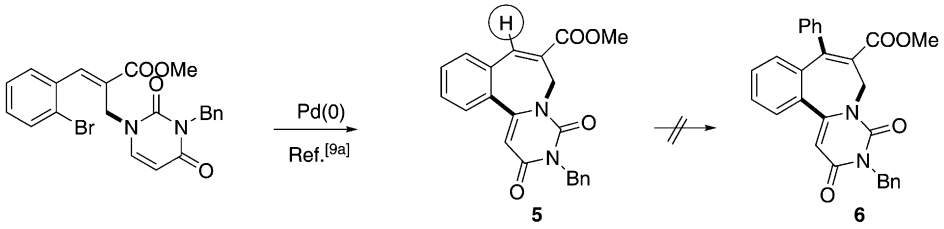
Scheme 6. Catalytic cycle of oxidative arylation.



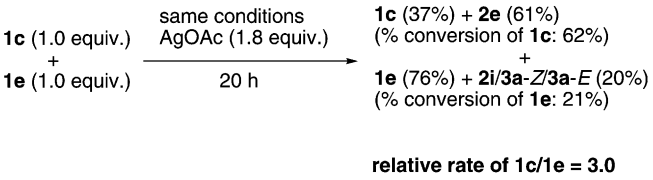
Scheme 7. Competitive arylation of **1c** with benzene and benzene-d_6.

In order to understand the mechanism more clearly, we carried out the reaction of **1c** in a mixed solvent of benzene/benzene-d_6 (1:1), as shown in Scheme 7. The reaction of **1c** and benzene showed a primary kinetic isotope effect, $k_H/k_D = 6.0$, which stated that the C–H (or C–D) bond cleavage of benzene is involved in the rate-limiting step.

In order to show the effect of a chelation for the rate increase in the reaction, we examined the reaction with a mixture of **1c** (with DG) and **1e** (without DG) in the presence of a limited amount of AgOAc (1.8 equiv.) under the same reaction conditions, as



Scheme 5. Attempted arylation of benzazepine **5**.



Scheme 8. The effect of DG in arylation rate.

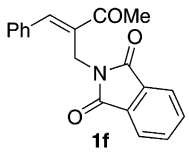
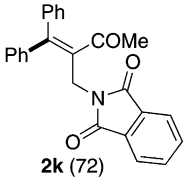
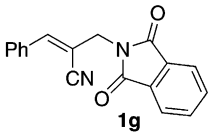
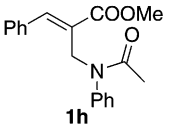
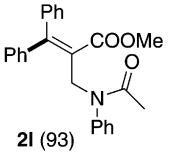
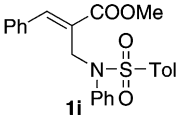
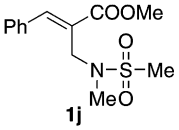
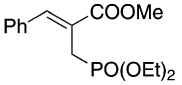
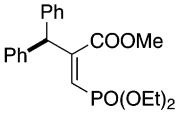
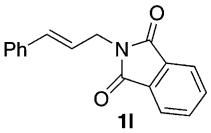
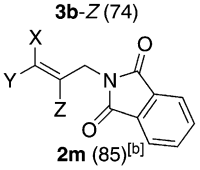
shown in Scheme 8. As expected, **1c** was converted to **2e** in 62% conversion yield while **1e** led to a mixture of arylated products in 21% yield. The results showed that the rate of arylation of **1c** is faster than that of **1e** by about three times, presumably due to a favorable chelation effect.

In order to check the scope of arylation, we examined the reactions with similar substrates **1f–l** (see the Supporting Information), as shown in Table 2. The reaction of acetyl derivative **1f** afforded **2k** (entry 1) in a moderate yield (72%); however, the reaction of nitrile derivative **1g** failed completely (entry 2) presumably due to the strong coordination of nitrile moiety to the electrophilic palladium species, $Pd(TFA)_2$ or $Pd(OPiv)_2$.[2g,i,12] The reaction of *N*-acetyl derivative **1h** afforded **2l** (entry 3) in good yield (93%). When we used *N*-phenyl-*N*-tosyl derivative **1i** (entry 4), the reaction was sluggish, and **1i** was recovered in appreciable amounts (27%) along with *N*-tosylaniline (63%) and a mixture of **3a**-*Z*/**3a**-*E* (60%). Thus, we prepared *N*-methyl-*N*-methanesulfonyl derivative **1j** in order to reduce the unfavorable steric factors and examined the reaction; however, the result was almost same as that of **1i**, and the formation of **3a**-*Z*/**3a**-*E* (64%) was observed again (entry 5). The reaction mechanism for the C–N bond cleavage of **1i** and **1j** is not clear at this stage. No reaction was observed with **1i** either without AgOAc or benzene. It is interesting to note that the reaction of phosphonate **1k** afforded alkenylphosphonate **3b**-*Z* (entry 6),[13] presumably due to the stabilizing conjugation effect between C=C and P=O bonds. As a last entry, the reaction of phthalimide derivative **1l** was examined (entry 7). The phenylation occurred at either site of the C=C double bond of **1l**, and **2ma** and **2mb** were obtained as a mixture (4:3) in 69% yield, along with some diphenyl compound **2mc** (16%).

In order to compare the reactivity of arylation using a typical Mizoroki–Heck reaction, the reaction of **1c** and iodobenzene was examined, as shown in Scheme 9. The reaction under the typical conditions (conditions a)[1g] did not produce **2e** in any trace amounts. The reason for the failure might be due to inefficient carbopalladation of PhPdI, because the palladium intermediate **II** bearing an iodide ligand is less stabilized by loose chelation. As reported in the literature,[1b,14] palladium intermediates bearing a pivalate or acetate ligand could dissociate readily to form a cationic palladium intermediate and form a tightly-chelated palladium intermediate (**III** and/or **IV**). Thus we used AgOAc as a base in order to strengthen the chelation by exchanging the iodide to acetate (conditions b).[1b] As expected, compound **2e** was obtained in moderate yield (51%). However, the yield was lower than our optimized yield of **2e** (85%) using benzene as an arene source.

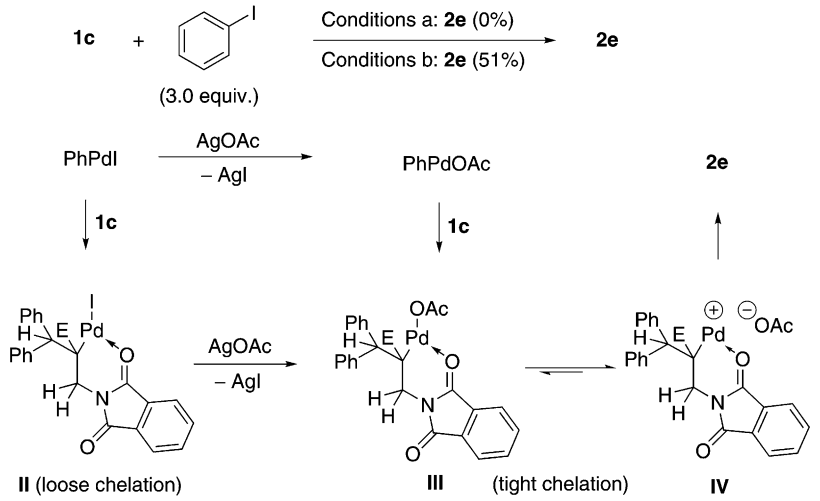
The other stereoisomers of **2b–d**, **2f** and **2g** could also be prepared by simply altering the reaction sequence. As an example, compound **2g**-*Z* (a stereoisomer of **2g**) was prepared from the MBH bromide of *p*-anisaldehyde by introduction of phthalimide to

Table 2. Chelation-assisted phenylation of various alkenes.[a]

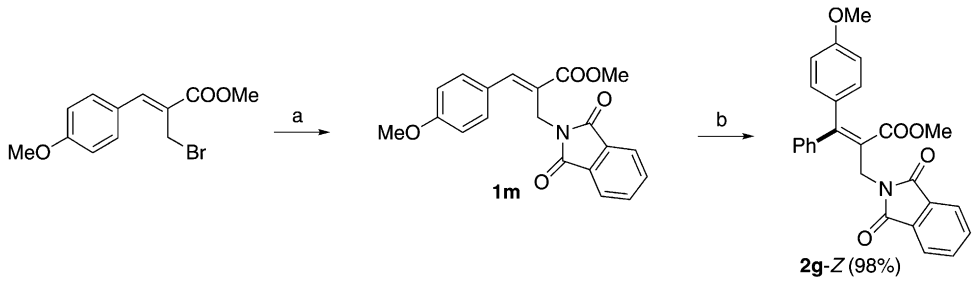
Entry	Substrate	Product [%]
1	 **1f**	 **2k** (72)
2	 **1g**	No reaction
3	 **1h**	 **2l** (93)
4	 **1i**	**3a**-*Z* + **3a**-*E* (60)
5	 **1j**	**3a**-*Z* + **3a**-*E* (64)
6	 **1k**	 **3b**-*Z* (74)
7	 **1l**	 **2m** (85)[b] **2ma**: X = Y = Ph, Z = H **2mb**: X = H, Y = Z = Ph **2mc**: X = Y = Z = Ph (16)

[a] *Conditions:* substrate (0.5 mmol), $Pd(TFA)_2$ (5 mol%), AgOAc (3.0 equiv.), PivOH (6.0 equiv.), benzene (100 equiv.), 24 h.

[b] Reaction time was 7 h, and **2ma** and **2mb** were separated as a mixture (69%, **2ma**:**2mb** = 4:3).



Scheme 9. Arylation of **1c** with iodobenzene. *Conditions a:* $Pd(OAc)_2$ (10 mol%), P(*o*-tol)$_3$ (20 mol%), $NaHCO_3$ (2.5 equiv.), TBAB (1.1 equiv.), DMF, 130 °C, 30 h. *Conditions b:* $Pd(OAc)_2$ (5 mol%), AgOAc (2.0 equiv.), HOAc, 110 °C, 6 h.



Scheme 10. Synthesis of **2g**-*Z*: a) potassium phthalimide, DMF, room temperature, 12 h, 88%; b) benzene, $Pd(TFA)_2$, AgOAc, PivOH, reflux, 12 h.

make **1m** and a subsequent phenylation, as shown in Scheme 10.

In summary, we have documented the synthesis of fully-substituted methyl cinnamate derivatives *via* a Pd(II)-catalyzed, chelation-assisted oxidative Heck arylation protocol in a completely stereo- and regioselective manner. The stereo- and regioselective outcome as well as excellent yields of products were originated from the stabilization of a palladium intermediate by a chelation between the palladium center and a directing group.

Experimental Section

Typical Procedure for the Synthesis of 2a

A stirred mixture of **1a** (195 mg, 0.5 mmol), $Pd(TFA)_2$ (8 mg, 0.025 mmol), AgOAc (250 mg, 1.5 mmol) and PivOH (306 mg, 3.0 mmol) in benzene (3.9 g, 50 mmol) was heated to reflux under nitrogen atmosphere for 20 h. After cooling to room temperature, the reaction mixture was filtered over a pad of Celite and washed with CH_2Cl_2 (100 mL). The filtrates were washed with a saturated solution of $NaHCO_3$ (20 mL × 3), and the organic layer was dried over $MgSO_4$. After removal of solvent and a column chromatographic purification process (hexanes/Et_2O, 1:2) compound **2a** was isolated as a white solid; yield: 214 mg (92%). No special equipment and precautions were required throughout the whole experiments.

Acknowledgements

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