Quaternary Stereogenic Centers through Enantioselective Heck Arylation of Acyclic Olefins with Aryldiazonium Salts: Application in a Concise Synthesis of (*R*)-Verapamil

Caio C. Oliveira,[a,b] Andreas Pfaltz,*[b] and Carlos Roque Duarte Correia*[a]

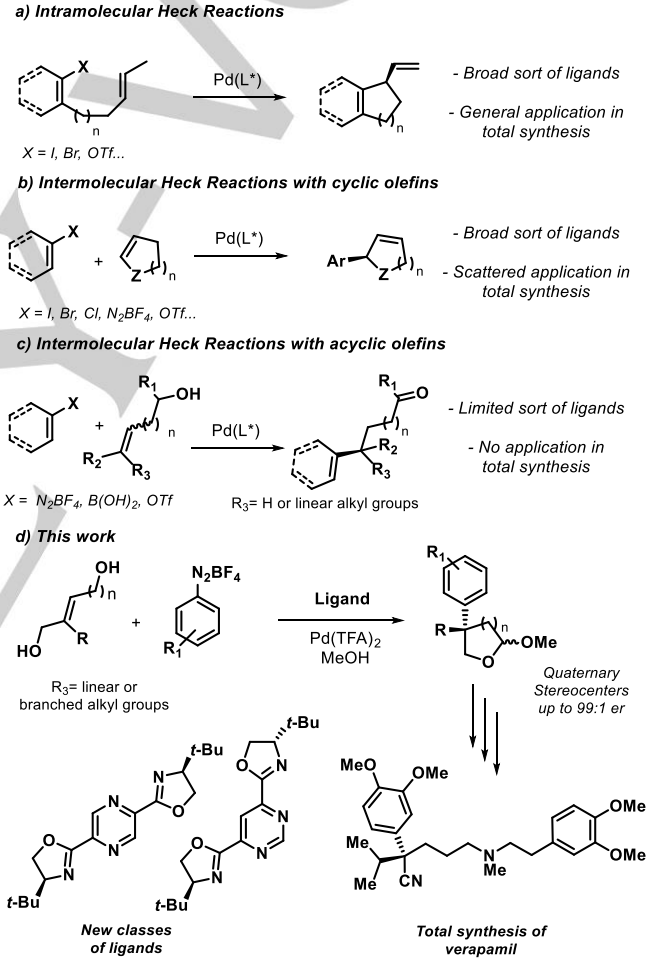
Abstract: We describe herein a highly regio and enantioselective Pd-catalyzed Heck arylation of unactivated trisubstituted acyclic olefins to provide all-carbon quaternary stereogenic centers. Novel chiral *N*,*N*-ligands of the pyrimidine- and pyrazino-oxazoline class were developed for that purpose providing the desired products in good to high yields with enantiomeric ratios of up to >99:1. Both linear and branched substituents on the olefins were well-tolerated. The potential of this new method is demonstrated by the straightforward synthesis of several *O*-methyl lactols and lactones containing quaternary stereocenters, together with a concise enantioselective total synthesis of the calcium channel blocker verapamil.

Enantioselective palladium-catalyzed Heck reactions have a prominent position in modern chemical synthesis.[1] A pivotal aspect of these C-C forming reactions is the precise control of the carbopalladation and β-elimination steps in the catalytic cycle. For these reasons, most applications in total synthesis were based on intramolecular variants where the substrate bias provides high level of regiocontrol (Scheme 1-a).[2] In contrast, intermolecular enantioselective Heck reactions have been mostly used for the evaluation of new chiral ligands with only scattered applications in organic synthesis (Scheme 1-b).[3]

A new development in this field was the arylation of acyclic alkenyl alcohols recently reported independently by Sigman and Correia using aryldiazonium salts as electrophiles.[4-6] The newly formed stereogenic centers in the carbopalladation step were preserved due to the high preference of the palladium hydride species for migration along the carbon chain followed by conversion of the alcohol into an aldehyde function (Scheme 1-c). Subsequently, Sigman expanded the scope of the enantioselective Heck reaction for the construction of both tertiary and quaternary stereo-centers using vinyl triflates and boronic acids as reactants.[7-9]

On the other hand, enantioselective intermolecular Heck reactions with acyclic olefins are still in the early stage of development. So far, only bisoxazoline **L1** and pyridine-oxazoline **L2** were described as effective chiral ligands for this important transformation (Scheme 2). While **L1** shows high efficiency for the desymmetrization alkenyl-diols,[6] **L2** was reported for the arylation of non-symmetrical alkenyl-alcohols bearing basically one free hydroxyl group and linear substituents on trisubstituted olefins (Scheme 1-c).[5,7-9]

In this context, we describe herein our results with novel chiral pyrimidine and pyrazine-oxazolines as chiral *N,N*-ligands for highly site and enantioselective palladium-catalyzed arylations of trisubstituted olefins using aryldiazonium salts as aryl-transfer agents. The unique reactivity of the newly developed catalytic systems allowed the use of both branched and linear substituents in the trisubstituted olefins, at low catalyst loading. Furthermore, a new route for the calcium channel blocker (*R*)-verapamil is disclosed using the enantioselective Heck reaction of acyclic olefins for the first time as a key step in total synthesis (Scheme 1-d).[9]



Scheme 1. Overview of enantioselective Heck reactions.

As an extension of our interest in the stereoselective arylation of allylic and homoallylic alcohols, we chose alkenol **1a** as a model for our studies (Scheme 2).[5,10] We began the investigation using our previous reported conditions, *i.e.*, $Pd(TFA)_2$ (5 mol%), bisoxazoline **L1** (10 mol %), and basic zinc carbonate (0.1 equiv) in methanol at 60 °C, to obtain *O*-methyl-lactol **3a** in 77% yield with an enantiomeric ratio (*er*) of 95:5. However, only moderate level of regiocontrol (9:1) was observed in favor of the desired γ–arylation.[5] Replacement of ligand **L1** by **L2** provided higher regioselectivity (14:1), but at the cost of a considerable lower yield (46%) of the Heck product **3a**. In view of the

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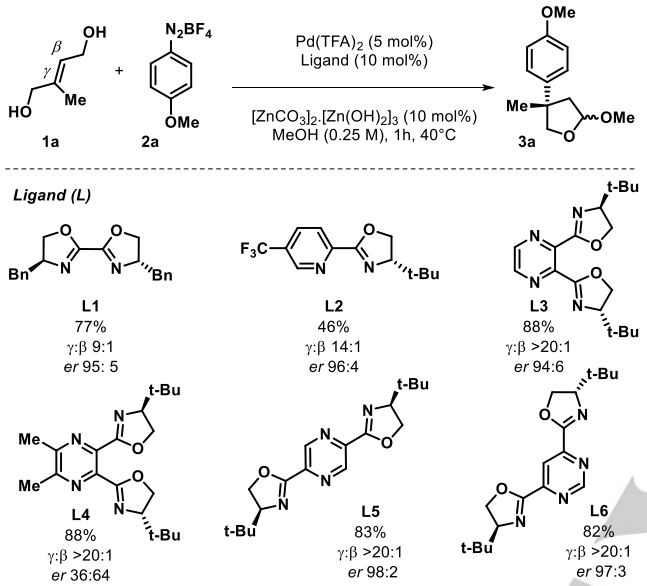
promising results with these two ligands and the knowledge that electron withdrawing groups at the ligand aromatic ring are beneficial to achieve higher levels of enantiodifferentiation, we decided to combine the C_2-symmetry of **L1** with the distinct donating properties of the metal binding nitrogen atoms present in the pyridine-oxazoline **L2** to access novel classes of *N*,*N*-scaffold. Based on the seminal work of Brunner in the enantioselective hydrosilylation of ketones,[11] we designed new pyrazine and pyrimidine ligands decorated with two oxazolines **L3-L6** (Scheme 2).



Scheme 2. Ligand screening for the enantioselective Heck reactions.

The new ligands **L3** and **L4** provided high levels of regiocontrol (>20:1), but only **L3** was capable of producing good *er* (94:6). Despite the lower *er* (36:64), an interesting inversion of absolute configuration at the quaternary center was observed with **L4**. This phenomenon can be rationalized by the presence of the methyl groups at C5 and C6, thus preventing the stabilizing C6−H-π interaction between the pyridine α–hydrogen and the aryl group after the oxidative addition and olefin coordination, as suggested by theoretical mechanistic investigations for **L2**.[12,13] Furthermore, crystallographic analysis of the pre-catalyst obtained from **L4** indicated the preferred formation of the 7-membered ring complex **C1,** where palladium is chelated by both oxazolines, instead of the pyrazine-oxazoline complex **C2**. This unanticipated behavior was supported by DFT analysis that predicted the 7-membered Pd complex **C1** to be 11.56 kcal/mol more stable than complex **C2** (Figure 1).

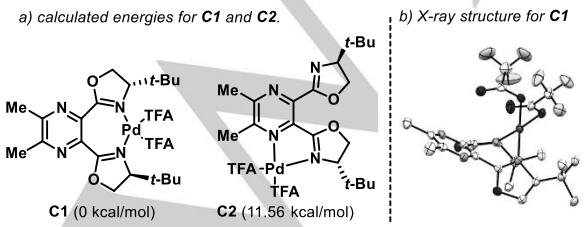
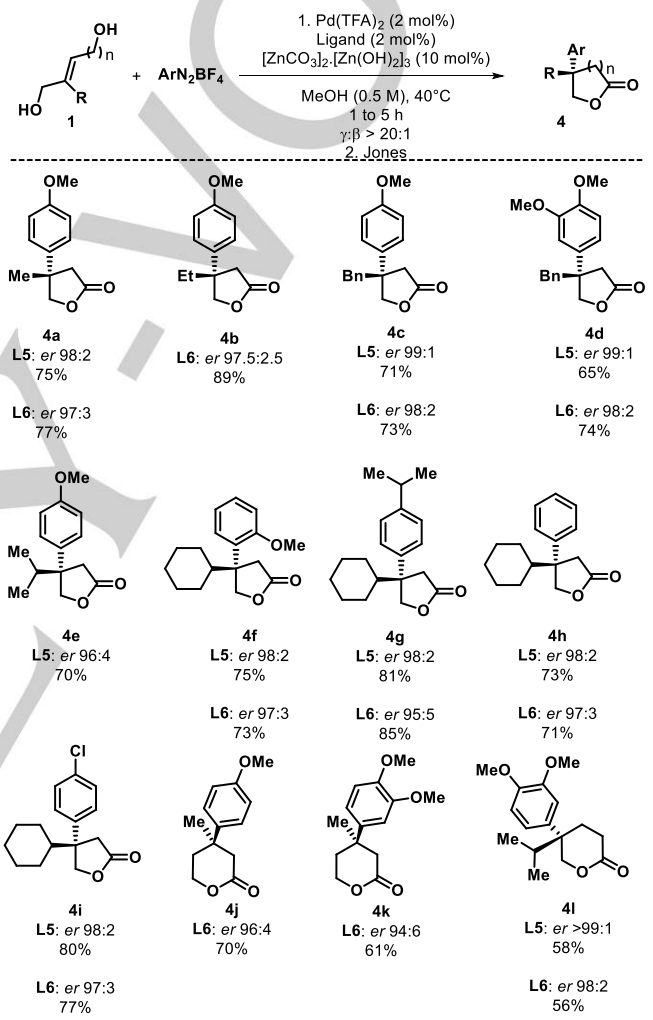


Figure 1. Energy profile for complexes C1 and C2.

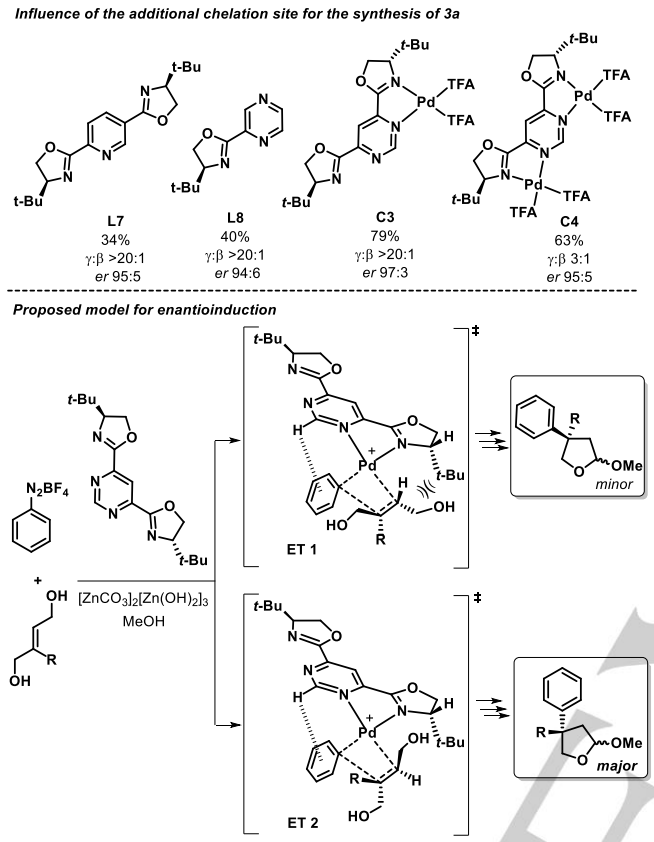
To circumvent the intrinsic formation of two isomeric complexes from 2,3-disubstituted pyrazines, we synthesized its 2,5 isomer (**L5**) and the 4,6-pyrimidine-bisoxazoline (**L6**). To our delight, Heck arylations with these ligands provided the Heck product **3a** in good yields (82-83%), high regiocontrol (> 20:1) and excellent enantiomeric ratios of 98:2, and 97:3, respectively (Scheme 2). Further optimization enabled us to decrease the loading of both $Pd(TFA)_2$ and **L5** or **L6** to only 2 mol%, the lowest reported catalyst loading for an intermolecular enantioselective Heck reaction with acyclic olefins, without losses in chemical yields or stereoselectivity.



Scheme 3. Enantioselective synthesis of lactones **4**.

Under the optimized conditions employing ligands **L5** and **L6**, we extended the application range of the intermolecular Heck reaction to other olefins and aryldiazonium salts (Scheme 3). To facilitate spectroscopic characterization and also to increase the synthetic value of our Heck adducts, the *O*-methyl lactols **3** were directly oxidized to the corresponding lactones **4** with Jones reagent. Attractive features of the new method include: (i) high site selectivity for the migratory insertion with the aryl group transferred to the more electron poor olefinic carbon regardless of the topology of the hydroxyl group, allowing the use of allylic and homoallylic diols without protecting groups; (ii) arylation of

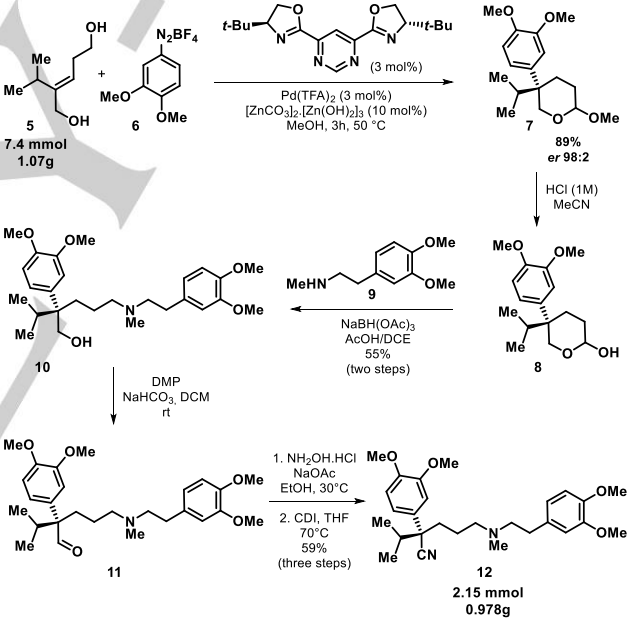
trisubstituted olefins bearing branched substituents with high stereo- and regio control, using a slight increase in catalyst loading (3 mol%) and temperature (50 ºC); (iii) use of either ligands **L6** or **L7** which proved equally efficient for the Heck reactions leading to **4a,c** and **d**.



Scheme 4. Enantioselective synthesis of lactones **4**.

To obtain additional information about the role of the second chelation site of these new ligands, we synthesized the pyridine-bisoxazoline ligand (**L7**) and the pyrazine-oxazoline ligand (**L8**). Despite the high level of regiocontrol, these ligands provided the Heck product **3a** in only modest chemical yields and slightly lower enantiomeric ratios than those observed with **L5** and **L6**. To evaluate the role of the possible mono and bis-chelated palladium pre-catalysts, we synthesized complex **C3** and **C4**. While complex **C3** gave essentially the same results as the catalyst generated *in situ*, the C2-symmetric binuclear complex **C4** provided only modest regiocontrol suggesting that this type of complex is not the major catalyst in our Heck arylations. However, the good *er* indicated its potential use in other enantioselective transformations, especially for those reactions where low catalyst concentrations are required.[14] Although our attempts to isolate the zinc complexes were unsuccessful, we believe that the free "chelation sites" present in **L5** and **L6** might coordinate to zinc in the reaction medium leading to a more electron-withdrawing portion on the ligand.[11] Finally, we propose that at the carbopalladation step the aryl group is placed *trans* to the oxazoline ring and is stabilized through the C6−H-π interaction.[12,13] The enantioselectivity is controlled by minimization of the repulsive interaction between the bulkier substituent at the secondary olefinic carbon and the *t*-butyl substituent at the oxazoline (**ET1** and **ET2**).

The structural complexity provided by our arylation method allowed the development of a straightforward enantioselective synthesis of the calcium channel blocker verapamil.[15] Although this drug is commercialized in its racemic form, the distinct pharmacological profiles of the enantiomers, makes an enantioselective synthesis highly desirable.[16,17] Our synthetic route started with a gram scale Heck arylation of diol **5** with aryldiazonium salt **6**. The six-membered *O*-methyl lactol **7** was obtained after filtration through a short pad of silica-gel as a single regioisomer in 89% yield and 98:2 *er* (Scheme 4). After hydrolysis using aqueous HCl solution in acetonitrile,[6,18] lactol **8** was directly used in a standard reductive amination with the *N*-methyl homoveratrylamine (**9**) to provide the neo-pentylic alcohol **10** in 55% yield over two steps.[19] Finally, (*R*)-verapamil **12** was obtained (0.98g, 2.15 mmol) after three additional steps: (i) Dess-Martin oxidation of the **11**, (ii) oxime formation and (iii) oxime decomposition after activation by 1,1′-Carbonyldiimidazole (CDI). It is worth mentioning that our 6 steps synthesis with an overall yield of 29% is the shortest and highest yielding enantioselective route for verapamil (Scheme 5).[17]



Scheme 5. Enantioselective synthesis of (*R*)-verapamil (**12**).

In conclusion, we described herein the development of novel chiral pyrimidine and pyrazine-oxazoline ligands and their effective application in the enantioselective palladium-catalyzed Heck reaction of acyclic trisubstituted olefins bearing linear or branched substituents. The Heck products were obtained in high enantiomeric ratios (up to 99:1) and regioselectivities, even in gram scale reactions. Moreover, we have successfully applied this enantioselective Heck-Matsuda reaction of acyclic olefins as the key step in a concise highly enantioselective total synthesis of the calcium channel blocker (*R*)-verapamil.

Acknowledgements

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Keywords: Enantioselective Heck • Palladium • Verapamil • Quaternary Stereocenters • *N,N*-ligands

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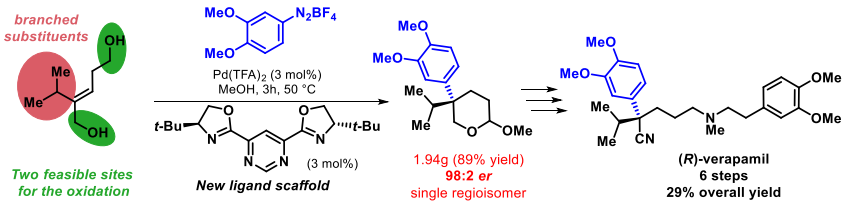

The fruitful combination of designed chiral *N,N*-based ligands and aryldiazonium salts allowed the enantioselective construction of all-carbon quaternary stereocenters through a Heck reaction with acyclic olefins. The molecular complexity provided by this new method enabled a concise total synthesis of the (*R*)-verapamil in 29% overall yield.

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