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A Scalable High-Yielding and Selective Oxidative Heck Cross-Coupling – A Key Step for the Synthesis of *trans*-Stilbenes

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A selective oxidative Heck cross-coupling method was developed and optimized as a pivotal step for a synthetic route leading to the *trans*-stilbene framework. The developed method and synthesis were needed in a SAR study in progress that concerned design and development of an inhibitor for the human cell xCT antiporter system. The developed oxidative Heck cross-coupling method was examined with a variety of substrates and reagents to produce a library of different substituted *trans*-stilbenes, which revealed the method to hold a very good tolerance for an assortment of functional groups. The final synthetic route was successfully scaled-up (from mg scale) and performed in a 150 g (>1000× up-scaled) batch run to obtain an overall yield of 73% (over three steps), which corresponds to a mean step yield of 90%. The inhibitor candidate **DC10** [(*E*)-5-(2-([1,1′-biphenyl]-4-yl)vinyl)-2-hydroxybenzoic acid] was produced in multi-gram quantities (≈33 g) that subsequently was forwarded for animal efficacy and toxicology studies. The scaled-up process constitutes the first example of an oxidative Heck cross-coupling on >100-gram scale.

Introduction

Stilbene is an ubiquitous molecular framework of an assorted selection of molecules for various applications areas across the field of the chemical science.[1] The stilbenes moiety are present as an integral part of natural products such as phytoalexins,[2] in anticancer drugs[3] and in synthetic dyes.[4] Due to their importance and versatility, series of various chemical strategies and methods have been developed for their synthesis, including Aldol-type condensation,[5] Wittig reactions,[6] Stille,[7] Negishi,[8] and Heck cross-coupling reactions,[9,10] olefin cross metathesis,[11,12] and McMurry reactions[13,14] constitutes an assortment of methods that can be used for the synthesis of the *trans*-stilbene framework.

For a SAR study devoted to the design and development of an inhibitor for the xCT antiporter,[15] we needed access to various substituted (*E*)-2-hydroxy-5-styrylbenzoic acid derivatives. All the above said methods were attempted, but none operated satisfactory with the variety of reagents and substrates we wanted to convert into their corresponding stilbene derivatives. Further screening revealed an oxidative Heck cross-coupling method that afforded our target molecular scaffold in moderate yield. This method was subjected to investigation and optimization. A concise scope and limitation study was also carried through.[16] One of our more promising xCT antiporter inhibitor candidates (**DC10**) was then subjected for a full development where all steps in the synthesis (four steps) were elaborated and scaled up >1000×(150 g scale) in a batch run.

Results and Discussion

Explorative synthetic route

The medicinal chemistry route leading to **DC10** is outlined in Scheme 1. The first step involves a protection of the free hydroxy group of 3-bromo-4-hydroxy-benzaldehyde **1**. This step was carried through by using chloromethyl methyl ether (MOM–Cl) to obtain 3-bromo-4-(methoxymethoxy)-benzaldehyde **2**, which in the next step was subjected to a Wittig reaction[17] where the aldehyde group was transformed into a vinyl group to afford 2-bromo-1-(methoxy-methoxy)-4-vinylbenzene **3**. The subsequent step comprised an oxidative Heck cross coupling method developed and adapted that made use of a boronic acid **5** as reagent, affording 2-bromo-1-(methoxymethoxy)-4-vinylbenzene **4** in high yield. Subsequently, a palladium-catalyzed hydroxyl carbonylation afforded target stilbene **DC10** needed in our medicinal chemistry project.[16]

Overall, the medicinal chemistry route was designed as a short linear synthesis using affordable reagents, to obtain the following overall yields (η) of **preDC10** and **DC10**, respectively [Eqs. (1) and (2)]:

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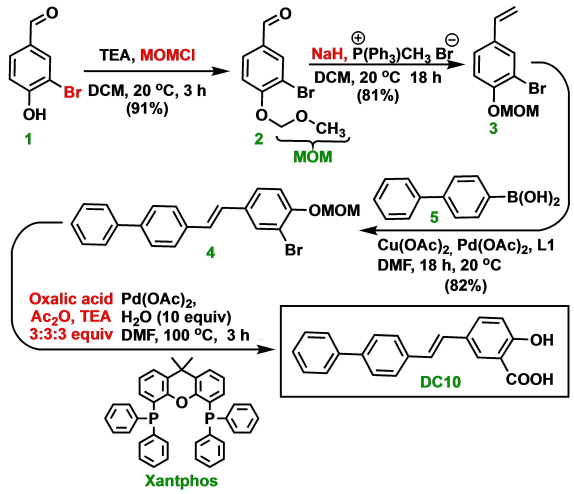


Scheme 1. Medicinal chemistry route for the synthesis of **DC10**. The chemicals in red color represents the challenges/issues for the scale-up.

$$\eta_{\text{preDC10}} = 100 \times \prod_{p=1}^{p} \frac{n_p^o}{n_p^i} = 100 \times (0.91 \times 0.81 \times 0.82) \approx 60\% \quad (1)$$

$$\eta_{\text{DC10}} = 100 \times \prod_{p=1}^{p} \frac{n_p^o}{n_p^i} = 100 \times (0.91 \times 0.81 \times 0.82 \times 0.46) \approx 28\% \quad (2)$$

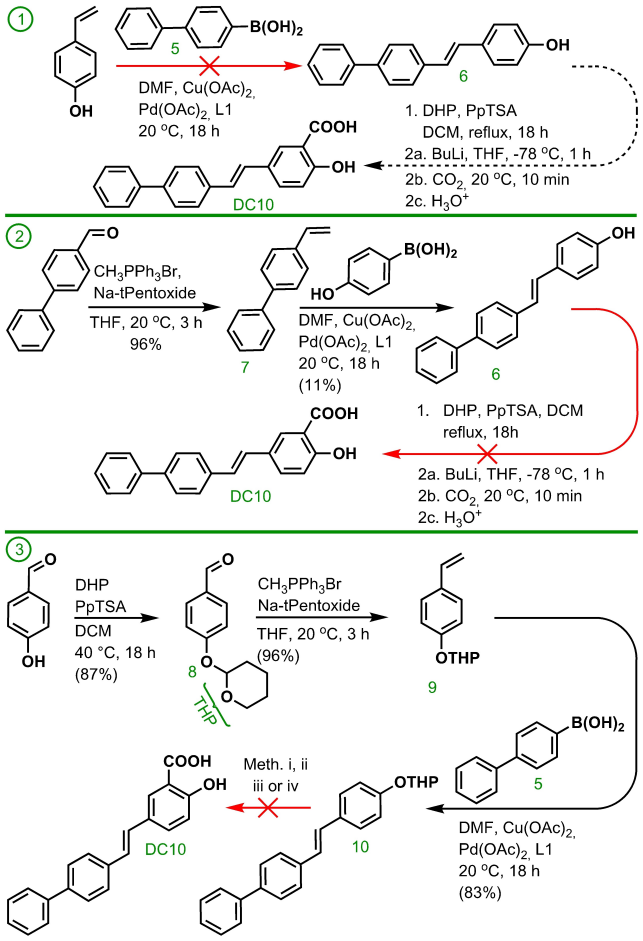
The excellent selectivity and the high yield obtained in the oxidative Heck cross-coupling reaction (step 3) were in particular noteworthy.[18] In the following, these results and findings were taken into account for a plan for a scaled-up (multi-gram) process. However, from a process chemistry point of view, some drawbacks were identified for the medicinal chemistry route, namely: (1) MOM–Cl is difficult to get access to in consistent quality on a large scale. The deprotection step gives rise to production of hazardous by-products (formaldehyde and derivatives),[19] (2) NaH and CO are hazardous compounds, (3) for three of four synthetic steps, the purification of reaction products was accomplished by means of chromatography, and (4) in green chemistry terms: when a bromide is present in a reagent or substrate as a leaving group, imply a lower atom economy of the actual reaction step. By means of an *ortho*-lithiation, a similar reaction can be conducted.[20]

An assessment of the methods used in the medicinal chemistry synthetic route revealed several challenges for the scale-up synthesis. In particular, the MOM protective group can be replaced by the chemical analogue THP, and in place of the dangerous base NaH, the safer sodium *tert*-pentoxide might be an alternative.[21] The palladium catalyzed hydroxyl carbonylation[22] can be replaced by the cheaper, safer, and the less environmentally harmful *ortho*-lithiation followed by carboxylation,[23] which avoids the need of aryl bromide. In this assessment, efforts were also made to avoid the use of chromatography in the purification and preparation of the various intermediates and target product.

Synthetic route improvement

Synthetic step 1 of Scheme 2 was the shortest among the three sketched synthetic routes. This synthetic route encompasses an oxidative Heck cross-coupling reaction and a carboxylation step. Unfortunately, target stilbene scaffold was not obtained after the oxidative Heck cross-coupling reaction that might be due to the presence of propylene glycol that is the solvent in which 4-vinylphenol is dissolved when supplied from the manufacturer.[24]

Synthetic route 2 of Scheme 2 involved an oxidative Heck cross-coupling reaction produces 4-vinyl-1,1′-biphenyl **7** that was obtained from a Wittig reaction step, using (4-hydroxyphenyl)boronic acid under identical conditions as for the Heck cross-coupling reaction used in the medicinal chemistry route.

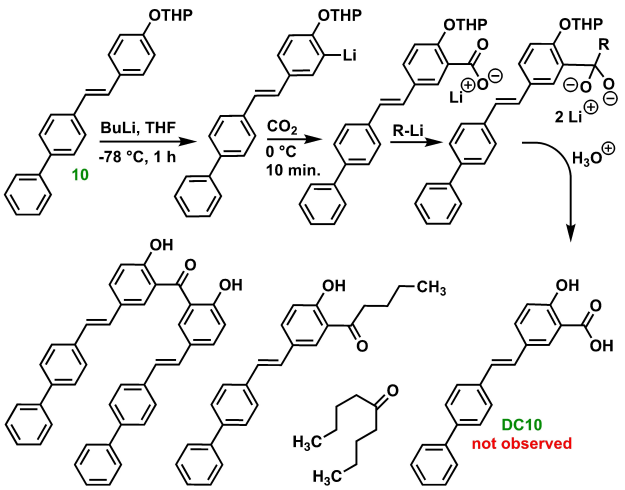


Scheme 2. Development synthetic routes. Method i: a) BuLi, –78 °C, THF, 1 h; b) CO_2, 10 min, 20 °C, c) H_3O^+; Method ii: a) BuLi, –78 °C, THF, 1 h; b) DMF (10 eq.), 1 h, 20 °C, c) H_3O^+, d) $NaClO_2$, NH_2SO_3H, NaH_2PO_4, THF-H_2O, 20 °C, 30 min. e) H_3O^+; Method iii: a) $POCl_3$, DMF, 20 to 80 °CC, 1 to 10 h; b) H_3O^+, c) $NaClO_2$, NH_2SO_3H, NaH_2PO_4, THF-H_2O, 20 °C, 30 min. d) H_3O^+; Method iv: a) HCl (aq), DMF, 40 °C, 18 h, b) $MgCl_2$, TEA, para-formaldehyde, ACN, 80 °C, on, c) $NaClO_2$, NH_2SO_3H, NaH_2PO_4, THF-H_2O, 20 °C, 30 min; d) $H_3O.^+$

After extraction and crystallization from toluene, the intermediate (*E*)-4-(2-([1,1′-biphenyl]-4-yl)vinyl) phenol **6** was isolated in a yield of 11% only. The poor yield, we assumed might be due to interactions with the free phenolic group. Further investigations of this synthetic pathway were therefore abandoned.

Synthetic route 3 of Scheme 2 involved a starting material for the oxidative Heck cross-coupling reaction that comprised a THP-protected 4-hydroxy benzaldehyde (compound **8**) to avoid the free phenol during the oxidative Heck cross-coupling reaction. The protected benzaldehyde was then subjected for a Wittig reaction to produce the styrene **9**. The steps 1–3 of route 3 afforded target intermediate **10** in an overall yield of 61%.

Encouraged by the realization of the first three synthetic steps, the final *ortho*-lithiation step was attempted to be implemented. However, the *ortho*-lithiation followed by carboxylation (method i) was not successful. The reaction did not take place when BuLi (1.6 M n-Butyllithium in hexanes) and CO_2 were investigated at different temperatures (–78 °C→20 °C). Various side-products were observed suggesting that once that CO_2 is sparged into the mixture, the carboxylate is formed, but it further reacts with an organolithium species to afford ketonic side-products, Scheme 3. This happens not only with the starting material, but also with BuLi, which after carboxylation and reaction with another BuLi affords nonan-5-one. Small quantities (< 5%) of **DC10** were detected when a solution of compound **10** and BuLi was transferred to a flask containing a large excess of dry ice. We assume that the formation of the ketones is due to the carbonylated intermediate bearing Li^+ as counterion, which has only one positive charge that does not prevent the reaction with other organolithium species, Scheme 3. It was postulated that an organo-magnesium reagent would avoid this issue. However, when *i*-PrMgClLiCl was employed, only the starting material was recovered, probably because it was not sufficiently basic to deprotonate the desired aromatic carbon.[25]



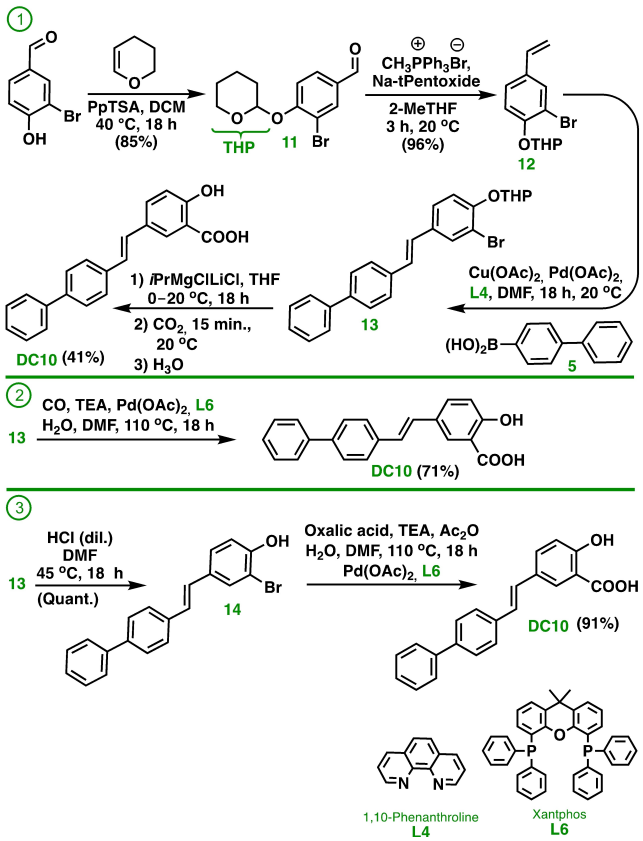
Scheme 3. During the carboxylation, target **DC10** was not observed. GC-MS and LC–MS revealed however two different ketones.

After the failed direct carboxylation, different approaches involving the insertion of an aldehyde followed by oxidation to carboxylic acid were evaluated. These methods either involved the *ortho*-lithiation followed by reaction with DMF (method ii), the Vilsmeier-Haack Reaction[26] with $POCl_3$ and DMF (method iii), or a phenol deprotection, followed by the *ortho*-formylation with *para*-formaldehyde, $MgCl_2$ and TEA[27] (method iv).

In these strategies, the oxidation to carboxylic acid would have been carried out through a Pinnick oxidation;[28] however, the aldehyde was never formed.

Multi-gram scale synthesis

The last step proved to be challenging without a halide in the *ortho*-position. Therefore, despite the original plan involved the C–H activation without a halide installed, the bromide in the *ortho*-position proved to be strictly necessary for the successful synthesis of the desired product. Consequently, we decided to perform both the *ortho*-metalation followed by carboxylation and palladium-catalysed hydroxyl carbonylation in presence of a bromide on the starting material. Both methods worked on a hundred-milligram scale. Therefore, this synthetic route was established as the multi-gram scale synthesis and each synthetic step were optimized, Scheme 4.



Scheme 4. Up-scaled synthetic route.

THP as protective group (PG)

Protection of 3-bromo-4-hydroxybenzaldehyde **1** was carried out under inert and anhydrous conditions[29] using a series of solvents (DCM, 2-MeTHF, 1,4-dioxane, acetonitrile, and toluene), whereof DCM was the only solvent that afforded satisfactory yield. Furthermore, different catalysts were studied and PpTSA (Pyridinium *p*-Toluenesulfonate) proved to be the optimal in these conditions giving satisfactory yields both at 5-and 10 mol-%. The work-up involved a simple basic extraction in the same reactor in order to transfer unreacted starting material and the acid catalyst to the water phase.

The oxidative Heck cross-coupling reactionWittig reaction

The benzaldehyde **11** was subjected to the Wittig reaction conditions using methyltriphenyl-phosphonium bromide as methylene source, sodium *tert*-pentoxide as base, and 2-methyl-THF as solvent. The reaction mixture was stirred at 20 °C for 3 h.

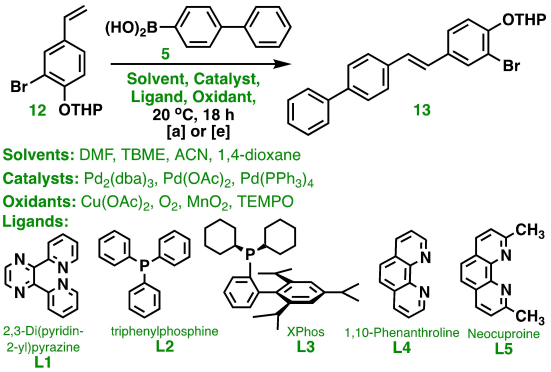
However, the purification and elimination of triphenylphosphoxide (TPPO) proved to be a challenging task. With the aim to avoid chromatography for this undertaking, various strategies were attempted for the removal of the by-product TPPO. Recently in the literature, the formation of insoluble adducts of TPPO with Lewis acids have been described.[30] In our investigation, the optimal removal of TPPO has been obtained by stirring the reaction crude in a mixture of nonpolar solvents (heptane: toluene = 90:10) in presence of 1.5 equiv. of anhydrous $MgCl_2$ at 20 °C for 18 h. In these conditions, the insoluble TPPO-$MgCl_2$ adduct was formed and removed through filtration.

The C–C bond formation leading to target *trans*-stilbene scaffold is crucial in the synthesis of **preDC10** and **DC10** and stilbenes in general. A series of experimental variables that included type of solvent, catalyst, ligand, and oxidant were investigated with the goal to establish whether: (1) the solvent DMF used in the medicinal chemistry synthetic route, could be replaced by a solvent with a lower boiling point and more easily to remove from the reaction product, (2) the reaction operates with different Pd catalysts, (3) the ligand **L1** could be substituted with another and cheaper ligand, and (4) $Cu(OAc)_2$ could be replaced by other oxidants that allow a simpler work-up and thus offer a reduced environmental footprint.

The reaction conditions for the oxidative Heck cross-coupling reaction were screened (Table 1). The solvent screening included the solvents DMF, TBME, ACN, and 1,4-dioxane, whereof only experiments conducted in DMF afforded high yield. Type of catalyst [$Pd_2(dba)_3$, $Pd(OAc)_2$, and $Pd(PPh_3)_4$] proved also to be crucial for the outcome.

Pd(0) catalyst afforded poor yields compared with Pd(II) catalyst, whereof $Pd(OAc)_2$ afforded the highest yield in addition to be the cheapest of the catalyst we investigated. 1,10-Phenanthroline-like ligands (**L1**, **L4**, **L5**) afforded good yields in comparison with the phosphine ligands (**L2**, **L3**). The ligand **L4** phenanthroline was chosen as it afforded the highest yield, as well as it is the cheapest among the investigated ligands (**L1**–**L5**).

Table 1. Investigation of the reaction conditions for the oxidative Heck cross-coupling reaction step.



#	Solvent	Catalyst	Ligand	Oxidant	Yield [%][d]
1	DMF	$Pd(OAc)_2$	**L1**	$Cu(OAc)_2$	95
2	TBME	$Pd(OAc)_2$	**L1**	$Cu(OAc)_2$	2
3	ACN	$Pd(OAc)_2$	**L1**	$Cu(OAc)_2$	35
4	1,4 Dioxane	$Pd(OAc)_2$	**L1**	$Cu(OAc)_2$	32
5[b]	DMF	$Pd(OAc)_2$	**L1**	$Cu(OAc)_2$	7
6	DMF	$Pd(PPh_3)_4$	**L1**	$Cu(OAc)_2$	4
7	DMF	$Pd_2(dba)_3$	**L1**	$Cu(OAc)_2$	17
8	DMF	$Pd(OAc)_2$	**L2**	$Cu(OAc)_2$	0
9	DMF	$Pd(OAc)_2$	**L3**	$Cu(OAc)_2$	0
10	DMF	$Pd(OAc)_2$	**L4**	$Cu(OAc)_2$	95
11	DMF	$Pd(OAc)_2$	**L5**	$Cu(OAc)_2$	95
12	DMF	$Pd(OAc)_2$	**L4**	O_2 (Baloon)	87
13	DMF	$Pd(OAc)_2$	**L4**	MnO_2	11
14	DMF	$Pd(OAc)_2$	**L4**	TEMPO	7
15[c]	DMF	$Pd(OAc)_2$	**L4**	$Cu(OAc)_2$	0

[a] General reaction conditions: Styrene **12** (0.1 mmol), Ligand (5%), Catalyst (5%), **5** (1.5 equiv.), oxidant (1.2 equiv.) in 1 mL of solvent stirred for 18 h at 20 °C. [b] $Cu(OAc)_2$ was added before $Pd(OAc)_2$. [c] Pinacol boronic ester was used in the place of the corresponding boronic acid. [d] Measured by means of ^{1}H NMR using DMTP (Dimethyl terephthalate) as internal standard. [e] Final procedure: 2-(2-Bromo-4-vinylphenoxy) tetrahydro-2*H*-pyran **12** (0.1 mmol), Ligand (**L4**) (5%), oxidant ($Cu(OAc)_2$ 1.2 equiv.) catalyst ($Pd(OAc)_2$ 5%), reagent [1,1′-biphenyl]-4-ylboronic acid **5** (1.5 equiv.), in 1 mL of solvent (DMF) was stirred for 18 h at 20 °C. The oxidant $Cu(OAc)_2$ should be added before the catalyst $Pd(OAc)_2$.

Furthermore, a series of oxidants comprising ($Cu(OAc)_2$, O_2, MnO_2, and TEMPO) were examined. At ambient temperature (20 °C), only $Cu(OAc)_2$ and O_2 afforded quantitative conversion of the styrene substrate **12**. $Cu(OAc)_2$ was chosen because it is safer and thus simpler to handle at larger scale. In addition, the order of addition of the reagents was revealed to affect the course of the reaction. In fact, the reaction did not take place if $Cu(OAc)_2$ was added after $Pd(OAc)_2$. Moreover, if pinacol ester was used in the place of the boronic acid, the reactions did not proceed.

The purification of the reaction product was performed by adding a water solution of EDTA to precipitate target stilbene scaffold.

DMF was then removed whereupon Cu-catalyst was filtered off. Afterwards, the crude was washed with different solvent to achieve the pure compound **13** without any other isomers present.

Scope of the oxidative Heck cross-coupling reaction

The developed method as a small-scale procedure was used for the synthesis of a series of *trans*-stilbenes bearing a variety of functional group, Table 2, from which three different vinylic compounds (**12a–c**) were prepared and reacted with the boronic acids (**5**, **5a–e**).

Target stilbenes **13a, c–f** were obtained reacting the styrenes (**12a–c**) with the boronic acids (**5**, **5a–e**) to obtained excellent selectivity and yields (80–89%). The achieved results prove the developed oxidative Heck cross-coupling to be a robust and high yielding method with respect to variation in the substituents.

Carboxylation

Method A

From route C, we observed that neither BuLi nor *i*PrMgClLiCl operated for the carboxylation. However, according to the literature,[31] an exchange Br-Metal could avoid the formation of undesired side products. The reaction was performed using 1 mmol of the starting material with either BuLi or with *i*PrMgClLiCl. Using the organolithium base, no product was observed, whereas with the organomagnesium base, a yield of 41% of target product was obtained. Attempt to scale-up (10 mmol) this reaction step, a yield of only 8% of target product was isolated.[31]

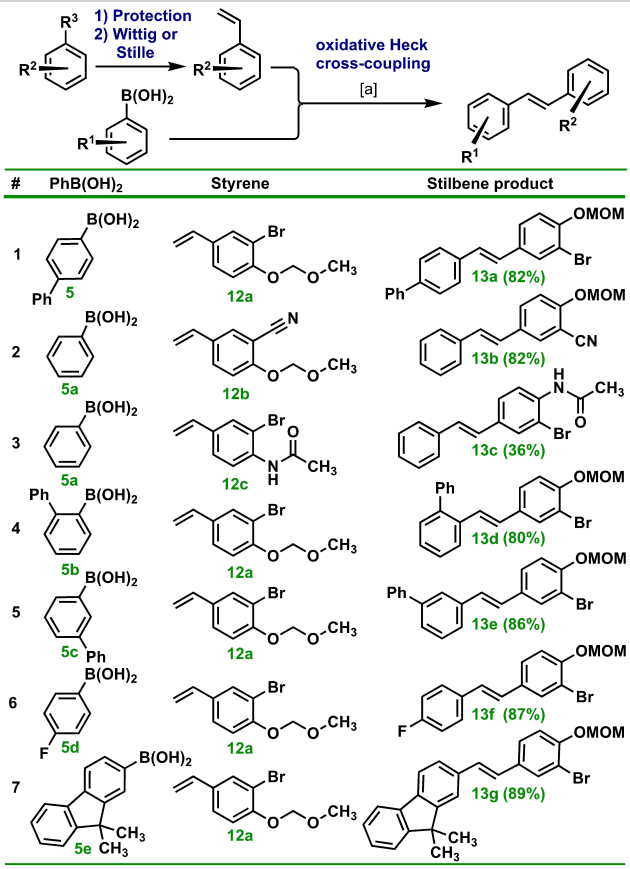
Method B

Since our attempt to scale-up the approach using CO_2 failed, we had to consider other alternative methods. In this context, a palladium-catalysed hydroxyl carbonylation involving gaseous CO was implemented (unfortunately, we could not fulfil the goal of entry 4 of Table 1). With the aim of developing a method that works with an increased quantity of substrate, the hydroxyl carbonylation was performed by using a Parr reactor system. With this technology, we could in a safe and successful way perform the carbonylation reaction at a high CO gas pressure to achieve target product was in a yield of 71%. The purification of target product involved extraction with acidic water and then precipitation of the pure product **DC10** in acetone.

Method C

Despite the good results achieved with Method B, an further improved outcome was achieved by performing a deprotection and then a hydroxyl carbonylation by means of oxalic acid degradation as a CO source in presence of Ac_2O and TEA.[32] This strategy afforded a yield of 91% over two steps. The purification was performed as described for method B. Table 2. Scope of the oxidative Heck cross-coupling reaction using the small-scale procedure.

Table 2. Scope of the oxidative Heck cross-coupling reaction.



[a] General reaction conditions: Vinylbenzene (2.81 mmol), 2,3-di(pyridin-2-yl)pyrazine (5%), $Pd(OAc)_2$ (5%), boronic acid (1.1 equiv.), $Cu(OAc)_2$ monohydrate (1.5 equiv.) in DMF (10 mL) stirred for 18 h at 20 °C.

Conclusion

The developed oxidative Heck cross-coupling method was assessed with a selection of substrates and reagents to produce a small library of different substituted *trans*-stilbenes, which exposed a good tolerance for an assortment of functional groups.

Target stilbene **DC10** was achieved via a four-step synthesis in an overall yield of ≈52% without the employment of chromatography. The valuable precursor **13** was obtained by means of a three-step synthesis in a yield of ≈73%. **DC10** can be synthesized by means of three various synthetic pathways. The formation of the Grignard salt followed by carboxylation, will be optimal for the synthesis of [^{11}C] **DC10**; the in situ formation of CO (using formic acid in the place of oxalic acid). The multi-gram scale synthesis of **DC10** employed the method involving CO.

Furthermore, the oxidative Heck cross-coupling method was scaled-up (150 g) that afforded excellent selectivity and yield (91%).

Experimental Section

Details Explorative synthetic route

3-Bromo-4-(methoxymethoxy)benzaldehyde 2 [162269-90-1]. 3-Bromo-4-hydroxybenzaldehyde **1** (7.0 g, 34.82 mmol) was transferred to a reaction flask and dissolved in DCM (25 mL) at 20 °C. TEA (1.5 equiv., 5.28 g, 7.3 mL, 52.23 mmol) was then added followed by (after 10 min.), chloromethyl methyl ether (1.5 equiv., 4.21 g, 3.97 mL, 52.23 mmol). The reaction mixture was stirred for 18 h at 20 °C. The reaction experiment was monitored by TLC, using as eluent hexane/ethyl acetate 9:1. The post-reaction mixture was extracted with DCM (3×200 mL) from acid water. The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain target compound 2 as a yellow oil in a yield of 91% (8.15 g, 33.26 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.09 (d, J = 2.0 Hz, 1H), 7.79 (dd, J = 8.5, 2.0 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 5.35 (s, 2H), 3.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.55, 158.42, 134.47, 131.45, 130.81, 115.06, 113.33, 94.79, 56.62.

2-bromo-1-(methoxymethoxy)-4-vinylbenzene 3 [NEW]. NaH 60% (3 equiv., 3.92 g, 97.93 mmol) was added to a mixture of methyltriphenylphosphonium bromide (1.5 equiv., 17.49 g, 48.97 mmol) in DCM (25 mL) that was stirred for period of 30 min. 3-Bromo-4-methoxybenzaldehyde (**2**) (8.00 g, 32.64 mmol) was then added to the reaction mixture and stirred for another 18 h at 20 °C. The reaction experiment was monitored by means of TLC, using hexane:ethyl acetate = 9:1 as eluent. The reaction experiment was quenched using a saturated solution of Na_2CO_3. This mixture was extracted with DCM (3×200 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure using a rotary evaporator. The mixture was purified using a small chromatography column filled with silica gel (eluent hexane:ethyl acetate = 95:5). Target compound **3** was obtained as a transparent oil in a yield of 81% (6.43 g, 26.45 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 2.1 Hz, 1H), 7.27 (dd, J = 8.5, 2.2 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.60 (dd, J = 17.6, 10.9 Hz, 1H), 5.64 (d, J = 17.3 Hz, 1H), 5.24 (s, 2H), 5.20 (d, J = 10.7 Hz, 1H), 3.52 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.29, 134.95, 133.10, 130.91, 126.39, 115.97, 113.57, 113.05, 95.11, 56.39.

(*E*)-4-(3-bromo-4-(methoxymethoxy)styryl)-1,1′-biphenyl 4 [NEW]. 2-Bromo-1-(methoxymethoxy)-4-vinylbenzene **3** (500 mg, 2.81 mmol), 2,3-di(pyridin-2-yl)pyrazine (5%, 33 mg, 0.140 mmol), $Pd(OAc)_2$ (5%, 32 mg, 0.140 mmol), compound 5 (1.1 equiv., 611 mg, 3.09 mmol), $Cu(OAc)_2$ (1.5 equiv., 764 mg, 4.21 mmol) were transferred to a round bottom flask and dissolved in DMF (10 mL). The reaction mixture was stirred for 18 h at 20 °C. The reaction experiment was monitored by means of TLC, using hexane:ethyl acetate = 9:1 as eluent. The post-reaction mixture was extracted with DCM (3×100 mL) from an EDTA water solution (0.2 M). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The mixture was purified using a small chromatography column packed with silica gel (eluent hexane/ethyl acetate 99.6:0.4). Target compound **4** was obtained as a white solid in a yield of 82% (910 mg, 2.30 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 2.1 Hz, 1H), 7.63–7.52 (m, 6H), 7.44 (dd, J = 10.6, 4.8 Hz, 2H), 7.38 (dd, J = 8.5, 2.2 Hz, 1H), 7.37–7.32 (m, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.02 (s, 2H), 5.26 (s, 2H), 3.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.20, 140.64, 140.42, 136.15, 132.89, 131.05, 128.83, 127.96, 127.39, 127.37, 126.93, 126.89, 126.74, 126.73, 116.14, 113.28, 95.14, 56.43.

(*E*)-5-(2-([1,1′-biphenyl]-4-yl)vinyl)-2-hydroxybenzoic acid DC10 [NEW]. Oxalic acid (3 equiv., 63 mg, 759 μmol), $Pd(OAc)_2$ (5%, 3 mg, 13 μmol), Xantphos (5%, 7 mg, 13 μmol), 4 (100 mg, 167 μmol), H_2O (10 equiv., 45 mg, 45 μL, 2.53 mmol) were transferred to a reactor tube and suspended in DMF (3 mL). The reactor tube was sealed and immersed in a preheated oil bath at 100 °C where the mixture was gently stirred. TEA (3 equiv., 77 mg, 106 μL, 759 μmol) was then added. Ac_2O (3 equiv., 77 mg, 74 μL, 759 μmol) was then added by means of a syringe pump over a period of 15 min. During the addition CO was formed through oxalic acid degradation. It is advisable to add a balloon to the sealed vial in order to avoid problems with the increasing pressure. The reaction mixture was stirred at 100 °C for 3 h. The reaction mixture was then poured into a separatory funnel containing DCM and water. The water phase was adjusted at a pH 12 and extracted with DCM (3×50 mL). Then the water phase was adjusted at pH 1 and extracted with DCM (3×50 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain target product **DC10** as a white solid in a yield of 46% (37 mg, 117 μmol). ^{1}H NMR (500 MHz, DMSO) δ 8.01 (d, J = 2.2 Hz, 1H), 7.84 (dd, J = 8.7, 2.3 Hz, 1H), 7.73–7.66 (m, 6H), 7.51–7.43 (m, 2H), 7.39–7.34 (m, 1H), 7.31 (d, J = 16.5 Hz, 1H), 7.19 (d, J = 16.5 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 171.72, 160.69, 139.64, 138.88, 136.38, 133.08, 128.92, 128.51, 128.50, 127.43, 127.40, 126.86, 126.84, 126.40, 126.31, 117.65, 113.20. HR-MS (ESI): $[M-H]^-$: Calcd for $C_{21}H_{15}O_3$ 315.10212, found 315.10201.

Developed synthetic route

(*E*)-4-(2-([1,1′-biphenyl]-4-yl)vinyl)phenol 6 [288589-35-5]. Compound **7** (653 mg, 3.63 mmol), 2,3-di(pyridin-2-yl)pyrazine (5%, 42 mg, 0.18 mmol), $Pd(OAc)_2$ (5%, 41 mg, 0.18 mmol), (4-hydroxyphenyl)boronic (1 equiv., 500 mg, 3.63 mmol), $Cu(OAc)_2$ (1.5 equiv., 988 mg, 5.44 mmol) were transferred to a round bottom flask and dissolved in DMF (10 mL). The reaction mixture was stirred for 18 h at 20 °C. The reaction experiment was monitored by means of TLC, using hexane/ethyl acetate 9:1 as eluent. The post-reaction mixture was extracted with DCM (3×100 mL) from a solution EDTA in water (0.2 M). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The desired compound 6 (30 mg, 0.564 mmol) is recrystallized as a white solid from toluene in a yield of 11%. ^{1}H NMR (400 MHz, DMSO) δ9.60 (s, 1H), 7.58–7.75 (m, 7H), 7.4–7.5 (m, 4H), 7.20 (d, J = 16.4, 1H), 7.06 (d, J = 16.4, 1H), 6.75–6.82 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ157.85, 140.18, 138.96, 137.26, 129.42, 129.08, 128.56, 128.41, 127.83, 127.32, 127.08, 126.86, 125.01, 116.04. Spectroscopic data are consistent with the literature.[33]

4-vinyl-1,1′-biphenyl 7 [2350-89-2]. In a round bottom flask (1 L) under inert and anhydrous conditions, methyltriphenylphosphonium bromide (1.1 equiv., 43.1 g, 120.73 mmol) was suspended in dry THF (200 mL), followed by the dropwise addition of sodium *tert*-pentoxide 40% in toluene (1.1 equiv., 31.63 mL, 120.73 mmol). No relevant increase of temperature is noticed during the addition and the suspension turns pale yellow. After 30 min, [1,1′-biphenyl]-4-carbaldehyde (20 g, 109.76 mmol) dissolved in dry THF (100 mL) was added drop-wise to the reaction mixture. The addition is exothermic, and the reaction was never let to reach 30 °C. After 3 h, the reaction reaches 20 °C. Full conversion of the reaction was confirmed by means of NMR. The reaction experiment was quenched by addition of water. The mixture was then evaporated under reduced pressure. To the dried mixture, anhydrous $MgCl_2$ (2 equiv., 21 g, 220 mmol) was added and suspended in 400 mL of hexane and stirred for 18 h at 20 °C. The suspension was filtered and the solid collected and suspended in hexane (400 mL). The filtrated mixtures were combined and evaporated under reduced pressure to afford **7** (18.99 g, 99% pure according to NMR, 105.54 mmol) as a yellow oil with a yield of 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.54 (m, 4H), 7.49 (d, J = 8.3 Hz, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.37–7.32 (m, 1H), 6.76 (dd, J =

17.6, 10.9 Hz, 1H), 5.80 (dd, $J=17.6$, 0.7 Hz, 1H), 5.28 (dd, $J=10.9$, 0.6 Hz, 1H). Spectroscopic data are consistent with the literature.[34]

4-((tetrahydro-2H-pyran-2-yl)oxy)benzaldehyde 8 [74189-56-3]. 4-Hydroxybenzaldehyde (1.83 g, 15 mmol) was suspended in anhydrous DCM (20 mL) at 20 °C. PpTSA (5%, 0.188 g, 0.75 mmol) was then added followed by drop-wise addition of DHP (1.5 equiv., 1.90 g, 2.06 mL, 22.5 mmol). The reaction mixture was heated at 40 °C and monitored by withdrawn samples on NMR (through the integration of the aldehyde peak). The reaction did not reach full conversion but terminated after 18 h when the NMR revealed a yield of 96%. The post-reaction mixture was then extracted using DCM (3×200 mL) from a solution of NaOH in water (200 mL) that was transferred to the reactor. The temperature of the mixture was monitored during this operation (exothermic reaction). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Target compound **8** was isolated as a yellow oil in a yield of 87% (2.691 g, 13.05 mol). NMR (400 MHz, $CDCl_3$) δ1.15–1.77 (m, 8H), 3.35 (d, 1H), 3.45–3.62 (m, 1H), 5.25 (t, 1H), 6.83–6.95 (m, 2H), 7.49–7.58 (m, 2H), 9.59 (s, 1H). Spectroscopic data are consistent with the literature.[35]

2-(4-vinylphenoxy)tetrahydro-2*H*-pyran 9 [65409-15-6]. Methyltriphenylphosphonium bromide (2 equiv., 1.732 g, 4.85 mmol) was transferred under inert and anhydrous conditions to a round bottom flask (100 mL) and suspended in dry THF (20 mL). Sodium *tert*-pentoxide 40% in toluene (2 equiv., 1.27 mL, 4.85 mmol) was then added dropwise and stirred for a period of 30 min, whereupon 4-((tetrahydro-2*H*-pyran-2-yl)oxy)benzaldehyde **8** (500 mg, 2.42 mmol) was added dropwise to the reaction mixture. The reaction mixture was then stirred for 3 h. The reaction was then quenched by adding a saturated solution of Na_2CO_3. The post-reaction mixture was extracted using DCM (3×200 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The mixture was purified using a small chromatography column packed with silica gel (eluent hexane:ethyl acetate = 95:5). Target compound **9** (474 mg, 2.32 mmol) was obtained as a colorless oil in a yield of 96%. Recorded spectroscopic data were consistent with the literature.[36]

(*E*)-2-(4-(2-([1,1′-biphenyl]-4-yl)vinyl)phenoxy) tetrahydro-2*H*-pyran 10 [NEW]. 2-(4-Vinylphenoxy)tetrahydro-2*H*-pyran **9** (0.600 g, 2.94 mmol), **5** (1.1 equiv., 0.640 g, 3.23 mmol), 2,3-di(pyridin-3-yl) pyrazine (5%, 0.034 g, 0.15 mmol), palladium(II) acetate (5%, 0.033 g, 0.15 mmol) were transferred to a round bottom flask (50 mL) and dissolved in DMF (12 mL). Copper (II) acetate (1.5 equiv., 0.800 g, 4.41 mmol) was then added to the reaction mixture, that was stirred for 18 h at 20 °C. The post-reaction mixture was extracted with DCM (3×100 mL) from a solution EDTA in water (0.2 M). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Target compound 10 was recrystallized as a white solid from toluene in a yield of 83% (870 mg, 2.44 mmol). ^{1}H NMR (400 MHz, DMSO) δ7.63–7.76 (m, 6H), 7.56 (d, 2H), 7.47 (t, 2H), 7.37 (d, 1H), 7.1–7.31 (m, 2H), 7.04 (d, 2H), 5.50 (t, 1H), 3.77 (s, 1H), 3.57 (d, 1H), 1.4–1.96 (m, 6H).^{13}C NMR (126 MHz, DMSO) δ156.72, 140.13, 139.24, 137.01, 131.03, 129.44, 128.61, 128.17, 127.89, 127.35, 127.27, 126.89, 126.42, 117.08, 96.16, 62.04, 30.30, 25.16, 19.09.

Up-scaled synthetic route

3-bromo-4-((tetrahydro-2*H*-pyran-2-yl)oxy) benzaldehyde 11 [NEW]. 3-Bromo-4-hydroxybenzaldehyde **1** (300 g, 1.49 mol) was transferred to a reactor (5 L) and suspended in anhydrous DCM (3 L) at 20 °C. PpTSA (5%, 18.75 g, 76 mmol) was then added, followed by drop-wise addition of DHP (1.5 equiv., 188 g, 204 mL, 2.24 mol), The reaction was heated at 40 °C and monitored by means of NMR to determine the conversion (through the integration of the aldehyde peak). The reaction does not reach full conversion, it was terminated after 17 h when the NMR conversion is 97%. After that the mixture was cooled at 20 °C, NaOH aqueous (1 L, 1 M) was added to the reactor, controlling the temperature during the addition. The mixture was stirred for 1 h and let set for 1 h. After checking that there was no product in the aqueous phase though NMR, the organic phase was separated, evaporated under reduced pressure. In order to remove residual water, a cycle of addition of toluene (1 L) and evaporation under reduced pressure was repeated three times. The target product **11** was obtained as an orange oil in a yield of 85% (471.20 g, 77% pure according to NMR, 1.27 mol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.96 (d, $J=$ 2.0 Hz, 1H), 7.66 (dd, $J=8.5$, 2.0 Hz, 1H), 7.16 (d, $J=8.5$ Hz, 1H), 5.55 (t, $J=2.5$ Hz, 1H), 3.69 (td, $J=11.2$, 2.8 Hz, 1H), 3.56–3.50 (m, 1H), 2.06–1.49 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.60, 158.14, 134.40, 131.14, 130.79, 115.45, 113.53, 96.58, 61.83, 29.85, 24.97, 17.98.

2-(2-bromo-4-vinylphenoxy)tetrahydro-2*H*-pyran 12 [NEW]. Methyltriphenyl-phosphonium bromide (1.1 equiv., 500 g, 1.49 mol) was transferred under inert and anhydrous conditions to a reactor (5 L) and suspended in dry 2-MeTHF (2 L). Sodium *tert*-pentoxide (40%) in toluene (1.2 equiv., 420 g, 458 mL, 1.53 mmol) was then added dropwise (exotherm reaction). The suspension turned into a pale-yellow color during the curse of reaction. 3-Bromo-4-((tetrahydro-2*H*-pyran-2-yl)oxy)benz aldehyde **11** (77% pure, 471 g, 1.27 mol) dissolved in dry 2-MeTHF (500 mL) was then added (after a period of 30 min.) dropwise to the reaction mixture. The reagent addition is exothermic, and the reaction temperature was kept <30 °C. After 2 h, the reaction reaches 20 °C. By means of samples analyzed using NMR, the full conversion was confirmed. The reaction mixture was then quenched by adding water (7 mL). The solvent was removed under reduced pressure. Anhydrous $MgCl_2$ (2 equiv., 242 g, 2.54 mmol) was then added and the solids were suspended in a mixture of heptane:toluene (9:1) (3 L) and stirred for 18 h at 20 °C. The suspension was then filtered and the solid collected and suspended again in a mixture of heptane: toluene = 9:1 (3 L). The suspension was filtered again. The two filtrates were combined (≈ 6 L). The solvent was then removed under reduced pressure to provide compound **12** as a yellow oil in a yield of 95% (455.8 g, 75% pure according to NMR, 1.21 mol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, $J=2.1$ Hz, 1H), 7.26 (dd, $J=8.5$, 2.1 Hz, 1H), 7.09 (d, $J=$ 8.5 Hz, 1H), 6.58 (dd, $J=17.6$, 10.9 Hz, 1H), 5.62 (dd, $J=17.6$, 0.4 Hz, 1H), 5.51 (t, $J=2.8$ Hz, 1H), 5.17 (d, $J=10.9$ Hz, 1H), 3.88 (td, $J=11.0$, 2.9 Hz, 1H), 3.63–3.56 (m, 1H), 2.22–1.41 (m, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 152.90, 135.09, 132.67, 130.77, 126.31, 116.31, 113.26, 113.22, 96.66, 61.77, 30.12, 25.21, 18.25.

(*E*)-2-(4-(2-([1,1′-biphenyl]-4-yl)vinyl)-2-bromo-phenoxy) tetrahydro-2*H*-pyran 13 [NEW]. 2-(2-Bromo-4-vinylphenoxy) tetrahydro-2*H*-pyran **12** (151 g, 75% pure according to ^{1}H NMR, 399 mmol) was transferred to a reactor (5 L) and dissolved in DMF (3 L) at 20 °C under inert conditions. [1,1′-Biphenyl]-4-ylboronic acid **5** (1.5 equiv., 118.54 g, 598 mmol), 1,10-phenanhtroline (5%, 3.60 g, 19.95 mmol) and $Pd(OAc)_2$ (5%, 4.48 g, 19.95 mmol) were added to the reaction mixture (no temperature increased was observed). After 10 min, the reaction mixture changes color from red to dark brown. $Cu(OAc)_2$ (1.20 equiv., 86.98 g, 478 mmol) was then slowly added to the mixture, and a small temperature increase (≈3 °C) was observed. The reaction mixture was stirred for 18 h at 20 °C. The progress of the reaction was monitored by means of NMR. Upon full conversion, EDTA in distilled water (2 M, 1 L) was added slowly to the post-reaction mixture and a small temperature increase (≈5 °C) was observed. The quenched reaction mixture was filtered through a glass sintered filter disc and washed with water. The blue-grey solids were stirred for 18 h in toluene (3 L). The

suspension was then filtered through a glass sintered filter disc and the clear light-brown solution was evaporated under reduced pressure and stirring for 18 h in a solution of hexane:toluene = 9:1 (3 L). The white powder that was formed was filtrated through a glass sintered filter disc and the mixture was evaporated under reduced pressure, and washed with a solution of hexane:toluene = 9:1 (1 L). Title compound **13** (158.4 g, >99% pure according to ^{1}H NMR, 363.84 mmol) was obtained as a white solid in a yield of 91%. ^{1}H NMR (500 MHz, DMSO) δ 7.90 (d, *J* = 2.1 Hz, 1H), 7.73–7.65 (m, 6H), 7.58 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.51–7.45 (m, 2H), 7.37 (tt, *J* = 6.8, 1.1 Hz, 1H), 7.26–7.22 (m, 3H), 5.69 (t, *J* = 2.9 Hz, 1H), 3.81–3.71 (m, 1H), 3.62–3.54 (m, 1H), 2.03–1.50 (m, 6H). ^{13}C NMR (126 MHz, DMSO) δ 151.96, 139.58, 139.06, 136.21, 132.32, 130.58, 128.94, 127.44, 127.43, 126.95, 126.89, 126.87, 126.68, 126.42, 116.73, 112.58, 95.84, 61.26, 29.50, 24.63, 18.04.

(*E*)-4-(2-([1,1′-biphenyl]-4-yl)vinyl)-2-bromophenol 14 [NEW]. (*E*)-2-(4-(2-([1,1′-biphenyl]-4-yl)vinyl)-2-bromophenoxy) tetrahydro-2*H*-pyran **13** (20 g, 45.9 mmol) was transferred to a round bottom flask (1 L) and dissolved in DMF (200 mL) followed by the addition of HCl 4 M (20 mL). The suspension was heated at 45 °C and stirred for 18 h. The crude was extracted with ethyl acetate (3×300 mL). The organic phases were combined and dried over anhydrous Na_2SO_4 and filtered through cotton. Since the DMF is the solvent for the following reaction, there was no need to evaporate it completely. Title compound **14** was obtained in a quantitative yield. ^{1}H NMR (500 MHz, DMSO) δ 10.44 (s, 1H), 7.80 (d, *J* = 2.1 Hz, 1H), 7.72–7.62 (m, 6H), 7.50–7.44 (m, 3H), 7.36 (ddd, *J* = 8.4, 2.1, 1.1 Hz, 1H), 7.18 (q, *J* = 16.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 1H).^{13}C NMR (126 MHz, DMSO) δ 153.75, 139.62, 138.79, 136.40, 130.76, 130.00, 128.92, 127.38, 127.08, 126.97, 126.83, 126.78, 126.38, 126.08, 116.50, 109.79.

***(E)*-5-(2-([1,1′-biphenyl]-4-yl)vinyl)-2-hydroxybenzoic acid DC10 [NEW]. Method A**: In a flask under inert and anhydrous conditions, **13** (500 mg, 1.15 mmol) was dissolved in anhydrous THF (6 mL). The solution was adjusted at 0 °C whereupon *iso*-propylmagnesium chloride lithium chloride complex solution 1.3 M in THF (1.5 equiv., 208 mg, 1.33 mL, 1.72 mmol) was added dropwise. After 12 h at 20 °C, CO_2 was bubble through the mixture using a gas diffuser for 10 min. The mixture was then extracted with DCM (3×100 mL) from acidic water (100 mL), the organic phases were combined and dried over Na_2SO_4. Purification was carried through using a chromatography column packed with silica gel using an eluent composed of DCM:methanol = 95:5 and 0.1% of formic acid. Target compound **DC10** (150 mg, 0.474 mmol) was obtained as a white powder in a yield of 41%.

Method B: (*E*)-2-(4-(2-([1,1′-biphenyl]-4-yl)vinyl)-2-bromo-phenoxy) tetra-hydro-2*H*-pyran **13** (60 g, 137 mol) was placed in a Parr pressure vessel (500-mL) and dissolved in DMF (250 mL). Then, $Pd(OAc)_2$ (5%, 1.55 g, 6.89 mmol), Xantphos (5%, 3.99 g, 6.89 mmol), H_2O (10 equiv., 24.8 g, 24.8 mL, 1.38 mol) and TEA (1.2 equiv., 16.74 g, 23.1 mL, 165 mmol) were added. The Parr reactor was closed, and the vessel was charged with CO (10 atm) and stirred in a preheated oil bath at 110 °C. When a pressure drop was observed (due to consumption of CO), the vessel was re-charged to attain a CO pressure of 10 atm. After 24 h, no further pressure drops were observed. The reaction mixture was extracted with ethyl acetate (3×300 mL) and acidic water (300 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was washed with DCM (2×50 mL) and then filtered through a glass sintered filter disc. The precipitate was collected and washed with acetone (2×50 mL) and then filtered through a glass sintered filter disc. The white precipitate was collected. **DC10** (30.96 g, >99% pure according to ^{1}H NMR, 97.95 mmol) was obtained as a white solid in a yield of 71%.

Method C: Oxalic acid (3 equiv., 1.54 g, 17.08 mmol), $Pd(OAc)_2$ (5%, 64 mg, 285 μmol), Xantphos (5%, 165 mg, 265 μmol), **14** (2 g, 5.69 mmol), H_2O (10 equiv., 1.03 g, 1.03 mL, 56.94 mmol) were transferred to a pressure resistant reactor tube and dissolved in DMF (20 mL). The reactor tube was sealed and immersed into a preheated oil bath at 110 °C under continuously stirring. TEA (3 equiv., 1.73 g, 2.38 mL, 17.08 mol) was then added, followed by addition of Ac_2O (3 eq., 1.74 g, 1.61 mL, 17.08 μmol) over a period of 1 h by means of a syringe pump. During the addition CO was formed by degradation of the oxalic acid. A balloon was added to the sealed reactor tube in order to avoid problems with the increasing pressure. The reaction was stirred at 110 °C for 14 h. The reaction mixture was transferred to a separatory funnel containing ethyl acetate (3×200 mL) and acidic water (200 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was dissolved in DCM (15 mL) filtered through silica gel. The solution was evaporated under reduced pressure and washed with acetone (10 mL) for 18 h at 20 °C. Target product was obtained as a white solid that was filtered a through a glass sintered filter disc to afford the desired product **DC10** (1.64 g, 5.18 mmol) in a yield of 91%. ^{1}H NMR (500 MHz, DMSO) δ 8.01 (d, *J* = 2.2 Hz, 1H), 7.84 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.73–7.66 (m, 6H), 7.51–7.43 (m, 2H), 7.39–7.34 (m, 1H), 7.31 (d, *J* = 16.5 Hz, 1H), 7.19 (d, *J* = 16.5 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 171.72, 160.69, 139.64, 138.88, 136.38, 133.08, 128.92, 128.51, 128.50, 127.43, 127.40, 126.86, 126.84, 126.40, 126.31, 117.65, 113.20. HR-MS (ESI): $[M-H]^-$: Calcd for $C_{21}H_{15}O_3$ 315.10212, found 315.10201.

Scope of the oxidative Heck cross-coupling

3-Bromo-4-(methoxymethoxy)benzaldehyde 15 [162269-90-1]. 3-Bromo-4-hydroxybenzaldehyde (7.0 g, 34.82 mmol) was dissolved in DCM (25 mL) and cooled at 0 °C and then added *N,N*-Dicyclohexylmethylamine (2 equiv., 13.61 g, 14.92 mL, 69.65 mmol) and chloromethyl methyl ether (1.5 equiv., 4.21 g, 3.97 mL, 52.23 mmol). The reaction mixture was stirred at 20 °C for 18 h. The progress of the reaction was monitored by TLC, using hexane:ethyl acetate = 9:1 as eluent. The reaction mixture was poured in HCl solution (0.1 M) and then extracted with DCM (3×250 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure using a rotary evaporator. The white solid obtained is filtered and washed with Et_2O. The filtrated was collect and concentrated under reduced pressure to afford title compound **15** (8.15 g, 33.26 mmol) as yellow oil and with a yield of 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.79 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 5.35 (s, 2H), 3.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.55, 158.42, 134.47, 131.45, 130.81, 115.06, 113.33, 94.79, 56.62.

2-bromo-1-(methoxymethoxy)-4-vinylbenzene 12a [NEW]. At 0 °C, methyltriphenylphosphonium bromide (1.2 equiv., 3.50 g, 9.79 mmol) was slowly added to a suspension of NaH 60% (3 equiv., 979 mg, 24.48 mmol) in anhydrous DCM (15 mL). The mixture was then left for stirring in 30 min., whereupon compound **15** (2.0 g, 8.16 mmol) was added to the mixture. The mixture was then stirred for 16 h at 20 °C. The reaction mixture was then quenched with a saturated solution of $NaHCO_3$ in water. The quenched post-reaction mixture was then extracted with DCM (3×250 mL). The combined organic layers was dried over Na_2SO_4, and then purified using column chromatography filled with silica gel (eluent hexane:ethyl acetate = 9:1), which afforded the title compound **12a** (1.76 g, 7.24 mmol) as transparent oil in a yield of 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.1 Hz, 1H), 7.27 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.60 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.64 (d, *J* = 17.3 Hz, 1H), 5.24 (s, 2H), 5.20 (d, *J* = 10.7 Hz, 1H), 3.52 (s, 3H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 153.29, 134.95, 133.10, 130.91, 126.38, 115.97, 113.57, 113.05, 95.11, 56.39.

(*E*)-4-(3-bromo-4-(methoxymethoxy)styryl)-1,1′-biphenyl 13a [NEW]. 2-Bromo-1-(methoxymethoxy)-4-vinylbenzene **12a** (500 mg, 2.81 mmol), 2,3-di(pyridin-2-yl)pyrazine (5%, 33 mg, 0,140 mmol), $Pd(OAc)_2$ (5%, 32 mg, 0,140 mmol), [1,1′-biphenyl]-4-ylboronic acid (1.1 equiv., 611 mg, 3.09 mmol), Cu(OAc)2 monohydrate (1.5 equiv., 764 mg, 4,21 mmol) in 10 mL of DMF were added to a flask (25 mL). The reaction mixture was stirred for 18 h at 20 °C and monitored by means TLC, using hexane:ethyl acetate = 9:1 as eluent. The mixture was then extracted with DCM (3×100 mL) from a solution EDTA in water (0.2 M). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The mixture was purified by means of column chromatography packed with silica gel (eluent hexane:ethyl acetate = 99.6:0.4). Title compound **13a** (910 mg, 2.30 mmol) was isolated as a white solid in a yield of 82%. 1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.1 Hz, 1H), 7.63–7.52 (m, 6H), 7.44 (dd, *J* = 10.6, 4.8 Hz, 2H), 7.38 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.37–7.32 (m, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 7.02 (s, 2H), 5.26 (s, 2H), 3.53 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.20, 140.64, 140.42, 136.15, 132.89, 131.05, 128.83, 127.96, 127.39, 127.37, 126.93, 126.89, 126.74, 126.73, 116.14, 113.28, 95.14, 56.43.

5-iodo-2-(methoxymethoxy)benzonitrile 16 [2090370-07-1]. 2-Hydroxybenzonitrile (2.0 g, 16.79 mmol) in acetonitrile (15 mL) cooled at 0 °C was transferred to a flask (25 mL) that was wrapped in aluminum foil. *para*-Toluenesulfonic acid monohydrate (1.1 eq., 3.51 g, 18.47 mmol) and by *N*-iodosuccinimide (1.1 eq., 4.16 g, 18.47 mmol) were added to the mixture that was stirred at 20 °C for 18 h. The progress of the reaction was monitored by TLC using hexane:ethyl acetate = 8:2 as eluent. The solvent was removed under reduced pressure. The crude was diluted with DCM and a saturated solution of $Na_2S_2O_3$ in water. The aqueous phase was extracted further with DCM (2×250 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure to obtain 2-hydroxy-5-benzonitrile that was dissolved in anhydrous DCM (20 mL) to proceed with the following reaction. The same flask was cooled at 0 °C and NaH 60% (3 eq., 2.01 g, 50.32 mmol) and chloromethyl methyl ether (1.5 eq., 2.03 g, 1.91 mL, 25.16 mmol) were added. The reaction was heated to 20 °C for 1 h and then quenched using a sat. $NaHCO_3$ (aq.). The mixture was extracted with DCM (3×250 mL). The organic phases were combined over anhydrous Na_2SO, filtered, and concentrated under reduced pressure to obtain compound **16** (4.1 g, 14.18 mmol) as a yellow oil in a yield of 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.2 Hz, 1H), 7.78 (dd, *J* = 2.2, 8.9 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 5.28 (s, 2H), 3.51 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.89, 143.03, 141.48, 117.02, 114.73, 105.14, 94.91, 82.89, 56.75.

2-(methoxymethoxy)-5-vinylbenzonitrile 12b [NEW]. Compound **16** (1.00 g, 3.46 mmol), $Pd(PPh_3)_4$ (8%, 319 mg, 276 μmol), tributyl (vinyl)stannane (1.1 equiv., 1.21 g, 3.81 mmol) and DMF (10 mL) were transferred to reactor tube that then was sealed. The mixture was flushed with Argon, and sonicated for 5 min. Then the reactor tube was immersed into the reactor cavity of a microwave oven and heated at 100 °C for 2 h. The progress of the reaction was monitored by TLC with hexane:ethyl acetate = 9:1 as eluent. The solvent was removed under reduced pressure and the mixture was extracted DCM (3×100 mL) from water. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude was purified using a chromatography column packed with silica gel using hexane:ethyl acetate = 95:5 as eluent to obtain target compound **12b** (603 mg, 3.19 mmol) as a yellow oil in a yield of 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ7.46(d, *J*2.3 Hz,1H),7.43(dd, *J* = 2.3, 8.8 Hz,1H), 7.08(d, *J* = 8.8 Hz, 1H), 6.50 (dd, *J* = 10.9, 17.6 Hz, 1H), 5.56 (d, *J* = 17.5 Hz, 1H), 5.14–5.18 (m, 4H), 3.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.38, 134.25, 131.87, 131.00, 121.91, 116.16, 115.05, 114.50, 103.01, 94.84, 56.53.

***(E)*-2-(methoxymethoxy)-5-styrylbenzonitrile 13b [NEW].** 2-(Methoxymethoxy)-5-vinylbenzonitrile **12b** (250 mg, 1.32 mmol), 2,3-di-(pyridin-2-yl)pyrazine (5%, 16 mg, 66 μmol), $Pd(OAc)_2$ (5%, 15 mg, 66 μmol), phenylboronic acid (1.1 equiv., 177 mg, 1.45 mmol), $Cu(OAc)_2$ monohydrate (1.5 equiv., 396 mg, 1.98 mmol) and DMF (6 mL) were transferred to a flask. The reaction mixture was stirred at 20 °C in 18 h. The progress of the reaction was monitored by TLC using hexane:ethyl acetate = 9:1 as eluent. The mixture was extracted with DCM (3×50 mL) from a solution of EDTA in water (0.2 M). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The mixture was purified using a column chromatography packed with silica gel with using hexane:ethyl acetate = 99.4:0.6 as eluent. Target compound **13b** (288 mg, 1.09 mmol) was obtained as a white solid in a yield of 82%. ^{1}H NMR (500 MHz, CDCl3) δ 7.71 (d, *J* = 2.2 Hz, 1H), 7.64 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.48–7.51 (m, 2H), 7.32–7.4 (m, 2H), 7.27–7.31 (m, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 3.5 Hz, 2H), 5.31 (s, 2H), 3.54 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 158.23, 136.69, 132.10, 131.79, 131.21, 129.45, 128.82, 128.08, 126.57, 125.86, 116.28, 115.24, 103.30, 94.90, 56.67.

***N*-(2-bromo-4-formylphenyl)acetamide 17 [475150-63-1].** *N*-(4-formylphenyl)acetamide (2.0 g, 12.26 mmol) in water (20 mL) were transferred to a aluminum foil wrapped flask. *N*-Bromosuccinimide (1.1 equiv., 2.40 g, 13.48 mmol) was then slowly added to the reaction mixture that was stirred at 20 °C for 18 h. The progress of the reaction was monitored by using TLC using hexane:ethyl acetate = 8:2 as eluent. The solvent was removed under reduced pressure. The crude was diluted with DCM (100 mL) and a saturated solution of $Na_2S_2O_3$ in water (100 mL). The aqueous phase was extracted further with DCM (2×100 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain title compound **17** (2.76 g, 11.40 mmol) as yellow oil and in a yield of 93%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.63 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 1.9 Hz, 1H), 7.82 (dd, *J* = 1.8, 8.5 Hz, 1H), 2.77 (s, 1H), 2.30 (s, 3H). Data consistent with the literature.

***N*-(2-bromo-4-vinylphenyl)acetamide 12c [NEW]**. A suspension of NaH 60% (3 equiv., 2.50 g, 30.98 mmol) in anhydrous DCM (20 mL) was slowly added methyltriphenylphosphonium bromide (1.2 equiv., 4.43 g, 12.39 mmol) at 0 °C, which was stirred for 30 min. Then, *N*-(2-bromo-4-formylphenyl)acetamide **17** (2.50 g, 10.33 mmol) was added to the mixture, which was stirred at 20 °C for 16 h. The reaction mixture was then quenched using sat. $NaHCO_3$ in water. The crude mixture was extracted with DCM (3×250 mL), dried over anhydrous Na_2SO_4, filter, and purified using column chromatography packed with silica gel with hexane:ethyl acetate = 9:1 as eluent to obtain title compound **12c** (2.01 g, 8.37 mmol) as a transparent oil in a yield of 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.35 (dd, *J* = 1.9, 8.5 Hz, 1H), 6.60 (dd, *J* = 10.9, 17.6 Hz, 1H), 5.69 (d, *J* = 17.5 Hz, 1H), 5.25 (d, *J* = 10.9 Hz, 1H), 2.24 (s, 3H).

***(E)*-N-(2-bromo-4-styrylphenyl)acetamide 13c [NEW].** *N*-(2-Bromo-4-vinylphenyl)acetamide **12c** (500 mg, 2.08 mmol), 2,3-di(pyridin-2-yl)pyrazine (5%, 24 mg, 104 μmol), $Pd(OAc)_2$ (5%, 23 mg, 104 μmol), phenylboronic acid (1.1 equiv., 279 mg, 2.29 mmol), $Cu(OAc)_2$ monohydrate (1.5 equiv., 623 mg, 3.12 mmol) were dissolved in DMF (8 mL). The reaction mixture was stirred at 20 °C for 18 h. The reaction progress was monitored by TLC using hexane:ethyl acetate = 9:1 as eluent. The mixture was extracted with DCM (3×50 mL) from a solution EDTA in water (0.2 M). The organic phases

were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The mixture was purified column chromatography packed with silica gel using hexane:ethyl acetate = 95:5 to obtain title product **13c** (241 mg, 0,762 mmol) as a white solid in a yield of 36%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 8.5 Hz, 1H), 7.59–7.63 (m, 1H), 7.55 (s, 1H), 7.41 (d, J = 7.4 Hz, 2H), 7.36 (dd, J = 1.8, 8.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 2H), 7.15–7.23 (m, 1H), 6.86–6.99 (m, 2H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 27 °C) δ 168.10, 136.91, 134.83, 134.71, 131.45, 129.81, 129.26, 128.75, 127.91, 126.56, 126.52, 121.68, 113.42, 22.72.

(*E*)-2-(3-bromo-4-(methoxymethoxy)styryl)-1,1′-biphenyl 13d [NEW]. 2-bromo-1-(methoxymethoxy)-4-vinylbenzene **12a** (500 mg, 2.06 mmol), 2,3-di(pyridin-2-yl)pyrazine (5%, 24 mg, 102 μmol), $Pd(OAc)_2$ (5%, 23 mg, 102 μmol), [1,1′-biphenyl-2-ylboronic acid (1.1 equiv., 448 mg, 2.26 mmol), and $Cu(OAc)_2$ monohydrate (1.5 equiv., 615 mg, 3.09 mmol) were transferred to a flask and dissolved with DMF (8 mL) that was stirred at 20 °C for 18 h. The progress of the reaction was monitored by TLC using hexane:ethyl acetate = 9:1 as eluent. The mixture was extracted with DCM (3× 50 mL) from a solution EDTA in water (0.2 M). The organic phases were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The mixture was purified using column chromatography packed with silica gel using hexane: ethyl acetate = 99.5:0.5 as eluent to obtain title compound **13d** (654 mg, 1.65 mmol) as a white solid in a yield of 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 7.4 Hz, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.23–7.39 (m, 9H), 7.13–7.17 (m, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.79–6.94 (m, 2H), 5.14 (s, 2H), 3.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.04, 141.15, 140.82, 135.22, 133.22, 131.32, 130.37, 129.89, 128.20, 127.69, 127.64, 127.61, 127.58, 127.22, 126.49, 125.84, 116.15, 113.16, 95.11, 56.41.

(*E*)-3-(3-bromo-4-(methoxymethoxy)styryl)-1,1′-biphenyl 13e [NEW]. 2-bromo-1-(methoxymethoxy)-4-vinylbenzene **12a** (500 mg, 2.06 mmol), 2,3-di(pyridin-2-yl)pyrazine (5%, 24 mg, 102 μmol), $Pd(OAc)_2$ (5%, 23 mg, 102 μmol), [1,1′-biphenyl-3-ylboronic acid (1.1 equiv., 448 mg, 2.26 mmol), and $Cu(OAc)_2$ monohydrate (1.5 equiv., 615 mg, 3.09 mmol) were transferred to a reaction flask (25 mL) and dissolved in DMF (8 mL). The reaction mixture was stirred at 20 °C for 18 h. The progress of the reaction was monitored by TLC with hexane:ethyl acetate = 9:1 as eluent. The mixture was extracted with DCM (3×50 mL) from a solution EDTA in water (0.2 M). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The mixture was purified using column chromatography packed with silica gel with hexane:ethyl acetate = 99.5:0.5 as eluent to obtain title compound **13e** (698 mg, 1.77 mmol) as a white solid in a yield of 86%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 2.2 Hz, 1H),7.71(t, J = 1.6 Hz, 1H),7.61–7.67(m, 2H),7.37–7.51 (m, 7H), 7.16 (d, J = 8.5 Hz, 1H), 7.07 (s, 2H), 5.28 (s, 2H), 3.55 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 27 °C) δ 153.27, 141.79, 141.09, 137.59, 132.83, 131.11, 129.16, 128.82, 128.38, 127.46, 127.22, 127.07, 126.79, 126.61, 125.39, 125.34, 116.14, 113.29, 95.15, 56.44.

(*E*)-2-bromo-4-(4-fluorostyryl)-1-(methoxymethoxy)benzene 13f [NEW]. 2-Bromo-1-(methoxymethoxy)-4-vinylbenzene **12a** (210 mg, 867.84 μmol), 2,3-di(pyridin-2-yl)pyrazine (5%, 10 mg, 43 μmol), $Pd(OAc)_2$ (5%, 9 mg, 43 μmol), (4-fluorophenyl)boronic acid (1.1 equiv., 133 mg, 950.23 μmol), $Cu(OAc)_2.H_2O$ (1.5 equiv., 258 mg, 1.30 mmol), and 7 mL of DMF (7 mL) was transferred to a round bottom flask (50 mL). This mixture was continuously stirred for 18 h at 20 °C. The course of the reaction was monitored by TLC, using hexane:ethyl acetate = 9:1 as eluent. The post reaction mixture was added a solution EDTA in water (10 mL, 0.2 M) that was extracted with DCM (3×50 mL). The organic phases were combined, dried over anhydrous Na2SO4 and concentrated under reduced pressure. The mixture was purified using column chromatography packed with silica gel with hexane:ethyl acetate = 99.6:0.4 as eluent. Target compound **13f** was achieved as a clear liquid in a yield of 87% (254 mg, 753.29 μmol).^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (s, 3H), 5.07 (s, 2H), 6.65–6.77 (m, 2H), 6.82–6.91 (m, 3H), 6.95 (d, 1H), 7.14 (dd, 1H), 7.21–7.27 (m, 2H), 7.53 (d, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.38 (d, J = 247.1 Hz), 153.26, 133.32 (d, J = 3.4 Hz), 132.68, 131.01, 127.97 (d, J = 7.8 Hz), 127.17, 126.67, 126.47 (d, J = 2.3 Hz), 116.07, 115.67 (d, J = 21.8 Hz), 113.28, 95.09, 56.36.

***(E)*-2-(3-bromo-4-(methoxymethoxy)styryl)-9,9-dimethyl-9*H*-fluorene 13g [NEW].** 2-Bromo-1-(methoxymethoxy)-4-vinylbenzene **12a** (500 mg, 2.06 mmol), 2,3-di(pyridin-2-yl)pyrazine (5%, 24 mg, 102 μmol), $Pd(OAc)_2$ (5%, 23 mg, 102 μmol), (9,9-dimethyl-9*H*-fluorene-2-yl)boronic acid (1.1 equiv., 538 mg, 2.26 mmol), $Cu(OAc)_2$ monohydrate (1.5 equiv., 615 mg, 3.09 mmol) were transferred to a reactor tube and dissolved in DMF (8 mL) and then stirred for 18 h at 20 °C. The progress of the reaction was monitored by means of TLC using hexane:ethyl acetate = 9:1 as eluent. The mixture was extracted with DCM (3×50 mL) from a solution EDTA in water (0.2 M). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The mixture was purified using a chromatography column packed with silica gel with hexane:ethyl acetate = 99.5:0.5 as eluent to obtain title compound **13g** (803 mg, 1.84 mmol) as a white solid in a yield of 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 2.1 Hz, 1H), 7.55–7.6 (m, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.43–7.46 (m, 1H), 7.31 (s, 2H), 7.24 (dd, J = 2.1, 8.5 Hz, 1H), 7.17–7.21 (m, 2H), 7.00 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 7.7 Hz, 2H), 5.11 (s, 2H), 3.39 (s, 3H), 1.39 (s, 6H).^{13}C NMR (126 MHz, $CDCl_3$, 27 °C) δ 154.22, 153.97, 153.18, 139.14, 138.95, 136.37, 133.15, 131.07, 128.96, 127.39, 127.15, 126.71, 126.14, 125.97, 122.68, 120.47, 120.35, 120.12, 116.20, 113.36, 95.18, 56.45, 46.85, 27.29.

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Conflict of Interest

The authors declare no conflict of interest.

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