**A Dynamic Kinetic Asymmetric Heck Reaction for the Simultaneous Generation of Central and Axial Chirality**

José Alberto Carmona, Valentin Hornillos, Pedro Ramírez-López, Abel Ros, Javier Iglesias-Sigüenza, Enrique Gómez-Bengoa, Rosario Fernández, José M. Lassaletta

5 Instituto de Investigaciones Químicas (CSIC-US) and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Avda. Américo Vespucio, 49, 41092 Sevilla, Spain.

1 Departamento de Química Orgánica, Universidad de Sevilla and Centro de Innovación en Química Avanzada (ORFEO-CINQA), C/ Prof. García González, 1, 41012 Sevilla, Spain.

1 Departamento de Química Orgánica I, Universidad del País Vasco, UPV/EHU, Apdo. 1072, 20080 San Sebastián, Spain

**ABSTRACT:** A highly diastereo- and enantioselective, scalable Pd-catalyzed dynamic kinetic asymmetric Heck reaction of heterobiaryl sulfonates with electron-rich olefins is described. The coupling of 2,3-dihydrofuran or N-boc protected 2,3-dihydropyrrrole with a variety of quinoline, quinazoline, phthalazine and picoline derivatives takes place with simultaneous installation of central and axial chirality, reaching excellent diastereoo- and enantiomeric excesses when in situ formed [Pd$^{0}$/DM-BINAP] was used as the catalyst, with loadings reduced down to 2 mol% in large scale reactions. The coupling of cyclic, electron-rich alkenes can also be performed using a [Pd$^{0}$/Josephs ligand] to obtain axially chiral heterobiaryl α-substituted alkenes in high yields and enantioselectivities. Products from Boc-protected 2,3-dihydropyrrrole can be easily transformed into N,N ligands or appealing axially chiral, bifunctional proline-type organocatalysts. Computational studies suggest that a β-hydride elimination is the stereocontrolling step, in agreement with the observed stereochemical outcome of the reaction.

**INTRODUCTION**

The Heck reaction is a fundamental palladium-catalyzed C–C bond-forming transformation with numerous applications in the synthesis of natural products and valuable synthetic intermediates. Since the first intermolecular asymmetric version reported in 1991 by the group of Hayashi, these couplings have become a benchmark to validate the design of novel chiral ligands and catalysts rather than finding suitable applications in stereoselective organic synthesis. Only very recently, the synthetic utility of the asymmetric Heck reaction has been expanded thanks to the outstanding performance of chiral mixed phosphine/phosphate oxide ligands in several representative transformations. Additionally, methods to enable the use of benzylic electrophiles and previously elusive aryl halides have also appeared. Moreover, conditions for the highly enantioselective construction of quaternary stereocenters from trisubstituted dihydrofurans have also been reported (Scheme 1A). The redox relay Heck-Matsuda reactions of acyclic alkanyl alcohols have also significantly expanded the synthetic value of the reaction, a strategy that has been also extended to oxidative Heck reactions using boronic acids as reactants (Scheme 1B). Mention is also due to the dynamic kinetic resolution of atropoisomeric o-iodoacrylanilides.

---

### Scheme 1. Asymmetric intermolecular Heck reactions.

**Previous work: generation of carbon stereogenic centers**

**A** Cyclic alkenes

![Image of Scheme 1A](image)

**B** Acyclic alkenes

![Image of Scheme 1B](image)

**This work:** Dynamic kinetic asymmetric Heck Reaction

![Image of Scheme 1C](image)

The direct asymmetric cross-coupling approach to axially chiral biaryls has failed so far for the synthesis of heterobiaryls such as QUINAP and related derivatives. Among a handful of
alternative approaches, our group has recently described Pdcatalyzed dynamic kinetic asymmetric C–C, C–P and C–N cross-coupling reactions of racemic heterobiaryl sulfonates 1. On the other hand, more complex ligands/catalysts combining central and axial chirality have found a number of recent applications in asymmetric catalysis, but their synthesis usually require tedious multi-step procedures. In fact, examples of catalytic procedures for the simultaneous generation of axial and central chirality are rare, and none of them were directed to the synthesis of catalysts/ligands with practical applications. In this context, the dynamic kinetic asymmetric Heck reaction from 1 appears as an appealing strategy for the synthesis of bifunctional heterobiaryls with central and axial stereogenic elements (Scheme 1C). This transformation, however, is particularly challenging for two main reasons: First, in contrast with the common cationic Heck reaction pathway, the oxidative addition intermediate \( \text{Pd}^0 \) has no vacant coordination sites; the relatively good isoquinoline/pyrididine N-ligand must be displaced by a neutral olefin on the Pd center. Second, the reaction with internal olefins can afford up to 8 different Heck stereoisomers considering the formation of two stereogenic elements and the possible double bond migration. Therefore, the chiral ligand will be required to perform an exquisite control of both the generation of the stereogenic axis and the migratory insertion event in order to afford a satisfactory result.

RESULTS AND DISCUSSION

In a preliminary experiment, it was observed that the reaction of 2-(pyridin-2-yl)phenyl nonaflate 1a and 2,3-dihydrofuran 2 fails to give any reaction product under common Heck conditions [Pd(dba)\(_2\)/[(R)-BINAP (cat.), DIPEA, toluene, 80 °C], thus confirming our initial concerns (Scheme 2). It was assumed that the formation of a very stable \( \text{Pd}^0 \) (R = R’ = H) intermediate prevents coordination of the olefin and further migratory insertion. Despite this discouraging result, we envisaged that in more strained (less stable) \( \text{Pd}^0 \) palladacycles (R = R’ ≠ H; e.g. from 1-(isoquinolin-1-yl)naphthalene-2-yl nonaflate 1b), dissociation of the N–Pd bond would be facilitated by release of steric strain.

Scheme 2. Preliminary experiments.

In fact, the reaction of 1b and 2 under the above conditions afforded the desired product as a 10:1 3b:3b mixture with a promising 82% ee for the major product 3b (Table 1, entry 1). An excess of dihydrofuran was used (8 equiv.), due to the volatility of this compound. A screening of ligands and conditions was then performed to optimize this reaction [Table 1 and Table S1 (supporting information)]. At lower temperatures (60 °C, entry 2) the conversion dropped substantially but the enantiosselectivity raised up to 88% ee. No improvements were observed using related P,P ligands such as L2 (entry 3) or L3 (entry 4), while Josiphos derivative L4 was unproductive (entry 5). Not surprisingly, hemilabile ligand L5 afforded the non-isomerized Heck product 3b exclusively with high diastereoselectivity, although in low ee (entry 6). Remarkably, though, ligands L6 or L7 were ineffective (entries 7 and 8); a faster alkene insertion may be favored with less σ-donating P,N and P,O ligands, since they form more electrophilic cationic aryl palladium(II) centers. However, a stronger binding of the pyridine/isoquinoline nitrogen is also expected in this case, preventing further coordination of the olefin.

Table 1. Screening of Reaction Conditions and Ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>L</th>
<th>T (°C)</th>
<th>conv (%)</th>
<th>3b:3b</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>80</td>
<td>50</td>
<td>10:1</td>
<td>&gt;20:1</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>L1</td>
<td>60</td>
<td>28</td>
<td>6:1</td>
<td>&gt;20:1</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>L2</td>
<td>60</td>
<td>27</td>
<td>11:1</td>
<td>&gt;20:1</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>L3</td>
<td>60</td>
<td>11</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>L4</td>
<td>60</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>&gt;20:1</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>L5</td>
<td>80</td>
<td>40</td>
<td>&lt;1:20</td>
<td>&gt;20:1</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>L6</td>
<td>60</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>L7</td>
<td>60</td>
<td>&lt;5</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>L8</td>
<td>60</td>
<td>16</td>
<td>8:1</td>
<td>&gt;20:1</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>L9</td>
<td>60</td>
<td>22</td>
<td>6:1</td>
<td>&gt;20:1</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>L9</td>
<td>80</td>
<td>&gt;99</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>L9</td>
<td>80</td>
<td>97</td>
<td>&gt;20:1</td>
<td>&gt;20:1</td>
<td>97</td>
</tr>
</tbody>
</table>

*Conditions: 0.1 mmol of rac-1b, 0.8 mmol of dihydrofuran in 0.5 mL of toluene. Determined by H NMR spectroscopy of the crude reaction mixture. Determined by chiral HPLC analysis. ee of 3b. [Pd] (5 mol%)/L9 (6 mol%).
Finally, a major improvement was observed after modification of the diarylphosphino group: use of Tol-BINAP L8 and DM-BINAP L9 afforded the desired product 5b with near perfect dr and ee, although the conversion remained low (entries 9 and 10). To our delight, full conversion, high diastereoselectivity (dr >20:1) and regioselectivity (>20:1) were achieved by using L9 at 80 °C without significantly affecting the enantioselectivity (97% ee, entry 11). Moreover, the catalyst loading could be reduced to 5 mol% to obtain a similar result (entry 12).

The Pd/DM-BINAP catalyst was successfully applied to the dynamic kinetic asymmetric Heck reaction of 2,3-dihydrofuran 2 with other heterobiaryl sulfonates, including quinazoline- (1c), phthalazine- (1d) and picoline (1e) derivatives. Different substituents at the naphthalene unit in isoquinoline derivatives 1f-h were also tolerated (Table 2). Importantly, the method could also be extended to the reaction with N-Boc-2,3-dihydropyrole 4 for the synthesis of derivatives 5, although in this case DMSO proved to be the solvent of choice. Remarkably, all products 3 and 5 were obtained with excellent dr’s (>20:1), along with very high ee’s (up to >99%). Good selectivity (s) ratios, ranging from 6:1 to >20:1, were observed for dihydrofuran derivatives (3/3’), while dihydropyrole products were obtained in slightly lower 5’S selectivities (s = 3:1 to 6:1). As a remarkable exception, and for unknown reasons, the pyrenyl 5’h isomer was formed exclusively, although again with an excellent diastereo- and enantioselectivity. The same absolute configuration for (S,S)-3b and the minor isomer (S,S)-5’b were determined by X-ray diffraction analysis (Figure 1); while those of other products 3 and 5 were assigned by analogy. These data indicate that in our case there is no kinetic resolution from hydrido-alkene Pd complex intermediates.\(^\text{18}\) Remarkably, a similar trend has been previously reported for asymmetric Heck reactions using 3,3’-disubstituted DM-BINAP ligands.\(^\text{19}\) Not surprisingly, the reaction performed with simple cycloalkenes such as cyclopentene or cyclohexene failed to give any products, even under forcing conditions. This lack of reactivity reflects again the difficult displacement of the heterocycle N atom by the olefin, which requires not only some steric strain in the palladacycle but also a relatively high electron richness in the C=C bond. Likewise, attempts to perform reactions with 5-methyl-2,3-dihydrofuran failed to give any reaction products. In this case, the lack of reactivity is attributed to the high level of steric crowding expected at the oxidative addition intermediate (see proposed mechanism below), thus preventing an effective coordination/carbometallation of hindered alklenes. Importantly, a large scale synthesis of 3b and 5b (1.8 mmol and 1.5 mmol, respectively) could be performed with a lower catalyst loading (2 mol% [Pd]; 2.4 mol% L9) to obtain the products with similar results (3b: 81% yield, s >20:1, dr >20:1, 97% ee; 5b: 60% yield (pure major isomer), s 6:1, dr >20:1, 99% ee).

We investigated also the reaction with acyclic electron rich alklenes. Unfortunately, the reaction of 1b with butyl vinyl ether 6 under the optimized conditions afforded the product 11b with a lower enantioselectivity (83% ee, Table S3 in the Supporting Information). However, further screening revealed that the Josiphos-type ligand L4 performs better in this case, reaching a satisfactory 92% ee (Table 3). This ligand was then used in the reactions of vinyl ethers 6-9 with heterobiaryl 1b,c,e to afford the corresponding Heck products 11-15 in high yields and enantioselectivities. On the other hand, L9 was required again in the reaction of 1b with vinyl acetamide 10 to yield product 15b in 90% yield and 82% ee.

**Table 2.** Scope of Heck reactions with cyclic alkenes.\(^\text{a}\)

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>R&lt;sup&gt;4&lt;/sup&gt;</th>
<th>R&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Entry</th>
<th>(%)</th>
<th>dr</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b: 90%</td>
<td>s &gt;20:1, 97% ee</td>
<td>3c: 92%</td>
<td>s 14:1, 94% ee</td>
<td>3e: 99%</td>
<td>s &gt;20:1, &gt;99% ee</td>
<td>3f: 52%</td>
<td>s 10:1, 90% ee</td>
<td>3g: 99%</td>
</tr>
<tr>
<td>3h: 53%</td>
<td>s 6:1, 99% ee</td>
<td>3i: 64%</td>
<td>s 4:1, 98% ee</td>
<td>3j: 66%</td>
<td>s 4:1, 98% ee</td>
<td>3k: 76%</td>
<td>s 6:1, 99% ee</td>
<td>5c: 76%</td>
</tr>
</tbody>
</table>

\(^{a}\)Reactions performed at 0.1 mmol scale in 0.5 mL of solvent (toluene for 2; DMSO for 5). *Isolated yields of pure major isomer after chromatography; dr’s (>20:1 for products 3 and 5) and selectivities were determined by H NMR in the crude reaction mixtures. Ee’s determined by HPLC on chiral stationary phases. *Yield of an inseparable mixture of 5d/5’d.

**Figure 1.** X-ray structures of (S,S)-3b and (S,S)-5’b. Thermal ellipsoids drawn for 50% probability. H atoms are omitted for clarity.
Preliminary experiments have also demonstrated that this DYKAT process can be extended to the hydroarylation of bicyclic olefins (Scheme 3). Thus, reaction of rac-1b with norbornadiene in the presence of formic acid as the hydride source and L4 as the ligand afforded product 16 as a single diastereomer in 98% ee, although in moderate yield. Nonetheless, no double hydroarylation was observed in this transformation. The structure of ent-16-HCl has been determined by X-ray diffraction analysis, and its absolute (R,R,S,R) configuration is consistent with a uniform stereochemical outcome with the Heck products 3 or 5.

**Scheme 3.** Hydroarylation of norbornadiene and X-ray structure of ent-16-HCl. Thermal ellipsoids drawn for 50% probability. H atoms, except NH, are omitted for clarity.

In a control experiment, biphenyl nonaflate 17 was made to react with 2 under the optimized conditions to afford the expected Heck product 18 with high selectivity but a negligible 9% ee (Scheme 4). This result highlights the synergistic effect between the chiral ligand and the heterobiaryl moiety during the stereocontrolling step of the reaction. Moreover, no coupling product was formed from the more sterically demanding nonaflate rac-19, showing that the coordinating isoquinolinyl/pyridyl N atom is required for a facile chelate-assisted oxidative addition step. Similarly, no reaction was observed with N-oxide rac-20, indicating that the formation of a five-membered cationic palladacycle is also essential to reactivity. Finally, a much slower reaction was observed when 1-(2-bromonaphthalene-1-yl)isoquinoline 1b(Br), in combination with NaOBut as the base, was used as the starting material (23% conversion after 72h at 80 °C). Interestingly, though, the non-isomerized product 3b was exclusively formed in 93% ee.

We next turned to DFT studies in order to gain insight into the reaction mechanism and the origin of the high levels of enantio- and diastereoselectivity observed. We assumed that the fundamental steps of the catalytic cycle would be the oxidative addition of the racemic substrates 1 to the Pd²⁺ catalyst leading to cationic intermediate 1’, followed by transligation (→11), insertion of the alkene into the Pd⁻–C bond (→11), and reinstallation of the double bond in the final products 3 by β-hydride elimination (→14), leading to the final products after decoordination or, eventually, double bond migration after reinsertion (hydropalladation) and a second β-hydride elimination. The reaction between 1b and 2 with the catalyst based on the optimal ligand L9 was chosen for the computational studies. Eight different isomeric products could be a priori formed by combination of the different configurations of the stereogenic axis and center, and the final position of the double bond (Figure 2). We started from diastereomeric complexes (S)⁴-A (G = 0) and (R)⁴-A (ΔG = +1.0 kcal/mol) formed by coordination of both enantiomers of substrate 1b to the [Pd⁴(L9)] catalyst (Figure 3). Transition states (R)⁴-TS0 and (S)⁴-TS0 for the oxidative addition step were located for both atropoisomers at ΔG° = 18.4 and 32.4 kcal/mol.
respectively, leading to intermediates (Sₐ)-I and (Rₐ)-I of similar energies (ΔG = −17.5 and −17.4 kcal/mol). As expected, displacement of the triflate by the isoquinoline N-atom to form cationic intermediates (Sₐ)-Iₐ and (Rₐ)-Iₐ provides an additional stabilization of 20.2 and 22.5 kcal/mol, respectively (Figure 3). To make possible an efficient dynamic kinetic resolution, these diastereomeric Pd(II) intermediates have to interconvert in a fast equilibrium and the subsequent steps must present different activation barriers for the different diastereomeric transition states. In fact, the low barrier computed for this epimerization (TSₑp: ΔGₑp = 21.0 kcal/mol) demonstrates the feasibility of the rotation around the chiral axis at this point.²² As expected, the coordination of the dihydrofuran substrate 2 to form intermediates II in the next step requires decoordination of the isoquinoline N-atom, and rotation of the biaryl group above or below the coordination plane. Surprisingly, the calculations indicate that the ligand exchange is concerted: in the located transition states TS₁, the dihydrofuran molecule is moving into the coordination sphere of palladium as the same time as the isoquinoline is rotating away from the metal center (Figure 4). In (Sₐ)-TS₁, for example, the Pd-N and Pd-alkene distances are 3.2 Å and 3.7 Å respectively. During this process, the ligands are moving in a very sterically crowded environment, inducing a significant activation barrier of ΔGₛ = 23.2 kcal/mol for (Rₐ)-TS₂. In the following alkene insertion into the C(aryl)-Pd bond, eight different transition states (TS₂) were located for the four forming diastereomers and two possible orientations for the isoquinoline ring (above or below the coordination plane) in each case. Noteworthy, some of them present relatively low free activation energies, with a minimum of ΔGفاعل = 21.3 kcal/mol for (Rₐ)-TS₂, which is actually lower than that of the previous step [(Rₐ)-TS₁]. The highest activation energy (ΔGفاعل = 27.7) corresponds to (Sₐ,Sₐ)-TS₂, in sharp contrast with the experimental results (obtention of Sₐ,Sₐ as the major stereoisomer, with high levels of selectivity). These inconsistencies suggest that TS₂ might not be the rate determining nor the stereocontrolling step, which should therefore be located at a later stage in the catalytic cycle. In this regard, the reaction evolves through TS₃ to reinstall the alkene functionality.
Figure 4. Computed energies for key intermediates and transition states performed at the M06/def2TZVP//B3LYP/6-31G(d,p) (Pd,SDD) (IEFPCM,toluene) level. Selected 3D structures are illustrated using CYLview.23
after a β-hydride elimination. We were pleased to find that this step also presents a notable activation barrier, especially due to the high stability of the insertion intermediate III. Interestingly enough, the isomer preference reverses at this point, and \((S_oS)\) - TS3 becomes the most favored diastereomer \((\Delta G^f = 14.6 \text{ kcal/mol})\), in fair agreement with the experimental results. Moreover, the \((R_oR)\) - TS3 or \((S_oR)\) - TS3, leading to experimentally undetected products are the highest in energy \((\Delta G^f = 25.4 \text{ and } 20.2 \text{ kcal/mol})\, \text{respectively}\), while \((R_oR)\) - TS3 has an activation barrier of \(\Delta G^f = 18.2 \text{ kcal/mol}\), accounting for the high levels of enantioselectivity observed. For these reasons, TS3 becomes a solid candidate to be the stereo-determining step of the reaction. This proposal requires that TS2 is a reversible step, and indeed, the barrier for the reversion from \((R_oR)\) - III to \((R_oR)\) - TS2 shows an affordable energy of 21.4 kcal/mol.

On the other hand, the inspection of the structure of the elimination transition states (TS3) indicates that they cannot be directly accessed from the previous III-type intermediates. A large reorientation and rotation of the biaryl moiety must take place to prepare the substrate for the β-hydride elimination. Indeed, a second intermediate structure III' was located, presenting an agostic interaction of palladium with the adjacent C–H bond, immediately preceding the β-elimination. The participation of intermediates III and III' in the mechanism could be also confirmed through forward and backward IRC calculations starting from TS2 and TS3 respectively. Unfortunately, any attempt to find suitable transition state(s) for the conversion of intermediates III into III' were unsuccessful, but a comparative analysis of their structures reveals that a major reorganization in a sterically very crowded environment is required. Remarkably, this reorganization appears to be particularly complex for the \((R,R)\) isomer. For instance, change in the \(P_{\text{syn}}^\text{e} - \text{Pd} - C\text{(furan)} - C\text{(furan)}\) dihedral angle serves as an illustrative index: it moves from 66.6° in \((R_oR)\) - III to 150.5° in \((R_oR)\) - III', while the same rotation in the \((S_oS)\) series is significantly shorter (from −93.0° to −144°) (Figure 5). Furthermore, a potential energy surface scan was performed for the variation of the dihedral angle in \((S_oS)\) - III from 93° to 144° without any noticeable limitation, while the angle in \((R_oR)\) - III presents a rotation restricted to the interval between 67° and 110° due to the steric collision between the quinoline and the aryl phosphine moieties at that point. To complete the rotation, the phosphines must move largely aside with the accompanying energetic cost.

From this point forward, intermediates IV evolve to either the minor products 3' by decoordination or, after reinsertion [→V via TS4] and a second β-hydride elimination [→VI via TS5], the major (or unique) products 3. The calculated activation energies for these last steps are very low \((\Delta G^f = 0.2 \text{ and } 4.2 \text{ kcal/mol})\) for \((S_oS)\) - TS4 and \((S_oS)\) - TS5, respectively) and, therefore, they don’t have any influence on the stereochemical outcome of the reaction.

**Figure 5.** Comparison of intermediates III and III' in the \((R_oR)\) and \((S_oS)\) series. Ligand omitted for the sake of clarity.

Summarizing, the combination of the reversibility of TS2, at least for some of the isomers, together with the large energy difference between the isomeric TS3 transition states and a difficult reorganization from III to III' can explain the preferential formation of the \(S_oS\) isomer. This unprecedented mechanistic profile appears to be governed by the heterobiaryl moiety: in reactions with simple aryl triflates, the insertion step appears to be the stereodetermining one. Consequently, the use of \((R_o)\) - BINAP \(^{18}\) or \((R_o)\) - DM-BINAP \(^{19}\) as the ligands in this case results in the formation of major products with the \(R\) configuration in low to moderate enantiomeric excesses.\(^{24}\)

In the reaction of 1b(Br), it is assumed that the precipitation of NaBr in toluene causes a ligand exchange (Br–O'Bu).\(^{14d}\) Therefore, the main difference with the original reaction from 1b is the basicity and coordination ability of the counteranion (O'Bu versus OTf). According to the proposed mechanism, the poor reactivity observed for 1b(Br) is then explained by the lower concentration of the reactive intermediate II, in equilibrium with the unproductive neutral species II(O'Bu) (Scheme 5). Similarly, the exclusive formation of 3b can tentatively be attributed to a fast deprotonation of the intermediate \((S_oS)\) - IV(O'Bu) with respect of the reinserter of the hydride.
Scheme 5. Singularities in the reaction of 1b (Br) with 2.

Several attempts to obtain and characterize the cationic oxidative addition intermediate I* with the optimal ligand (R,)-DM-BINAP L9 were unsuccessful. We hypothesized that the very high steric crowding in this intermediate could be responsible for its instability. (R,)-BINAP L1 is a very similar ligand that provided also good reactivity and selectivity, but the corresponding intermediate has a lower steric demand around the Pd center. In fact, equimolar amounts of \([\text{Pd(Cp})(\text{allyl})]\) as the Pd^{I} precursor, rac-1b(OTf) and L1 cleanly reacted to afford the expected intermediate L1_{1}(OTf) as a relatively stable, crystalline compound whose structure was unequivocally confirmed by X-ray diffraction analysis (Figure 6). Interestingly, the stereogenic axis in the solid state shows the same (R,)-configuration as the most stable calculated intermediate (R,)-1'. Nevertheless, the stoichiometric reaction of this isolated intermediate with dihydrofuran 2 in toluene at 80 °C afforded the product (S,S)-3a in 82% yield and 77% ee.

Figure 6. Synthesis of L1_{1}(OTf) and ORTEP drawing of the cation L1_{1}^{+}.

In order to illustrate the synthetic utility of the methodology, compound 5b was subjected to N-Boc deprotection with TFA and the resulting cyclic imine 21 was employed as ligand for the synthesis of the chiral Pd^{II}(allyl) complex 22 (Scheme 6). Additionally, reduction of the imine group of 21 with NaBH4 afforded bifunctional pyrrolidine derivative 23 possessing appealing structural characteristics for its use in asymmetric organocatalysis. Importantly, no epimerization was observed in any of these transformations.

Scheme 6. Representative transformations from 5b.

CONCLUSION

In summary, we have developed a highly regio-, diastereoselective dynamic kinetic asymmetric Heck reaction of racemic heterobiaryl sulfonates with electron-rich olefins. This transformation represents the first example of the use of an asymmetric Heck reaction to resolve both a stereogenic axis and stereocenter simultaneously, showing a broad scope of axially chiral heterobiaryl compounds with electron-rich cyclic and acyclic olefins using L9 and L4, respectively. Facile stereoretentive transformations led to appealing axially chiral heterobiaryl complexes and bifunctional organocatalysts whose applications are currently under investigation in our laboratories.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, optimization studies, characterization data, NMR spectra for new compounds, and HPLC traces (PDF).

Crystallographic data for (S,S)-3b (CIF)

Crystallographic data for (S,S)-5b (CIF)

Crystallographic data for ent-16-HCl (CIF)

Crystallographic data for L1_{1}(OTf) (CIF)

Detailed computational study. Calculated structures and energies (PDF)

Three-dimensional structural data of (S)-A (PDB)

Three-dimensional structural data of (R)-A (PDB)

Three-dimensional structural data of (S)-TS0 (PDB)

Three-dimensional structural data of (R)-TS0 (PDB)
Three-dimensional structural data of (S,)-I (PDB)
Three-dimensional structural data of (R,)-I (PDB)
Three-dimensional structural data of (S,)-I' (PDB)
Three-dimensional structural data of (R,)-I' (PDB)
Three-dimensional structural data of TS,p (PDB)
Three-dimensional structural data of (S,)-TS1 (PDB)
Three-dimensional structural data of (S,S)-TS2 (PDB)
Three-dimensional structural data of (S,S)-TS-I (PDB)
Three-dimensional structural data of (R,R)-III (PDB)
Three-dimensional structural data of (R,R)-III' (PDB)
Three-dimensional structural data of (S,S)-TS3 (PDB)
Three-dimensional structural data of (S,S)-TS-IV (PDB)
Three-dimensional structural data of (S,S)-TS4 (PDB)
Three-dimensional structural data of (S,S)-TS-IV (PDB)
Three-dimensional structural data of (S,S)-TS5 (PDB)
Three-dimensional structural data of (S,S)-TS-VI (PDB)

ACKNOWLEDGMENT

Dedicated to Professor Miguel Yus on the occasion of his 70th birthday. We thank the Spanish Ministerio de Ciencia e Innovación (Grants CTQ2016-76908-C2-1-P, CTQ2016-76908-C2-2-P, CTQ2016-78083-P and contract RYC-2013-12585 for A.R.), European funding (ERDF), Junta de Andalucía (Grant 2012/FQM 10787 and fellowship for J. A. C.). VH thanks the Junta de Andalucía and the European Union’s Seventh Framework Program, Marie Skłodowska-Curie actions for a Joint Hub fellowship (COFUND - Grant Agreement nº 291780) and the University of Seville for a research grant (no 1800511201).

REFERENCES


AUTHOR INFORMATION

Corresponding Author
*vhornillos@iiq.csic.es.
*fiermann@us.es.
*jmlassa@iiq.csic.es.

Notes
The authors declare no competing financial interests.
(22) For a similar result using a related [Pd(QUINAP)] system see ref 14b.
(23) Legault, C. Y. CYLview, 1.0b; Université de Sherbrooke: Sherbrooke, Canada, 2009 (http://www.cylview.org).
(24) Remarkably, an erosion of the enantioselectivity of the major product is observed when the original system reported by Hayashi [Ref. 18, PhOTf / (R)-BINAP; 82% ee (R)] is modified with a bulkier ligand [ref 17: PhOTf / (R)-DM-BINAP, 21% ee (R)] or combination of bulkier ligand and substrate [this work, biphenyl triflate / (R)-DM-BINAP, 9% ee (S)]. This observation puts in context the excellent results observed with heterobiaryl substrates.
up to 94% ee

>20:1 dr’s

up to 99% ee