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Enantioselective non-covalent substrate directable Heck-Matsuda and oxidative Heck arylations of unactivated five-membered carbocyclic olefins

Juliana Manso de Oliveira,[a] Ricardo Almir Angnes,[a] Ismat Ullah Khan,[a,b] Ellen Christine Polo,[a] Gabriel Heerdt,[a] Bruno M. Servilha,[c] Vitor H. Menezes da Silva,[a] Ataualpa A. C. Braga,[c] and Carlos Roque Duarte Correia*[a]

Dedication ((optional))

Abstract: Highly diastereo and enantioselective non-covalent substrate directable Heck desymmetrizations of cyclopentenyl olefins bearing hydroxymethyl and carboxylate functional groups are presented. These conformationally unbiased cyclic olefins underwent effective arylations in yields of up to 97%, diastereoselectivity up to >20:1, and enantiomeric excesses of up to 99%. Non-covalent directing effects were shown to be prevalent in both Heck-Matsuda and oxidative Heck reactions allowing the preferential formation of *cis*-substituted aryl cyclopentenes containing two stereocenters, including quaternary stereocenters. These results further validate the internal out-of-coordination-sphere ion-dipole interaction concept directing the reaction diasteroselectivity to the *cis*-Heck product. This approach is complementary to existing methods using bisphosphine monoxide ligands giving the opposite *trans*-diastereoisomer. The applicability of the method is showcased by a straightforward synthesis of a potent phosphodiesterase 4 (PDE4) inhibitor in a diastereoselective and enantioselective manner. The reaction is operationally simple and has broad scope regarding the nature of the arenediazonium salt and boronic acid employed. The mechanism and origin of stereoselectivity were investigated with control experiments and DFT calculations which fully support the stabilizing internal out-of-coordination-sphere ion-dipole interaction between the resident functional group and the cationic palladium.

Introduction

The Heck reaction is an extremely versatile and robust synthetic tool for the arylation and vinylation of olefins.[1] Arylation reactions are of great importance in view of the presence of at least an aromatic ring in a large number of pharmacological and therapeutically active compounds.[2] The operationally simple Heck-Matsuda version stands as a very reliable arylating reaction employing arenediazonium salts. We have been showcasing its applicability in the total synthesis of many biologically relevant molecules.[3] Similar fate has been going on with the oxidative Heck reactions, performed with boronic acids or boronates.[4] Despite its maturity, the Heck reaction and its variations continue to demonstrate potential for further developments and applications in organic synthesis, mainly because the diastereo- and enantioselective versions of these reactions have now been progressing at unprecedented rates.[5] Since the seminal work of Hallberg and others, the substrate directable Heck reactions constitute a special chapter in this area.[6] In a broad sense, substrate directable reactions rely on a general feature regarding the presence of a functional group in the substrate capable of complexing to a metal center, and thereby directing the diasteroselectivity of the process. In this respect, Cacchi and co-workers disclosed that an unprotected hydroxyl group could act as a directing group in Heck reactions.[7] Oestreich has also proposed a similar role for alcohol functionality in an enantioselective Heck desymmetrization of an acyclic alkenol substrate. However, later studies by the same group showed that the alcohol functionality did not act as a directing group, but that it rather played a role in a critical isomerisation step.[8] In spite of a considerable number of publications reporting directing group effects, their effective participation in enantioselective in Heck reactions remains somewhat elusive. This is likely due to the use of bidentate ligands - the most effective ligands in enantioselective Heck reactions - acting in the migratory insertion step. At this step, the migratory insertion requires two coordination sites for the ligand while the other two (for square planar complexes) are occupied by the olefin and the aryl or vinyl group.

Recently, we disclosed the first examples of enantioselective Heck-Matsuda reactions using bidentate N,N-type ligands in which resident functional groups act as non-covalent ancillary ligands. This strategy was successfully applied with a variety of directing functional groups, including secondary hydroxyl, suphoxides, sulphones, phospholenes and lactone/lactam carbonyl groups in somewhat conformationally restricted settings.[9] We have also demonstrated that the origins of these non-covalent directing effects arise from stabilizing ion-dipole interactions between the cationic palladium (II) complex, whose Lewis acidity is enhanced by the weaker σ-donicity of N,N-ligands, and the resident functional group.

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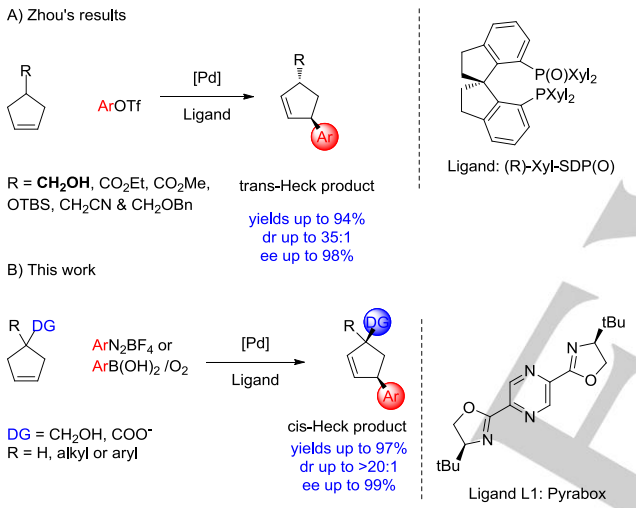
We describe herein several examples of the enantioselective non-covalent substrate directed arylation of olefins bearing non-conformationally restricted directing groups. These results indicate that the concept of non-covalent directing groups in cationic coordinatively saturated aryl-palladium intermediates is more general than initially thought. For example, it is operational in both Heck-Matsuda and oxidative Heck reactions. The importance and the complementarity of this approach to conventional Heck reactions is demonstrated by an interesting reversal of the diastereoselectivity reported by Zhou for the arylation of substituted cyclopentenes using aryl triflates and bisphosphine monoxide ligands (Scheme 1A).[10] Moreover, our strategy using *N*,*N*-ligand **L1** provides almost exclusively the corresponding *cis*-diastereomer in high yield and enantioselectivity (Scheme 1B). This novel desymmetrization strategy has also allowed the synthesis of carbocyclic compounds containing all-carbon quaternary stereocenters, thus greatly expanding its synthetic potential.

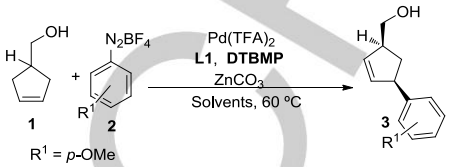


Scheme 1. Complementarities between approaches developed by Zhou and ours.

Results and Discussion

We initiated our studies with the arylation of olefin **1** using $Pd(TFA)_2$, Pyrabox ligand **L1**[3h] and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as base in solvents of different polarities (Table 1). The commonly used MeOH led to a low yield and diastereoselectivity (Table 1, entry 5), but good enantioselectivity. On the other hand, pure toluene was associated with moderate yields, but higher diastereo and enantioselectivities (Table 1, entry 1). Several other solvents were also evaluated, such as trifluorotoluene, dioxane, MTBE and THF, and an optimal condition was found when we employed a mixture of 5% MeOH in toluene (Table 1, entry 8). Interestingly, although not strictly necessary, the addition of 6 mol% of $ZnCO_3$ as coadjuvant base was shown to be beneficial to the diastereoselectivity and enantioselectivity of the reaction as well.

Table 1. Effect of the Solvents[a]



entry	solvent	yield (%)[b]	*ee* (%)[c]	*dr* (%)[d]
1	Toluene	50	97	6:1
2	Trifluorotoluene	27	94	10:1
3	1,4-dioxane	42	95	7:1
4	MTBE	23	71	6:1
5	MeOH	33	89	5:1
6	THF	65	97	3:1
7	Toluene/ 2% MeOH	50	95	10:1
8	**Toluene/ 5% MeOH**	**75**	**91**	**>20:1**
9	Toluene/ 10% MeOH	51	95	3:1
10	Toluene/ 25% MeOH	51	97	3:1

[a] Reaction conditions: **1** (2 equiv, 0.2 mmol), **2** (1 equiv, 0.1 mmol), $Pd(TFA)_2$ (5 mol%), Ligand **L1** (6 mol%), $ZnCO_3$ (6 mol%), DTBMP (1 equiv, 0.1 mmol). [b] ^1H NMR yields determined from the crude reaction mixtures using 1,3-bis (trifluormethyl)-5-bromobenzene as internal standard. [c] Determined by chiral HPLC. [c] The *dr* values were measured by ^1H NMR.

With the optimized conditions in hand, we evaluated a variety of electronically distinct arenediazonium salts (Scheme 2). All reactions were completed within 12 h with isolated yields varying from a moderate 52% (**3c**) up to an excellent 91% (**3j**), with both electron donating and withdrawing substituents on the arenediazonium salt being well tolerated (Scheme 2). Gratifyingly, in all cases the diastereoselectivities of the Heck-Matsuda reaction were always toward the *cis*-arylated product in the range of 7:1 (**3h**) up to >20:1 (**3a** and **3k**).

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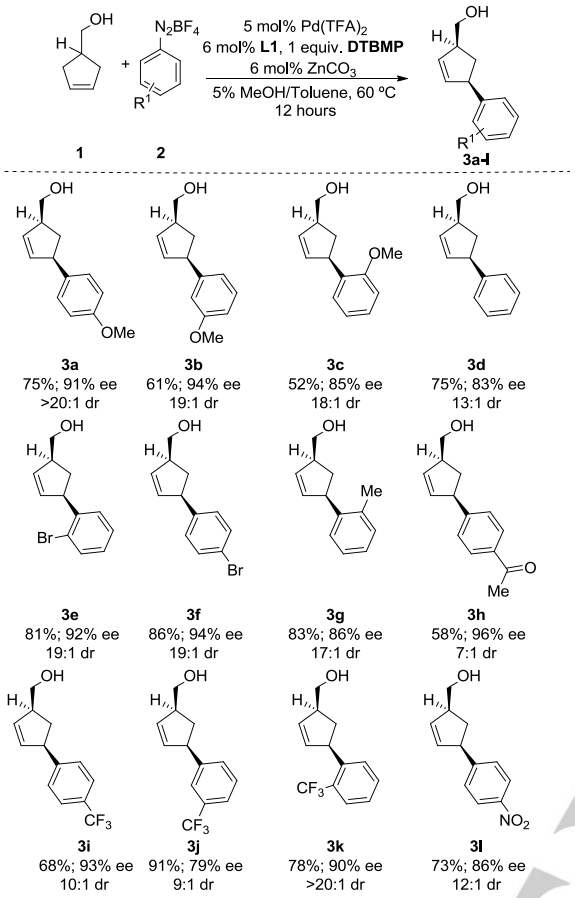


Scheme 2. Enantioselective substrate directable arylation of olefin **1**.

Somewhat surprisingly, *ortho* substituted arenediazonium salts led to superior diastereoselectivity irrespective of their electronic nature. To our satisfaction, the enantioselectivity of the reaction varied from a good 79% ee for **3j** up to an excellent 96% ee for **3h**. It is important to highlight that the relative and absolute stereochemistry of the Heck products was confirmed by X-ray diffraction analysis of the *p*-bromobenzenesulfonate derivative of compound **3a** (Figure 1).[11]

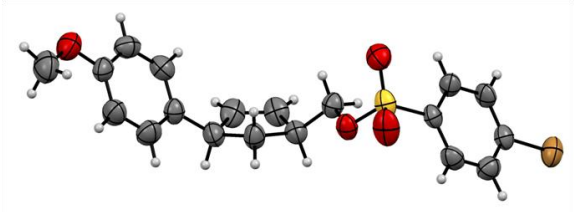
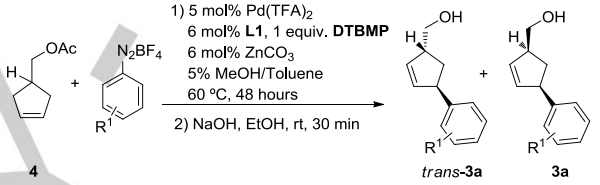


Figure 1. ORTEP diagram for the *p*-bromobenzenesulfonate derivative compound ***deriv*-3a**.

Notably, the hydroxymethyl group directing effect appears to be a ligand-dependent feature, since the *trans*-diastereomer of compound **3h** was reported as almost exclusive product in the literature by an enantioselective cationic Heck reaction using a bisphosphine monoxide ligand as reported by Zhou.[10]

Acetylation of the interacting hydroxyl group resulted in complete loss of the directing effect. As shown in Table 2, arylation of acetyl cyclopentenol **4** under the same reaction conditions described in Scheme 2, followed by ester hydrolysis, led to a mixture favoring the *trans* aryl Heck product in a ratio of 3:1. Moreover, the reaction was much slower (48 h against 12 h), and it resulted in low yields (Table 2). The diastereoselectivity was also shown to be independent to the electronic nature of the arylating agent, since both the 4-methoxy and the 4-acetyl substituted arenediazonium salts led to similar results.

Table 2. Heck-Matsuda arylation of the acetylated cyclopentenol **4**

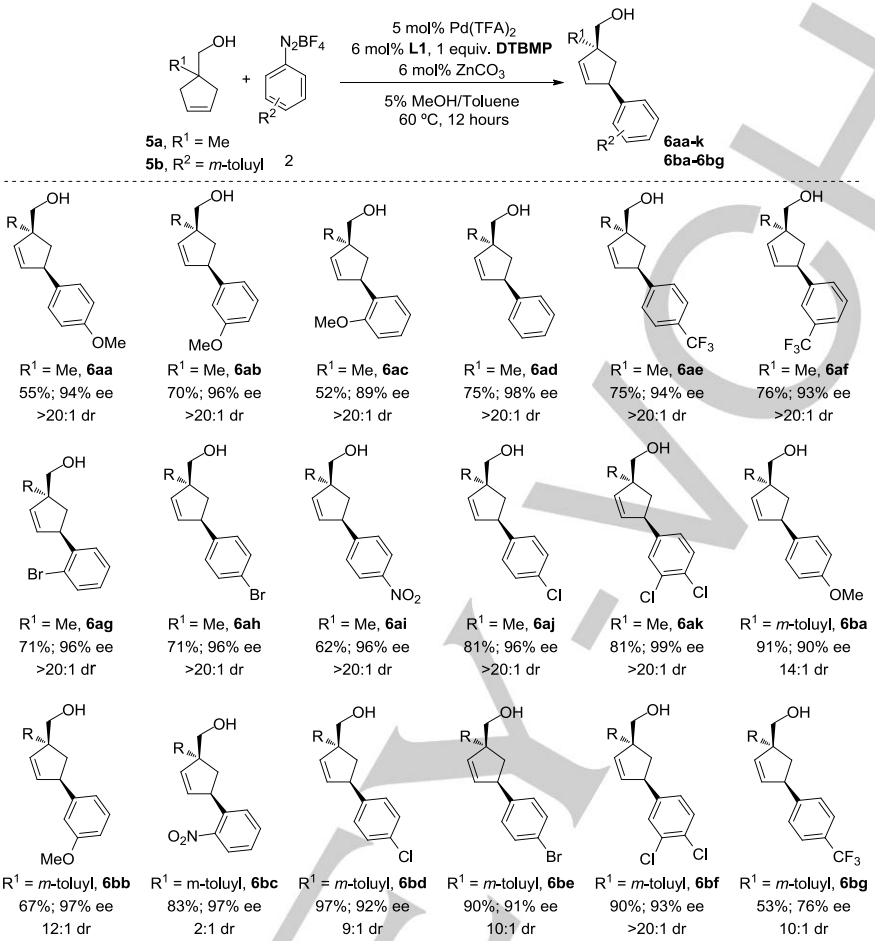


entry	R^1	yield (%)[a]	*dr* (%)[b]
1	*p*-OMe	27	3:1
2	*p*-acetyl	12	3:1

[a] Isolated yield for the combined diastereomeric mixture. [b] dr measured by ^{1}H NMR. For the complete characterization of compound *trans*-**3a** see ref. 9.

The results obtained with 4-hydroxymethyl cyclopentene **1** prompted us to question whether the tertiary center of this olefin could be replaced by an all-carbon quaternary center without impairing the reaction selectivity. The synergetic association of the directing effect of the hydroxyl group with the steric effect provided by the quaternary center should improve the diastereoselectivity of the reaction, but its effect on the enantioselectivity could not be anticipated.

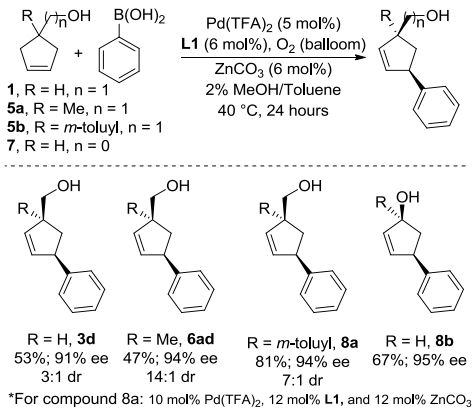
Compounds **5a-b** (**5a**, R= Me; **5b**, R= *m*-tolyl) were then synthesized according to the literature and evaluated in the Heck reaction.[12] Gratifyingly, arylation of **5a-b** under the same conditions used in Scheme 2 furnished the expected Heck products with very high *cis*-diastereoselectivity irrespective of the arenediazonium salt employed (Scheme 3). While the isolated yield varied from 52% for **6ac** up to 81% to **6aj** and **6ak**, the enantioselectivities were always higher than 90%, with a single exception for Heck product **6ac** with 89% ee.



Scheme 3. Substrate directable desymmetrization of cyclic alkenols containing all carbon quaternary centers.

Replacing the methyl group by a bulkier *m*-tolyl substituent (compound **5b**) followed the same trend, providing the arylated Heck product in excellent yields and high enantioselectivity, although a curious drop in the diastereoselectivity was observed on a few occasions. Arylation of cyclopentenol **5b** furnished the Heck products in yields varying from 53% for **6bg** up to an excellent 97% for **6bd**. Once again, we were very pleased to learn that the enantioselectivity of the Heck reactions were very high, usually above 90% ee, with the exception of product **6bg** (*p*-CF_3), obtained in 76% ee.

Since the participation of a cationic palladium intermediate is also invoked in other versions of the Heck reaction, we decided to evaluate non-covalent directing effects under oxidative Heck conditions employing boronic acids (Scheme 4). Some adjustments in the reaction conditions were necessary in order to make the reaction effective, with yields varying from 47% for (**6ad**) up to 81% for (**8a**). As hypothesized, arylations were diastereoselective with the hydroxymethyl group directing the reaction to the major *cis*-aryl Heck product. Compared to the Heck-Matsuda reactions, there were a slight decrease in the diastereoselectivity of these oxidative Heck reactions, but the enantioselectivities were essentially the same (see **3d** in Scheme 2; and **6ad** in Scheme 3). These results clearly illustrate the generality of the non-covalent directing group effect on cationic Heck reactions.



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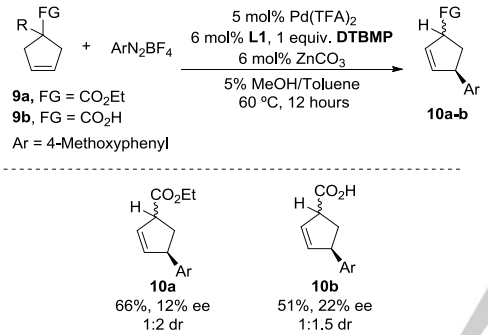
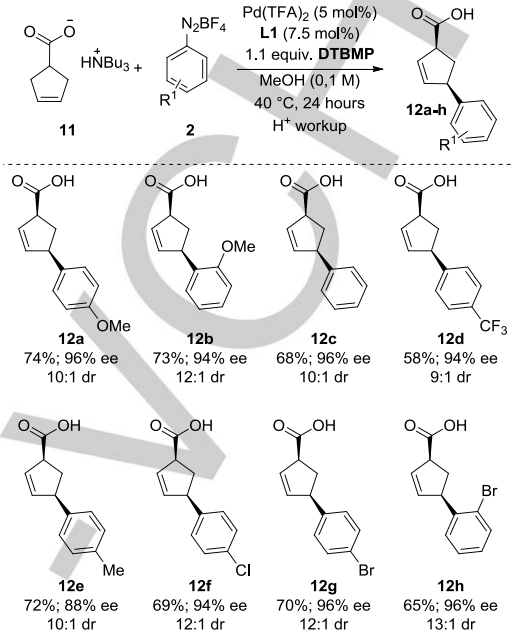
Scheme 4. Enantioselective substrate directable oxidative Heck reaction.

Functional groups such as esters and carboxylic acids were also evaluated and found to be less effective in directing the Heck arylation in the cyclopentene scaffold. A previous report from our group on the Heck-Matsuda arylation of ester **9a** indicated basically no diastereoselectivity and only moderate enantioselectivity, although the reaction could be carried out in good yield.[9a] Curiously, a carboxylic ester was used by Zhou as a model compound for a conventional Heck arylation (triflate and bisphosphine monoxide ligand) and the *trans*-Heck product was obtained as the almost exclusive diastereomer.[10] Application of the optimized reaction conditions described in the present study on carboxylic ester **9a**, or on the corresponding free carboxylic acid **9b**, provided the *trans*-Heck product as the major diastereomer in moderate yield, and low diastereo- and enantioselectivities, as indicated in Scheme 5.



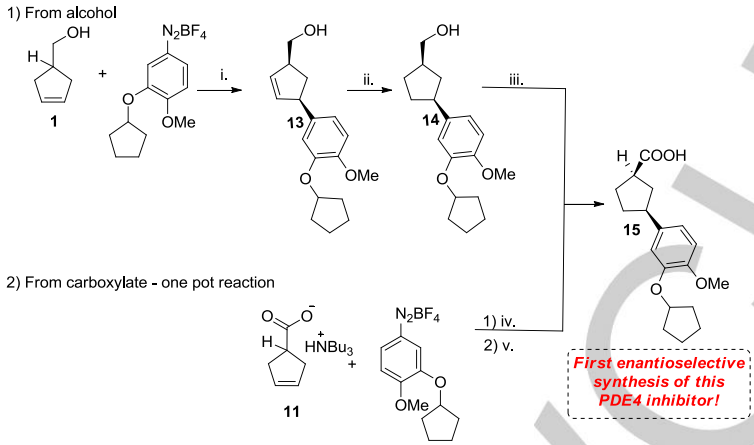
Scheme 5. Evaluation of other potential directing groups.

However, we envisioned that carboxylates could provide the necessary electronic interaction to the cationic palladium via an ion-pair interaction. The corresponding sodium and ammonium salts were then prepared from carboxylic acid **9a** and submitted to the reaction conditions displayed in Scheme 6.[13] Gratifyingly, after some optimization of the reaction conditions, the ammonium carboxylates furnished good yields of the *cis*-Heck products in diastereoselectivities ranging from 9:1 up to 13:1. With the exception of compound **12e** (88% ee; *p*-methyl), all enantioselectivities were higher than 90% ee. The relative and absolute stereochemistry of the carboxylated Heck adducts were confirmed by conversion of carboxylic acid **12a** into alcohol **3a** (Scheme 6 and Scheme 2) and their spectroscopic data and optical rotations compared.



Scheme 6. Carboxylates as directing group on the enantioselective Heck-Matsuda reaction.

To showcase the synthetic potential and applicability of these non-covalent, directable Heck reactions, we devised a straightforward enantioselective synthesis of the phosphodiesterase 4 (PDE4) inhibitor **15**. *Cis*-cyclopentanecarboxylic acid **15** is frequently used as a benchmark in the development of new phosphodiesterase inhibitors.[14] Surprisingly, this interesting compound has been synthesized only in its racemic form and the biological properties of each enantiomer are yet to be determined. Two approaches were used for its synthesis, one starting from alcohol **1** and the other one starting from carboxylate **11**. *Cis*-aryl-cyclopentanecarboxylic acid **15** could be synthesized in 80% ee and 4:1 dr via three steps from alcohol **1**, or in 94% ee and 10:1 dr by means of a one-pot procedure involving Heck arylation of the ammonium carboxylate **11** followed by catalytic hydrogenation (Scheme 7).



Conditions: i. Conditions described at Scheme 2, 46% yield, 87% ee, 9:1 dr; ii. Pd/C, H_2, MeOH, rt, 71% yield, 83% ee, 6:1 dr; iii.TEMPO/BAIB, H_2O/MeCN, rt, 68 % yield, 80% ee, 4:1 dr; iv.Conditions described at Scheme 6; v. H_2 (balloon), MeOH, rt, 6 h, 68% yield, 94% ee, 10:1 dr.

Scheme 7. First enantioselective synthesis of the PDE4 inhibitor **15**.

In order to understand the factors governing the stereochemical outcome of these reactions, we performed DFT calculations for a variety of transition states that are usually invoked in the mechanistic rationale.[9c] Key to this transformation is the migratory insertion transition state, which is generally treated as an irreversible step with prior rapid equilibration of intermediates (Curtin-Hammet scenario).[9f] In addition, the enantioselective arylation of similarly non-activated five-membered cyclic olefins with Pyrabox **L1** ligand is known to proceed through complexes in which the aryl group is *trans* to the ligand's oxazoline moiety. Moreover, these systems also indicated that the enantioselectivity of the reaction arises primarily from a repulsive interaction between the allylic hydrogens of the cyclic alkene and the *t*Bu group in the oxazoline. On the other hand, the diastereoselectivity is proposed to arise from the non-covalent directing group effect of either the hydroxyl or carboxylate functionalities present in the olefin coupling partner. We therefore focused our attention into these interactions.

Taken together, the conformational analysis of alkene **1** and its migratory insertion modes support the presence of a cation-dipole interaction between the palladium center and the hydroxyl group (Figure 2; A and B). Conformational analysis of alkene **1** shows that the conformation **1a** avoids extra butane gauche-like interaction and it is 0.6 kcal mol^{-1} lower in energy than **1b**. However, when the transition state structures were evaluated for the migratory insertion of arylpalladium complex into the same olefin, the favored conformation was found to be different, as seen in transition state **TS1**.

The arylation of alkene **1** through a transition state in which the hydroxyl group has an *endo* orientation is favored by 1.9 kcal mol^{-1} (**TS1**) with respect to **TS4** (Figure 2-B). Mulliken population charges for palladium (*q(Pd)* = +1.0) and oxygen from the hydroxyl group (*q(OH)* = -0.68) are consistant with the existence of an ion-dipole attractive interaction in **TS1** (For more information see Table S1.1). Likewise, the Pd···O distance was found to be 2.73 Å, which is substantially longer than the estimated sum of covalent radii of 2.05 (Figure 3).[15]

These results are in acoordance with the hypothesis that the magnitude of this interaction is dependent on the nature of the ancillary ligand bound to the cationic palladium(II) center. In short, the weak δ-donating *N,N*-ligands enhances the Lewis acidity of the metal center strengthening the non-covalent interaction and therefore **TS1** is favoured when Pyrabox **L1** is employed (Figure 2-B).

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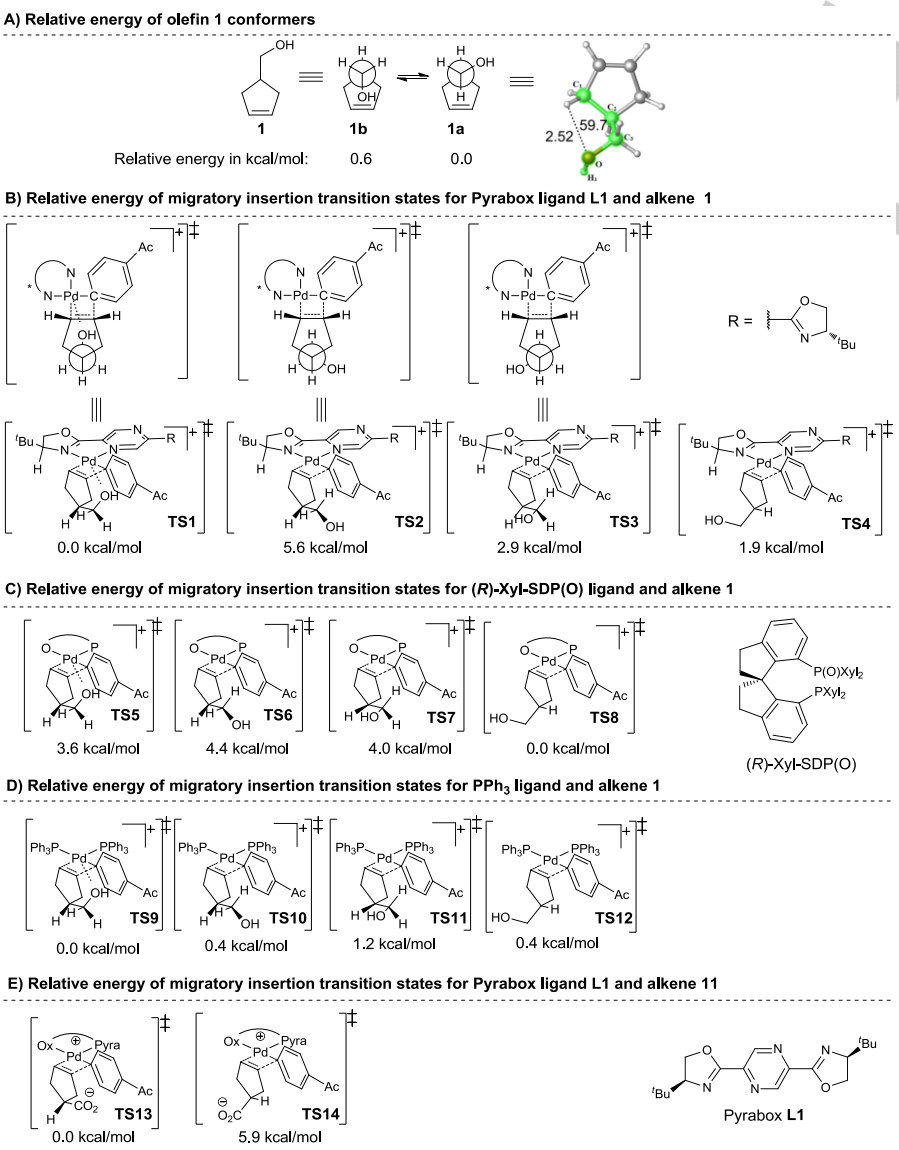

Figure 2. Relative free energies (in kcal mol^{-1} at 333 K) for the migratory insertion transition states (TS) using the Pyrabox **L1**, (*R*)-Xyl-SDP(O) and PPh_3 ligands.

On the other hand, cationic Heck arylation of olefin **1** performed by Zhou and co-workers with a bisphosphine monoxide ligand provided the inverted diastereoselectivity to that obtained by our *N,N*-ligand (Scheme 1). We then decided to investigate the origin of diastereoselectivity of phosphine ligands by using either bisphosphine monoxide or triphenylphosphine ligands.

As suggested by its bulkiness, Zhou's ligand leads to high energy differences between transitions states leading to *cis* (**TS5**, **TS6** and **TS7**) and *trans* (**TS8**) arylated products. Indeed, during the migratory insertion transition state, the *exo* hydroxyl orientation is favored by 3.6 kcal mol^{-1} relative to the *endo* hydroxyl (Figure 2-C; **TS5** vs **TS8**), with the hydroxyl group very distant from the palladium center (Pd···O = 4.39 Å). When triphenyl phosphine was evaluated, despite a shorter Pd···O length of 2.76 Å, the activation energy was barely influenced by the olefin orientation (Figure 2-D). Therefore, the steric hindrance is the most important factor to govern the diastereoselectivity with bisphosphine monoxide ligands. These data highlight the differences among the electronic properties of phosphine and *N*,*N*-ligands. We rationalized these electronic differences by the sigma-donicity character of phosphine ligands that diminishes the cationic nature of palladium rendering the cation dipole interaction weaker. Indeed, the palladium center of transition state **TS9**, supported by $P(Ph)_3$ ligands, was estimated to be less positively charged (*q(Pd)* = +0.72) than the **TS1** with pyrabox *N*,*N*-ligand (*q(Pd)* = +1.01).

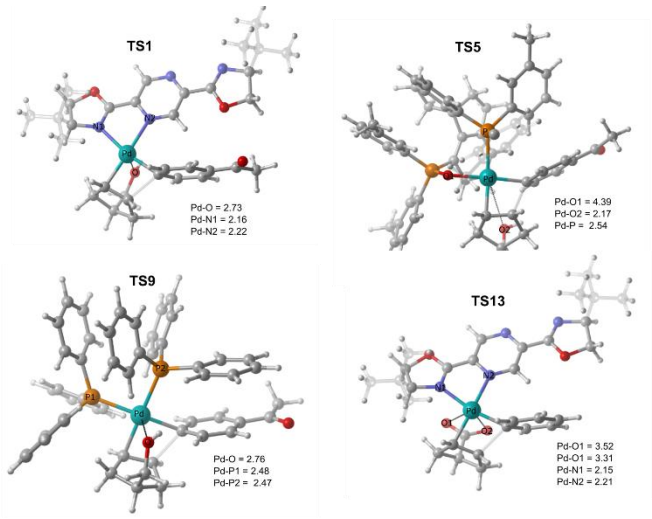

Figure 3. Optimized structures of key migratory insertion transition states. Select distances are given in angstroms (Å).

Finally, for the arylation of the carboxylate containing olefin, DFT calculations showed a clear preference for the formation of the *cis* product (Figure 2-E). The migratory insertion transition state **TS13**, leading to the *cis* product involving Pyrabox ligand **L1**, is favoured by 5.9 kcal mol^{-1} over the *trans* product as calculated for **TS14**. Although this energy difference predicts a much higher diastereoselectivity, the theoretical data agree well with the experimental results, which showed a high preference for the *cis*-arylated products of ~10:1 (Scheme 6). We believe that *in situ* generation of stoichiometric Bronsted acid during the Heck reaction causes a partial protonation of the carboxylate starting material. As shown in Scheme 5, arylation of cyclopentyl carboxylic acid has low diastereoselectivity, and therefore it could be the source of the lower-than-expected diastereoselectivity observed with the carboxylates.

Conclusions

New non-covalent enantioselective substrate directable Heck reactions are presented. These results demonstrate that the non-covalent principle is a general one involving an internal and stabilizing out-of-coordination-sphere ion-dipole interaction between the resident donor functional and the cationic palladium. This aspect was fully illustrated by means of not only Heck-Matsuda reactions using arenediazonium salts but also by oxidative Heck reactions. To some extent, this method complements strategies previously reported in the literature using bisphosphine monoxide ligands in which no interaction between the cationic metal and the hydroxyl or carboxylate functional groups are evident. Both substrate directable Heck reactions are operationally simple, and they have a broad scope. In particular, the applicability of the non-covalent Heck-Matsuda arylation is showcased by a straightforward synthesis of a potent phosphodiesterase 4 (PDE4) inhibitor in an enantioselective manner for the first time. The DFT calculations showed that the observed non-covalent interactions is mainly due to the use of *N,N*-ligands in the Heck reactions. Theoretical results matched well with the experimental data, thus supporting the evidence that ion-dipole non-covalent interactions govern the observed diastereoselectivities. These results, associated with previous ones developed in our research group, also indicate that the stabilizing non-covalent ion-dipole or ion-ion interactions are subtle but general phenomenona which might affect several other cross-coupling reactions. Further examples highlighting these non-covalent directing effects are ongoing and will be reported in due course.

Experimental Section

General procedure for the Heck-Matsuda reaction

To a 4 mL screw-top vial containing a magnetic stirrer, 5 mol% (1.66 mg) of $Pd(TFA)_2$, 6 mol% (2.0 mg) of the ligand **L1**, 6 mol% (0.75 mg) of $ZnCO_3$ and 1 mL of a MeOH:toluene mixture (5:95 v:v) were added. The yellowish solution was stirred at 60 ºC for 5-10 min. Then, it was added 0.1 mmol of DTBMP (20.5 mg), 0.2 mmol of the compound **1** or 0.1 mmol in the case of the compounds **5a**-**5b** and 0.1 mmol of the arenediazonium salt. The vial was then capped and stirred overnight (caution, pressure might develop inside the reaction flask due to the N_2 released by the reaction!). The reaction vessel was then carefully opened and the reaction mixture was poured into a pad of silica gel (230-400 mesh) (column height ~3 cm; diameter ~2 cm) previously washed with a 30% ethyl acetate/hexane mixture. The silica pad was then washed with about 50 mL of the same eluent. The solvent was removed with a rotary evaporator and the resulting mixture was purified in a column chromatography using silica gel, ethyl acetate and *n*-hexanes.

General procedure for the Oxidative Heck reaction

To a 10 mL microwave vial with a magnetic stirrer, it was added 5 mol% (1.66 mg) of $Pd(TFA)_2$, 6 mol% (1.98 mg) of ligand **L1**, 6 mol% (0.75 mg) of $ZnCO_3$ and 0.5 mL of toluene. The vial was then capped and a balloon of oxygen was added. The yellowish solution was stirred at 40 ºC for 15 min. Then, a solution of 0.1 mmol of the corresponding olefin in 0.5 mL of toluene was added followed by addition of 0.2 mmol of the phenyl boronic acid, and 20 µL of methanol. The vial was then capped and a balloon of oxygen was added, the mixture was left stirring for 24 h at 40 ºC under oxygen atmosphere. The reaction vessel was then opened and the reaction mixture was poured into a pad of silica gel (230-400 mesh) (column height ~3 cm; diameter ~2 cm) previously washed with a 50% ethyl acetate/Hexane mixture. The Silica pad was then washed with about 50 ml of the same eluent. The solvent was removed with a rotary evaporator and the resulting mixture purified in a column chromatography using silica gel, ethyl acetate and *n*-hexanes.

General procedure for the Heck-Matsuda reaction of carboxylate containing olefin

To a 4 mL screw-top vial containing a magnetic stirrer, it was added $Pd(TFA)_2$ (5 mol%, 0.01 mmol, 3.3 mg), ligand **L1** (7.5 mol%, 0.015 mmol, 5.0 mg) and 1.5 mL of methanol. The

resulting light orange solution was then stirred at 60 °C for 8 minutes to result in the formation of catalyst complex. In another 4 mL vial, Cyclopent-3-ene-1-carboxylic acid (0.2 mmol, 22.43 mg, 20 µL) and tributylamine (0.2 mmol, 37.1 mg, 47.5 µL) were stirred at room temperature in 0.5 mL of methanol for 8 minutes. After 8 minutes stirring at 60 °C, the catalyst complex was cooled to room temperature and was transferred to the vial containing the tributylaminecarboxylate salt. Then DTBMP (0.22 mmol, 41 mg) was added to it, followed by the addition of the appropriate arenediazonium salt (0.15 mmol). The reaction progress was monitored by TLC using a 1:1 ethyl acetate/n-hexane mixture and stained by PMA (phosphomolybdic acid) solution. On complete consumption of the olefin shown by TLC, the reaction mixture was filtered through a short pad of silica gel (2-3 cm long) in 24 mL plastic syringe and washed with ethyl acetate to remove the more polar impurities. The resulting filtrate was concentrated at low pressure on rotary evaporator. The crude product was purified by flash column chromatography using 30% ethyl acetate/n-hexanes as eluent to afford the Heck products with the reported yields. For determining enantiomeric excess (*ee*), the compounds were first reduced using lithium aluminium hydride to their corresponding alcohols and then analysed.

Procedure for the synthesis of (PDE4) inhibitor 15

*I. From the alcohol **1***

a) Synthesis of compound **13** from the olefin **1**

In a 40 mL vial containing a stirrer bar were added 5 mol% (16.6 mg) of $Pd(TFA)_2$, 6 mol% (19.8 mg) of **L1** ligand, 6 mol% (7.5 mg) of $ZnCO_3$ and 10.5 mL of a MeOH:toluene mixture (5:95). The yellowish solution was stirred at 60 ºC for 5-10 min. Then, it was added 205.3 mg (1.0 mmol) of DTBMP, 196.3 mg (2.0 mmol) of olefin **1** and 306.1 mg (1.0 mmol) of the arenediazonium salt. The vial was then capped and stirred overnight (caution, pressure might develop inside the reaction flask due to the N_2 released by the reaction!). The reaction vessel was then carefully opened and the reaction mixture was poured into a pad of silica gel (230-400 mesh) (column height ~3 cm; diameter ~2 cm) previously washed with a 50% ethyl acetate/hexane mixture. The silica pad was then washed with about 150 mL of the same eluent. The solvent was removed with a rotary evaporator and the resulting mixture purified in a column chromatography using silica gel, ethyl acetate and n-hexanes.

b) Synthesis of compound **14** from alcohol **13**

In a 25 mL round bottom flask containing a stirrer bar, 130 mg (0.45 mmol) of the previous prepared Heck product **13**, 8 mL of methanol and 4.8 mg (0.00451 mmol, 1 mol%) of 10% Pd/C were added. The flask was capped with a rubber septa and H_2 balloon was added. The reaction was left stirring for 2 hours. The reaction mixture was poured into a pad of silica gel (230-400 mesh) (column height ~3 cm; diameter ~2 cm) previously washed with ethyl acetate. The silica pad was then washed with about 150 mL of ethyl acetate. The solvent was removed with a rotary evaporator and the resulting mixture purified in a column chromatography using silica gel, ethyl acetate and *n*-hexanes.

c) Synthesis of compound **15** from the reduced product **14**

To a 25 mL round bottom flask containing 49 mg (0.17 mmol) of compound **14** and a stirring bar were added 2 mL of H_2O, 2 mL of MeCN, 218 mg (0.68 mmol) of BAIB and 18 mg (0.12 mmol) of TEMPO. The round bottom flask was wrapped in an aluminium foil and the mixture was stirred at room temperature for 4 h. The mixture was then diluted with 4 mL of H_2O and 10 mL of ethyl acetate. The organic phase was separated and the aqueous phase was extracted 3 times with 10 mL of ethyl acetate. The combined organic phases were dried with Na_2SO_4, filtered and the volatiles were removed with the help of a rotary evaporator. The crude mixture was purified using flash chromatography with ethyl acetate/n-hexanes.

II. From the carboxylate – "one pot synthesis"

a) Synthesis of compound **15** from carboxylate containing olefin **11**

To a 4 mL screw-top vial containing a magnetic stir-bar, it was added $Pd(TFA)_2$ (5 mol%, 0.01 mmol, 3.3 mg), ligand **L1** (7.5 mol%, 0.015 mmol, 5.0 mg) and 1.5 mL of methanol. The resulting light orange solution was then stirred at 60 °C for 8 minutes to result in the formation of catalyst complex. In another 4 mL vial, Cyclopent-3-ene-1-carboxylic acid (0.2 mmol, 22.43 mg, 20 µL) and tributylamine (0.2 mmol, 37.1 mg, 47.5 µL) were stirred at room temperature in 0.5 mL of methanol for 8 minutes to generate the carboxylate **11**. After 8 minutes stirring at 60 °C, the catalyst complex was cooled to room temperature and was transferred to the vial containing the tributylaminecarboxylate salt. Then DTBMP (0.22 mmol, 41 mg) was added to it, followed by the addition of the arenediazonium salt (0.15 mmol). On complete consumption of the olefin shown by TLC, a H_2 balloon was placed in the reaction vial and stirred for 6 hours at room temperature. The reaction mixture was filtered through a short pad of silica gel and washed with ethyl acetate to remove the more polar impurities. The resulting filtrate was concentrated at low pressure on rotary evaporator. The crude product was purified by flash column chromatography using 30% ethyl acetate/*n*-hexanes as eluent to afford the desired product.

*Preparation of p-bromobenzenesulfonate **deriv-3a***[16]

The compound **3a** (108.0 mg, 0.53 mmol, 1.0 equiv.) was dissolved in DCM (5 mL); 4-$BrPhSO_3Cl$ (161.0 mg, 0.63 mmol, 1.2 equiv.) was added, followed by Et_3N (58.80 mg, 81 µL, 1.1 equiv.). The mixture was stirred for 48 hours at room temperature. A saturated $NaHCO_3$ solution was added to quench the reaction. The organic phase was extracted with ethyl acetate (3X), dried over Na_2SO_4 and then concentrated. The crude residue was purified by flash chromatography. After recrystallization from *n*-hexanes compound, **deriv-3a** was submitted to X-ray analysis.

Computational details

Transition state calculations were based on density functional theory (DFT) using Gaussian 09 package.[17] All the structures are fully optimized with the density functional M06. The standard 6-31+G(d,p) basis set was adopted for lighter atoms, while valence basis set with an SDD effective core potential (ECP-SDD)[18] was used for the palladium atom (Pd). Frequency calculations were also performed at the M06/6-31+G(d,p), SDD(Pd) high level of theory, in order to verify the nature of transition states. Solvent effect was introduced in all the calculations through the SMD continuum solvation method.[19] In

some cases, explicit solvent molecules were introduced to better evaluate their effect in the reaction profiles. Single-point calculations, also considering the solvation effects, were performed using the Ahlrichs *et al*.[20] quadruple-ζ (def2-QZVP) basis set combined with ECPSDD for Pd and the 6-311++G(2d,p) basis set for the remaining atoms. The final energy was corrected adding the free energy correction at 313/333 K, depending on the reaction, and 1 atm. Explicit solvent calculations were carried out by introducing a single solvent molecule to the structures. This single molecule was oriented to the olefin polar portion, hydroxyl or carboxylate groups. The structures were fully re-optimized, also considering the SMD continuum solvation model. Only reactions involving the Pyrabox ligand **L1** were considered for these calculations, since it is a smaller ligand and more accessible to the solvent effects.

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Keywords: Heck reaction • Oxidative Heck reaction • Palladium catalysis • Noncovalent interactions • Density functional calculations

[1] a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev*. **2000**, *100*, 3009–3066; b) F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2005**, *61*, 11771–11835; c) A. Roglans, A. Pla-Quintana, M.Moreno-Mañas, *Chem. Rev.* **2006**, *106*, 4622–4643; d) J. G. Taylor, A. V. Moro, C. R. D. Correia, *Eur. J. Org. Chem.* **2011**, *2011*, 1403–1428; e) F.-X. Felpin, L. Nassar-Hardy, F. Le Callonnec, E.Fouquet, *Tetrahedron* **2011**, *67*, 2815–2831; f) M. Oestreich, *Angew. Chem. Int. Ed.* **2014**, *53*, 2282–2285.; *Angew. Chem*. **2014**, *126*, 2314–2317; g) M. Oestreich, The Mizoroki-Heck reaction, *Wiley*, 2009.

[2] Representative examples of therapeutic agents include: Verapamil, a) R. Mannhold, R. Steiner, W. Haas, R. Kaufmann, *NaunynScmiedeberg's Arch. Pharmacol.* **1978**, *302*, 217-226. Tolterodine, b) A. Graul, A.M. Martel, J. Castaner, *Drugs Fut.* **1997**, *22*, 733-737. Sertraline, c) W. M. Welch, A. R. Kraska, R. Sarges, B. K. Koe, *J. Med. Chem.* **1984**, *27*, 1508-1515; Escitalopram, d) S. Dhillon, L. J. Scott, G. L. Plosker, *CNS Drugs* **2006**, *20*, 763-790.

[3] a) P. Prediger, L. F. Barbosa, Y. Génisson, C. R. D. Correia, *J. Org. Chem.* **2011**, *76*, 7737–7749; b) J. G. Taylor, C. R. D. Correia, *J. Org. Chem.* **2011**, *76*, 857–869; c) D. A. Barancelli, A. G. Salles Jr., J. G. Taylor, C. R. D. Correia, *Org. Lett.* **2012**, *14*, 6036–6039; d) C. C. Oliveira, E. A. F. Santos, J. H. B. Nunes, C. R. D. Correia, *J. Org. Chem.* **2012**, *77*, 8182–8190; e) K. Canto, R. S. Ribeiro, A. F. P. Biajoli, C. R. D. Correia, *Eur. J. Org. Chem.* **2013**, *2013*, 8004–8013; f) C. C. Oliveira, R. A. Angnes, C. R. D. Correia, *J. Org. Chem.* **2013**, *78*, 4373–4385; g) P. Prediger, A. R. Silva, C. R. D. Correia, *Tetrahedron* **2014**, *70*, 3333–3341; h) C. C. Oliveira, A. Pfaltz, C. R. D. Correia, *Angew. Chem. Int. Ed.* **2015**, *54*, 14036–14039; i) I. U. Khan, S. Kattela, A. Hassan, C. R. D. Correia, *Org. Biomol. Chem.* **2016**, *14*, 9476–9480; j) A. R. Silva, E. C. Polo, N. C. Martins, C. R. D. Correia, *Adv. Synth. Cat.* **2018**, *360*, 346–365; k) C. Frota, E. C. Polo, H. Esteves, C. R. D. Correia, *J. Org. Chem.* **2018**, 83, 2198-2209. For reviews on the application of Pd catalyzed C−C bond forming reactions on total synthesis pharmaceuticals synthesis, see: a) A. B. Dounay and L. E. Overman, in *The Mizoroki–Heck Reaction*, ed. Martin Oestreich, John Wiley & Sons, Ltd, **2009**, pp. 533–568; b) A. F. P. Biajoli, C. S. Schwalm, J. Limberger, T. S. Claudino, A. L. Monteiro, *J. Braz. Chem. Soc*. **2014**, *25*, 2186–2214; c) M. M. Victor, G. S. B. Silva, *Química Nova* **2016**, *39*, 859–875.

[4] A.-L. Lee, *Org. Biomol. Chem.* **2016**, *14*, 5357–5366.

[5] a) Z.-M. Chen, M. J. Hilton, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 11461–11464; b) H. H. Patel, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 14226–14229; c) E. Yamamoto, M. J. Hilton, M. Orlandi, V. Saini, F. D. Toste, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 15877–15880; d) C. Zhang, B. Tutkowski, R. J. DeLuca, L. A. Joyce, O. Wiest, M. S. Sigman, *Chem. Sci.* **2017**, *8*, 2277–2282; e) C. Wu, J. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 650–652; f) X. Wu, J. (Steve) Zhou, *Chem. Commun.* **2013**, *49*, 4794–4796; g) G. Yue, K. Lei, H. Hirao, J. (Steve) Zhou, *Angew. Chem. Int. Ed.* **2015**, *54*, 6531–6535; h) D. Cortés-Borda, K. V. Kutonova, C. Jamet, M. E. Trusova, F. Zammattio, C. Truchet, M. Rodriguez-Zubiri, F.-X. Felpin, *Org. Process Res. Dev.* **2016**, *20*, 1979–1987; i) W. Khodja, A. Leclair, J. Rull-Barrull, F. Zammattio, K. V. Kutonova, M. E. Trusova, F.-X. Felpin, M. Rodriguez-Zubiri, *New J. Chem.* **2016**, *40*, 8855–8862; j) G. M. Borrajo-Calleja, V. Bizet, T. Bürgi, C. Mazet, *Chem. Sci.* **2015**, *6*, 4807–4811; k) T. Y. Chaudhari, A. Hossian, M. K. Manna, R. Jana, *Org. Biomol. Chem.* **2015**, *13*, 4841–4845.

[6] a) C. M. Andersson, J. Larsson, A. Hallberg, *J. Org. Chem.* **1990**, *55*, 5757–5761; b) P. Nilsson, M. Larhed, A. Hallberg, *J. Am. Chem. Soc.* **2001**, *123*, 8217–8225 and references cited herein; c) K. Itami, K. Mitsudo, K. Fujita, Y. Ohashi, J.-i. Yoshida, *J. Am. Chem. Soc.* **2000**, *122*, 12013-12014; d) M. R. Rivero, J. C.de la Rosa, J. C. Carretero, *J. Am. Chem. Soc.* **2003**, *125*, 14992-14993 and references cited therein; e) M. Oestreich, *Eur. J. Org. Chem.* **2005**, *2005*, 783–792. For an excellent review on substrate directable Heck reactions, see: f) M. Oestreich, *Top OrganometChem* **2007**, *24*, 169-192. For excellent reviews on the general concept of substrate directable reactions, see: g) A. H. Hoveyda, , D. A. Evans, G. Fu, *Chem. Rev*. **1993**, *93*, 1307-1370; h) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356-363; i) V. Snieckus, *Chem. Rev*. **1990**, *90*, 879-933; j) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552-560; k) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206-2225. For a recent review on substrate directable reactions, see: l) S. Bhadra, H. Yamamoto, *Chem. Rev*. **2018**, *118*, 3391-3446.

[7] E. Bernocchi, S. Cacchi, P. G. Ciattini, E. Morera, G. Ortar, *Tetrahedron Lett*. **1992**, *33*, 3073-3076.

[8] a) M. Oestreich, F. Sempere-Culler, A. B. Machotta, *Angew. Chem. Int. Ed.* **2005**, *44*, 149–152; b) A. B. Machotta, B. F. Straub, M. Oestreich, *J. Am. Chem. Soc.* **2007**, *129*, 13455–13463.

[9] a) C. C. Oliveira, A. G. Salles Jr., E. A. F. Santos, C. R. D. Correia, *Tetrahedron Lett.* **2012**, *53*, 3325-3328; b) R. A. Angnes, J. M. Oliveira, C. C. Oliveira, N. C. Martins, C. R. D. Correia, *Chem. Eur. J.* **2014**, *20*, 13117–13121; c) J. O. Silva, R. A. Angnes, V. H. M. Silva, B. M. Servilha, M. Adeel, A. A. C. Braga, A. Aponick, C. R. D. Correia, *J. Org. Chem.* **2016**, *81*, 2010–2018; d) F. de Azambuja, R. C. Carmona, T. H. D. Chorro, G. Heerdt, C. R. D. Correia, *Chem. Eur. J.* **2016**, 22, 11205–11209; e) S. Kattela, G. Heerdt, C. R. D. Correia, *Adv. Synth. Catal.* **2017**, *359*, 260-267; f) V. H. M. Silva, A. P. L. Batista, O. Navarro, A. A. C. Braga, *J. Comput. Chem.* **2017**, *38*, 2371-2377.

[10] S. Liu, J. (Steve) Zhou, *Chem. Commun.* **2013**, *49*, 11758–11760.

[11] CCDC 1539715 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre.
[12] For the preparation of 5a see: a) S. Elahipanah, P. J. O'Brien, D. Rogozhnikov, M. N. Yousaf, *Bioconjugate Chem*. **2017**, *28*, 1422–1433. For the preparation of 5b see: b) Y.-J. Wu, H. He, R. Bertekap, R. Westphal, S. Lelas, A. Newton, T. Wallace, M. Taber, C. Davis, J. E. Macor, J. Bronson, *Bioorg. Med. Chem.* **2013**, *21*, 2217–2228.
[13] Initial attempts were carried out with sodium carboxylates. However, as sodium salts were insoluble in the reaction solvent we used the ammonium salt instead.
[14] S. B. Christensen, A. Guider, C. J. Forster, J. G. Gleason, P. E. Bender, J. M. Karpinski, W. E. DeWolf, M. S. Barnette, D. C. Underwood, D. E. Griswold, L. B. Cieslinski, M. Burman, S. Bochnowicz, R. R. Osborn, C. D. Manning, M. Grous, L. M. Hillegas, J. O. Bartus, M. D. Ryan, D. S. Eggleston, R. C. Haltiwanger, T. J. Torphy, *J. Med. Chem.* **1998**, *41*, 821–835. (a) EP1292563 (A2) Abstract of corresponding document: WO0200593 (A2), **2003**.
[15] B. Cordero, V. Gómez, A. E. Platero-Prats, M. Revés, J. Echeverría, E. Cremades, F. Barragán, S. Alvarez, *Dalton Trans.* **2008**, *21*, 2832–2838.
[16] W. Zi, F. D. Toste, *Angew. Chem. Int. Ed.* **2015**, *54*, 14447–14451.
[17] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox "Gaussian 09, Revision D.01", Gaussian Inc. Wallingford CT **2009**.
[18] D. Andrae, U. Häußermann, M. Dolg, H. Stoll, H. Preuß, *Theor. Chem. Acc.* **1990**, *77*, 123-141.
[19] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378-6396.
[20] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys*. **2005**, 7, 3297-3305.

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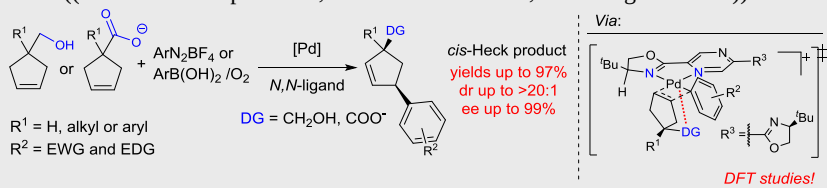

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Enantioselective non-covalent substrate directable Heck-Matsuda and Oxidative Heck arylations of unactivated five-membered carbocyclic olefins

Getting some extra help! Substrate-directable diastereo- and enantioselective Heck arylation of unactivated cyclopentenes can be accomplished by a key out-of-coordination-sphere interaction of an ion-dipole or ion pair between the cationic palladium and an electron rich functional group at the olefinic coupling partner. This effect was shown to be operative in both Matsuda and oxidative Heck reactions. The *N*,*N*-ligands are at the origin of the high diastereoselectivity as investigated by DFT calculations.