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Synthesis of α,β-unsaturated aryl esters via Heck reaction of unsymmetrical aryl tellurides

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ABSTRACT

A variety of α,β-unsaturated aryl esters were prepared by the direct reaction of unsymmetrical aryltellurides and ethyl acrylate, catalyzed by $PdCl_2$ via a Heck cross-coupling reaction.

1. Introduction

The importance of palladium-catalyzed coupling reactions is reflected in the numerous reports on their development and applications, which have revolutionized synthetic efforts toward the construction of carbon–carbon bonds in complex organic structures that are pursued today in both academia and industry.[1]

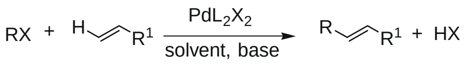
Along with other known cross-coupling reactions, including Kumada and Corriu, Negishi, Migita, and Kosugi, Stille, Sonogashira, Suzuki–Miyaura, and others, the Heck reaction is a very convenient protocol for forming carbon–carbon bonds at unsaturated vinylic positions.[2] This reaction allows for the direct coupling of activated arenes and olefins with an unactivated alkene through palladium catalysis via a formal C–H activation, creating a σ-bond between two sp^2 carbon centers[3] (Scheme 1).

A relevant feature of the Heck reaction is that one can obtain good results with a broad variety of olefins bearing different functional groups.[4] The most important of these olefins are the electron-deficient substrates.

Chalcogenide compounds have become attractive synthetic targets because of their chemo-, regio-, and stereoselective reactions.[5] They are used in the presence of a wide variety of functional groups, thus avoiding the need for protecting group chemistry and useful biological activities.[6] In this line, many classes of organotellurium compounds have been prepared and studied to date. Aryl tellurides are certainly useful and promising compounds in view of their utility in organic synthesis.[7] Numerous methodologies have been reported for the preparation of these compounds.[5d,7b–d] However, limited synthetic methods have been reported for the synthesis of unsymmetrical diaryl tellurides. In recent years, transition-metal-catalyzed reactions of diaryl dichalcogenides with aryl halides or boronic acids have become versatile tools for the synthesis of unsymmetrical diaryl chalcogenides.[8] Recently, Taniguchi described the preparation of numerous unsymmetrical organotellurides by reaction of organoboronic acids with ditellurides via copper-catalyzed cleavage of a Te–Te bond.[8a]

Uemura et al. found that diphenyltellurium(IV) dichloride reacted with a variety of olefins in the presence of a catalytic amount of $PdCl_2$ together with NaOAc in HOAc to afford the corresponding arylated (*E*)-olefins in variable yields (3–98%).[9] A suitable oxidant such as *tert*-butyl hydroperoxide or copper(I) or (II) chloride had to be added for the reaction to proceed catalytically with palladium. The stereoselectivity was very high, except for with acrylonitrile (*Z*/*E* 26:74). Transmetalation of tellurium with palladium was suggested as the key step in the reaction. Alternatively, diaryltellurides can be used as arylating agents for a variety of olefins in the presence of Et_3N as base and AgOAc as oxidant.[10]

Kamigata and co-workers used aryldimethyltellurium iodides for palladium-catalyzed Heck-type reactions with electron-deficient olefins and styrene in the presence of a stoichiometric amount of silver(I) acetate.[11] For the telluronium salt partner, the best results were obtained when the aryl moiety bore electron-donating substituents at the *para* position; those at the *ortho*



X = I, Br, OSO_2CF_3
Solvent = MeCN, HMPA, *N*-Methylpyrrolidine, MeOH
Base = Et_3N, R_2NH, NaOAc, KOAc, Na_2CO_3/H_2O

Scheme 1.

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position retarded the reaction. The yields were good to excellent, although a threefold excess (with respect to the olefin) of the expensive silver acetate was needed for the anion exchange and oxidation steps in the catalytic cycle.

Unsymmetrical diaryltellurides can be prepared from alkali tellurides and non-activated aryl halides, sodium telluride or potassium tellurocyanate and arenediazonium fluoroborates, tellurium(IV) halides, and arylmagnesium halides, or elemental tellurium and diarylmercury compounds.[12]

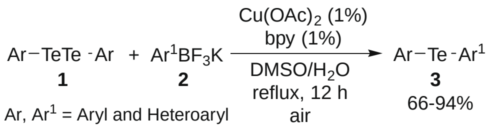
Potassium organotrifluoroborate salts have been developed as a superior class of nucleophilic coupling reagents in terms of their stability and functional group tolerance as compared to those of the corresponding boronic acids or boronate esters.[13,14] They have been successfully employed as useful synthetic intermediates in palladium-catalyzed cross-coupling reactions,[15] in rhodium-catalyzed conjugate additions,[16] and in the allylation of aldehydes[17] and *N*-toluenesulfonylimines.[18] Organotrifluoroborate salts also have the inherent advantage of being commercially available, quite air stable, and easily isolated. They show enhanced reactivity in some cases compared to that of other organoboron compounds.[19]

2. Results

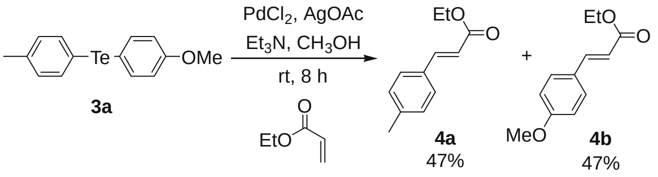
The unsymmetrical diaryltellurides starting materials were prepared in good to excellent yields through the reaction of diarylditellurides[20] with potassium aryltrifluoroborate salts bearing electron-withdrawing, electron-donating, and neutral substituents, using a catalytic amount of $Cu(OAc)_2$ and bypiridine in $DMSO/H_2O$ at reflux under an air atmosphere.[17,21] (Scheme 2).

We started our investigations by testing catalysts to evaluate their ability to promote the cross-coupling Heck reaction of (4-methoxyphenyl)(*p*-tolyl)telluride with ethyl acrylate (Scheme 3).

The yield of both products was high when the reaction was performed with $Pd_2(dba)_3$ (42%/48%, Table 1, entry 2). Similar results were obtained with $Pd(OAc)_2$ and Pd PEPPSI (44%/40% and 45%/42%, respectively, Table 1, entries 3 and 5). Better yields were obtained when the reaction was performed using Pd(dppf), $PdCl_2$(benzonitrile), and $PdCl_2$ (49%/40%, 48%/42%, and 44%/49%, respectively, Table 1, entries 4, 6, and 8). Since the yields were high, we chose to work with $PdCl_2$ because of its availability in our laboratory and its efficiency in the reaction. Unfortunately, no reaction was observed in the absence of catalyst or in presence of a $Fe(acac)_3$ catalyst.

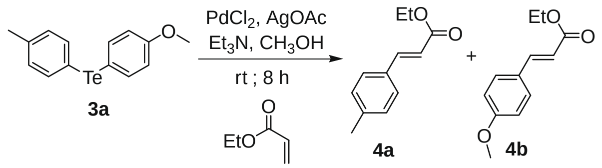


Scheme 2.



Scheme 3.

Table 1
Screening of catalysts for the Heck reaction



Entry	Catalyst	Yields % **4a**/**4b**
1	No catalyst	nr
2	$Pd_2(dba)_3$	42/28
3	$Pd(OAc)_2$	44/40
4	Pd(dppf)	49/42
5	Pd PEPPSI	45/42
6	$PdCl_2$(benzonitrile)	48/42
7	$Fe(acac)_3$	nr
8	$PdCl_2$	44/49

To optimize the reaction conditions, we evaluated the dependence of the arylation of ethyl acrylate with diaryl telluride on the nature of the base. Inorganic bases such as K_2CO_3, CS_2CO_3, Na_2CO_3, and NaOAc gave 72%/20%, 65%/20%, 60%/31%, and 51%/38% yields, respectively, of products **4a** and **4b**. Of the bases tested, Et_3N gave the best result (47%/47% yield of products I and II).

To get more information on optimal reaction conditions, we carried out investigations to define the best solvent for this transformation. Apolar solvents such as toluene, dichloromethane, and 1,4-dioxane all gave poor yields of compounds **4a** and **4b** (12%/4%, 25%/13%, and 19%/18%, respectively). DME afforded a moderate yield (46%/34%) of products **4a** and **4b**. When protic polar solvents, such as methanol and ethanol, were used, the yields were high, giving the desired products **4a** and **4b** in 47%/47% and 50%/41%, respectively.

After identifying the most efficient catalyst, solvent, and base for the cross-coupling Heck reaction of aryl tellurides and ethyl acrylate, we decided to explore the scope of this process[22] with a variety of different aryl tellurides (Table 2). As can be seen in the following table, a large array of *ortho*-, *para*-, or *meta*-substituted (e.g., –OMe, –Me, –Cl, –F, and $–CF_3$) aryl tellurides underwent the coupling reaction, giving the desired α,β-unsaturated aryl esters in good to excellent yields.

The reactions of the substrates with electron-donating substituents such as methyl and methoxy groups on the aryl group afforded the products **4R** and **4R**^{1} in 50%/44%, 47%/40%, 55%/44%, and 61%/31% yields (Table 2, entries 4, 5, and 8, respectively). In the case of electron-withdrawing substituents such as F or Cl, very good yields were also achieved, with 44%/37%, 43%/56%, 71%/25% yields for compounds **4R** and **4R**^{1}, respectively (Table 2, entries 3, 6 and 9). In general, reaction yields were not severely affected by the electronic influence of the groups connected to the aromatic ring. In no example was isomerization of the carbon–carbon double bond observed.

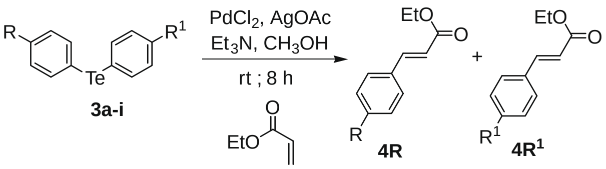
To further investigate the scope and limitations of this methodology, we carried out the cross-coupling of unsymmetrical aryltellurides with two different α,β-unsaturated carbonyl compounds, as summarized in Table 3.

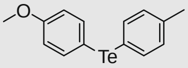
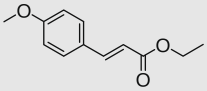
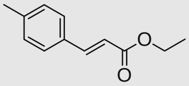
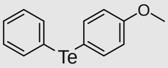
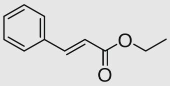
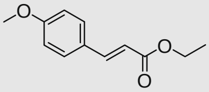
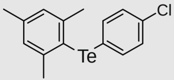
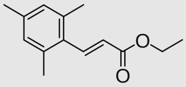
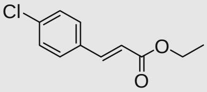
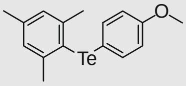
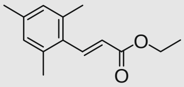
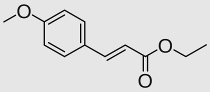
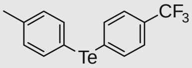
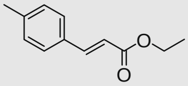
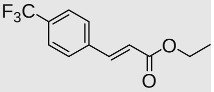
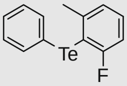
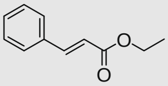
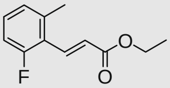
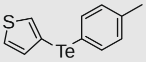
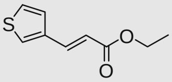
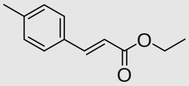
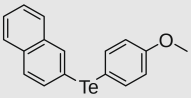
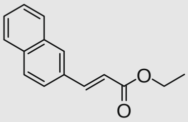
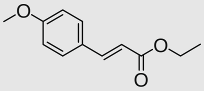
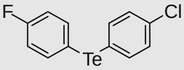
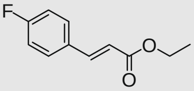
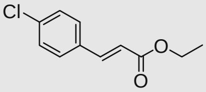
Both compounds (**5R** and **5R**^{1}) were obtained in low to good yields.

3. ESI-MS(/MS) mechanistic investigation

Electrospray ionization mass spectrometry (ESI-MS and its tandem version ESI-MS/MS) has recently been incorporated as a suitable technique for mechanistic studies of organic and inorganic

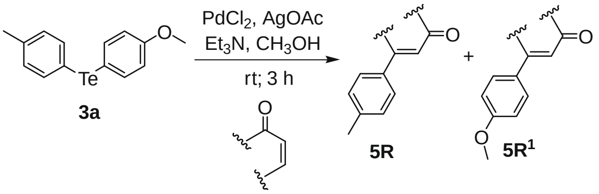
Table 2
Heck reaction of unsymmetrical aryl tellurides with ethyl acrylate

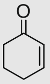
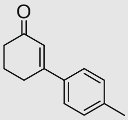
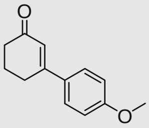
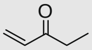
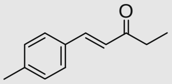
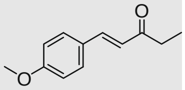


Entry	Aryl telluride	Product **4R** (%)	Product **4R**^{1} (%)
1	 **3a**	 **49 (4a)**	 **44 (4a^1)**
2	 **3b**	 **50 (4b)**	 **44 (4b^1)**
3	 **3c**	 **44 (4c)**	 **37 (4c^1)**
4	 **3d**	 **47 (4d)**	 **40 (4d^1)**
5	 **3e**	 **55* (4e)**	 **44* (4e1)**
6	 **3f**	 **43* (4f)**	 **56* (4f^1)**
7	 **3g**	 **13**	 **72**
8	 **3h**	 **61 (4h)**	 **31 (4h^1)**
9	 **3i**	 **71 (4i)**	 **25 (4i^1)**

[*] Not separable mixture.

Table 3
α,β-Unsaturated carbonyl compounds



Entry	α,β-Unsaturated carbonyl	Product **5R** (%)	Product **$5R^1$** (%)
1		 **30 (5a)**	 **11 ($5a^1$)**
2		 **51 (5b)**	 **32 ($5b^1$)**

reactions. Its usefulness arises mainly from its outstanding ability to ‘fish’, with high sensitivity and gentleness, ionic or ionized intermediates directly from the reaction solutions and into the gas phase,[23] providing therefore continuous snapshots of the composition of reaction solutions.[24]

To scrutinize the catalytic cycle for the reaction investigated herein, we monitored via ESI-MS(/MS) the cross-coupling of aryl tellurides with olefins promoted by $Pd(OAc)_2$. We first studied the reaction of **1** with ethyl acrylate in the presence of $Pd(OAc)_2$. In the ESI-MS (Fig. 1), a series of cationic species were detected and some ions were identified as key reaction species, that is, those of *m/z* 313, 344, and 450.

The ion of *m/z* 344 is the ionized reactant $1^{+\bullet}$, whereas species of *m/z* 313 and *m/z* 450 are key reaction intermediates. The ion *m/z* 450 results from Pd insertion into the Te–Ar bond and its oxidative addition to the olefin forms the key intermediate of *m/z* 313. Structures were corroborated via characteristic Pd/Te multi-isotopic patterns and via ESI-MS/MS. For instance, the collision-induced dissociation (CID) of the ion of *m/z* 313 involves substantial molecular rearrangement, which enables the loss of the final product **4a**

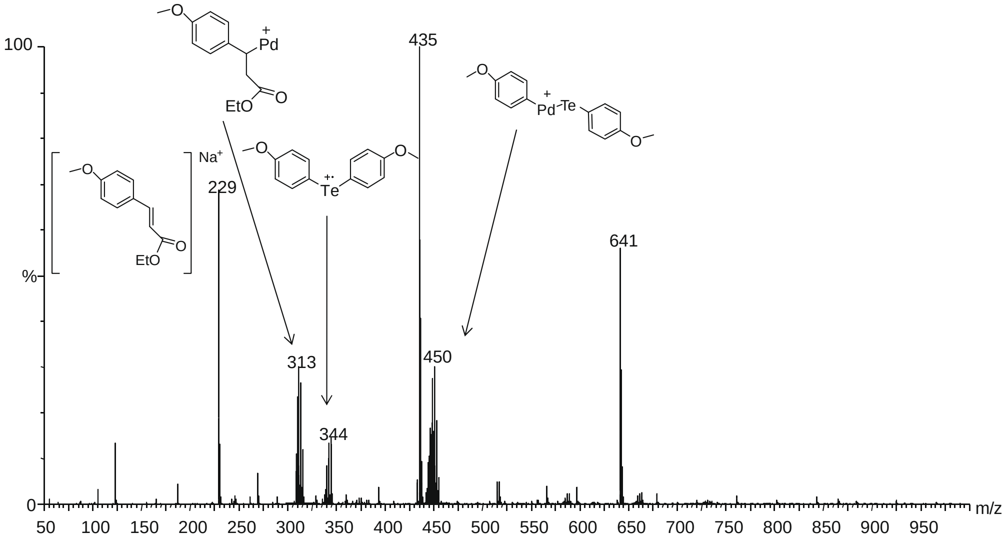


Figure 1. ESI(+)-MS of the reaction solution of aryl telluride with ethyl acrylate after 1 h.

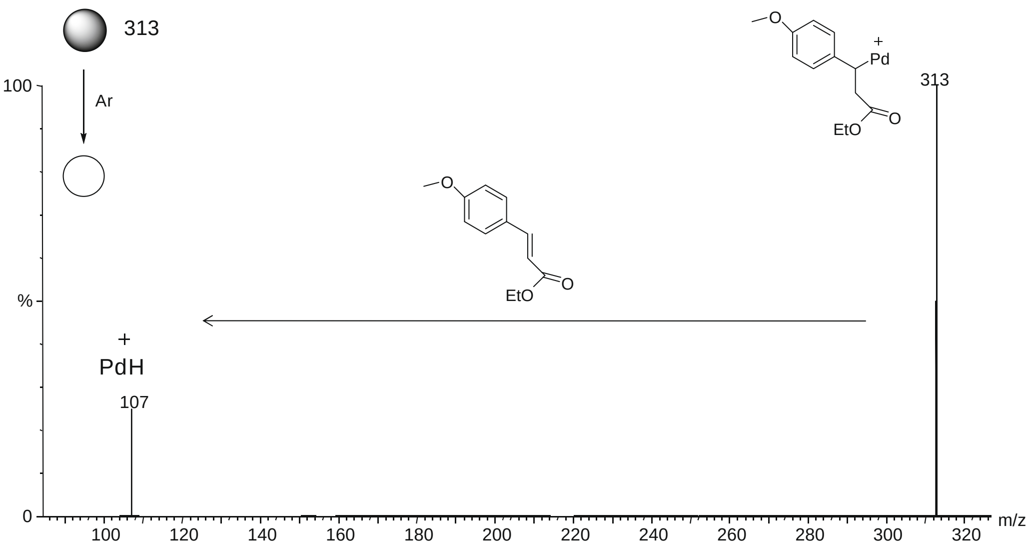
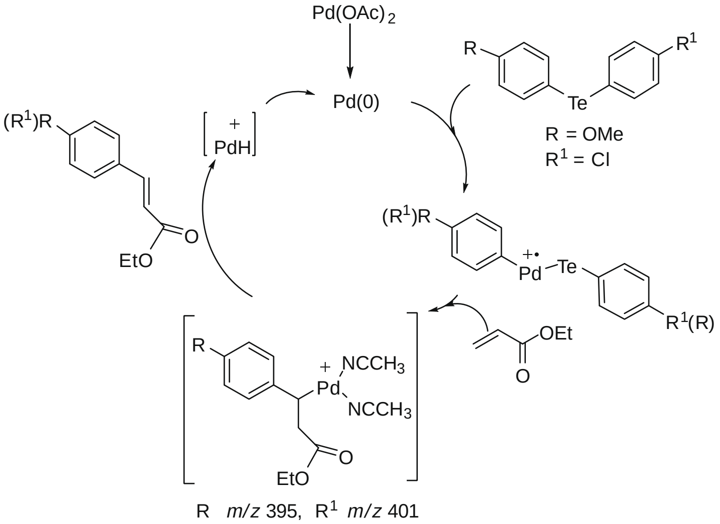


Figure 2. ESI-MS/MS for the key intermediates of *m/z* 313.



Scheme 4. Proposed mechanism for the palladium-catalyzed Heck reaction of aryl telluride with ethyl acrylate, with key intermediates intercepted by ESI-MS and characterized by ESI-MS/MS.

as a neutral molecule thus yielding the fragment ion PhH^+ of *m/z* 107.

When the reaction of the unsymmetrical **2** was monitored, two key cationic palladium species of *m/z* 395 and 400 (Fig. 3), analogous to that of *m/z* 313, were detected by ESI-MS now as the MeCN adducts. They dissociated extensively upon CID via ESI-MS/MS to form ions of *m/z* 354 and 359 by MeCN loss, and subsequently to form an ion of *m/z* 189 after loss of the final Heck products (see supporting information).

With the ESI-MS(/MS) data in hand, we rationalize a mechanism for the palladium-catalyzed Heck reaction with tellurides (Scheme 4). The first step is an oxidative insertion of Pd(0) into the telluride, forming an arylpalladium telluride species which was intercepted and detected by ESI-MS as its molecular ion. This intermediate then undergoes carbopalladation of the olefin double bond (**1**) to yield a Pd cationic intermediate (*m/z* 313 or *m/z* 395 and 401). These species then undergo β-elimination of PdH to yield the final cross-coupling products, and a similar process occurs under CID (Fig. 2). PdH is reduced to Pd(0) in the presence of base (carbonate). The fade of TeAr species is still unclear since no late Te-intermediates could be detected.

In summary, we have shown that tellurium can be a good electrophilic alternative to the halides that are traditional in the cross-coupling Heck reaction. Further studies associated with other species containing tellurides as electrophilic partners in the Heck reaction are currently in progress.

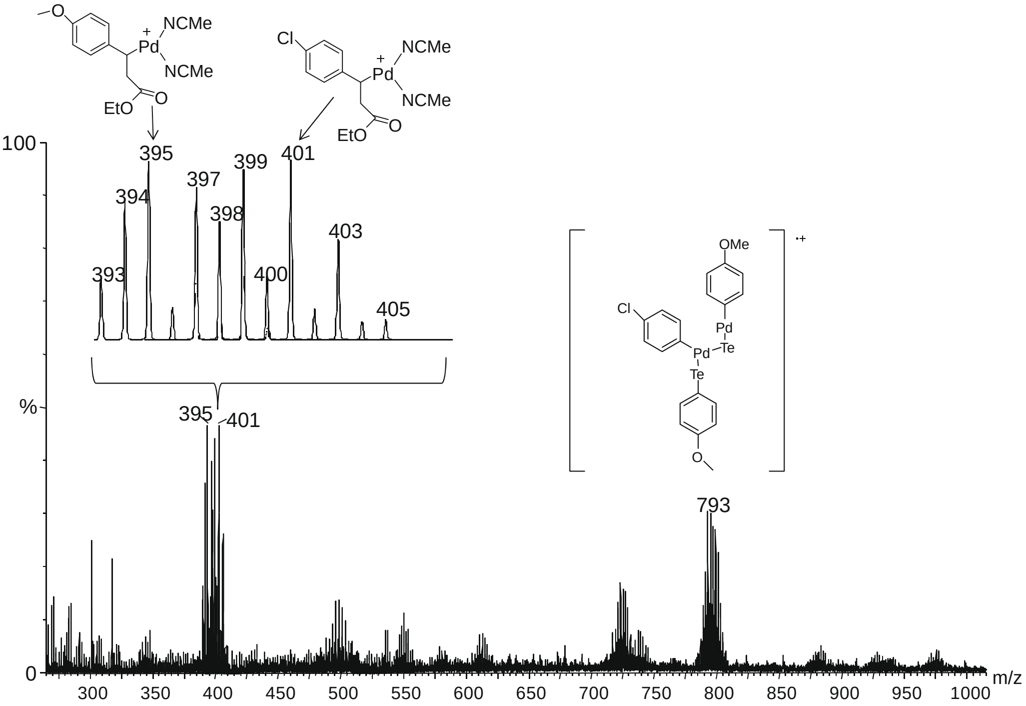


Figure 3. ESI(+)-MS for the reaction solution of aryl telluride with ethyl acrylate acquired after 1 h.

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21. *General procedure for the cross-coupling reaction of diaryl ditellurides with potassium aryltrifluoroborates*: To a round-bottomed flask containing diaryl ditelluride (0.25 mmol), potassium aryltrifluoroborate salt (0.5 mmol), $Cu(OAc)_2$ (1 mol %), and bpy (1 mol %) were added DMSO (1 mL) and H_2O (0.5 mL). The reaction mixture was allowed to stir at reflux for 12 h. After this time, the solution was cooled to room temperature, diluted with dichloromethane (20 mL), and washed with saturated aqueous NH_4Cl (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. Selected spectral and analytical data for *p-methoxyphenyl-p-tolyl-telluride* **3a**: Yield: 0.146 g (90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.8 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 3.80 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.64, 140.36, 137.25, 137.02, 130.10, 115.26, 111.21, 103.48, 54.96, 20.96. MS (relative intensity) m/z: 328 (28), 198 (100), 183 (74), 155 (25), 91 (23), 65 (17). HRMS calcd for $C_{14}H_{14}OTe$: 328.0107. Found: 328.0111.
22. *General procedure for the Heck cross-coupling reaction of unsymmetrical diaryl telluride* **3a** *with ethyl acrylate*: Into a two-necked 25-mL round-bottomed flask containing $PdCl_2$ (0.05 mmol), AgOAc (2.00 mmol), and unsymmetrical diaryl telluride **3a** (0.50 mmol) were added dry methanol (10 mL), Et_3N (2.00 mmol), and ethyl acrylate (1.00 mmol). After the heterogeneous reaction mixture had been stirred at 25 °C for 8 h, the solid part was filtered. The filtrate was poured into brine (60 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The

residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. Selected spectral and analytical data for *(E)-Ethyl 3-(4-methoxyphenyl)acrylate* (**4a**): ^{1}H NMR (300 MHz, CDCl$_3$): 1,34 (t, J = 6,12 Hz, 3H); 2,35 (s, 1H); 4,23 (q, J = 6, 54 Hz); 6,37 (d, J = 15,99 Hz, 1H); 7,17 (d, J = 7,92 Hz, 1H); 7,40 (d, J = 7,89 Hz, 1H); 7,64 (d, J = 15,96 Hz, 1H). ^{13}C NMR (125.8 MHz, CDCl$_3$): 14,10; 19,56; 60,26; 119,09; 126,12; 129,71; 130,54; 133,21; 137,40; 142,06; 166,85. CG/MS: m/z (%) 190 (25); 175 (3,6); 162 (12); 145 (100); 131 (8,8); 115 (46,5); 102 (5); 91 (21,8); 65 (12,4); 51 (5,7). *(E)-Ethyl 3-p-tolylacrylate* (**4b**): ^{1}H NMR (300 MHz, CDCl$_3$): 1,32 (t, J = 7,0 Hz, 3H); 3,8 (s, 3H); 4,24 (q, J = 7,14 Hz, 2H); 6,30 (d, 15,96 Hz, 1H); 6,88 (d, 2H); 7,47 (d, 2H); 7,63 (d, 15,96 Hz, 2H). ^{13}C NMR (125.8 MHz, CDCl$_3$):14,12; 55,13; 60,09; 114,07; 115,53; 126,98; 129,44; 161,09; 167,11. CG/MS: m/z (%) 206 (64,4); 191 (2,1); 178 (10,9); 161 (100); 147 (5,4); 134 (49,9); 118 (11,8); 103 (5,8); 89 (14,7); 77 (13,8); 63 (10).

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