Kinetic Resolution of Sulfur-Stereogenic Sulfoximines by Pd(II)-MPAA Catalyzed C−H Arylation and Olefination

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Supporting Information Placeholder

ABSTRACT: A direct Pd(II)-catalyzed kinetic resolution of heteroaryl-enabled sulfoximines through an ortho-C−H alkenylation/arylation of arenes has been developed for the first time. The coordination of sulfoximine pyridyl-motif and the chiral amino acid MPAA ligand to the Pd(II)-catalyst controls the enantiodiscriminating C(aryl)−H activation. This method provides access to a wide range of enantiomerically enriched unreacted aryl-pyridyl-sulfoximine precursors and C(aryl)−H alkenylation/arylation products in good yields with high enantioselectivity (up to >99% ee), and selectivity factor up to >200; which are inaccessible by conventional methods. The coordination preference of the directing group, ligand effect, geometry constraints, and the transient six-membered concerted-metalation-deprotonation species dictate the stereoselectivity; DFT studies validate this hypothesis.

The directing group (DG) assisted desymmetrization of prochiral C−H bonds provides a suitable way to construct carbon, phosphorus, silicon, and sulfur centred functionalized chiral molecules. However, this approach requires achiral precursors with two identical enantiotopic groups, which prevents its application for broad synthetic benefits. On the other hand, kinetic resolution (KR) of C−H bonds offers booming advantages for making functionalized enantioenriched molecules. In this regard, Yu’s pioneering work on DG assisted chiral amino acid (MPAA) enabled Pd-catalyzed carbon centred KR of arene C−H bonds through alkenylation, arylation, and/or iodination is undoubtedly a breakthrough (Fig 1A). In spite of this success, the related strategy of Pd-catalyzed heteroatom centred KR of arenes remains unknown, although exceedingly appealing.

Sulfoximines, which are configurationally stable motifs with S-stereogeneity, are found in molecules of medicinal importance and agrochemicals. Notably, sulfoximines have emerged as chiral auxiliaries and DG for C−H functionalizations. The syntheses of enantioenriched sulfoximines have invariably relied on resolution techniques, stereoselective imination, and oxidation

Figure 1. Kinetic resolution via C−H activation (Free energies at 343.15 K in DCE)
Table 1. Optimization for α-C–H Alkenylation Kinetic Resolution of Sulfoximines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives</th>
<th>C&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>(R)-1a-1</th>
<th>(S)-3a-1</th>
<th>s&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BQ</td>
<td>18</td>
<td>17</td>
<td>78</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2-chloro BQ</td>
<td>39</td>
<td>50</td>
<td>77</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2,5-dichloro BQ</td>
<td>35</td>
<td>40</td>
<td>75</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: rac-1a-1 (0.1 mmol), ethyl acrylate 2a (0.6 equiv), Pd(OAc)<sub>2</sub> (10 mol%), ligand (30 mol%), Ag<sub>2</sub>CO<sub>3</sub> (2.0 equiv), 2-Cl-BQ (0.3 equiv), 1,2-DCE (1.0 mL), N<sub>2</sub>, 75 °C, 3 days.

<sup>b</sup>Calculated conversion, C = eeSM/(eeSM + eePR).

<sup>c</sup>Determined by chiral HPLC analysis.

<sup>d</sup>Selectivity (s) = ln[(1 − C)/(1 − eeSM)]/ln[(1 − C)/(1 + eeSM)].

<sup>e</sup>2a (2.0 equiv) used.

The generality of the Pd-catalyzed C–H alkenylation KR of sulfoximines was then surveyed (Table 2).<sup>10</sup> Compound 3b (98.2:1.8 er) was isolated in 26% yield. The alkenylation occurred at the less-hindered aren C–H bond and the chiral sulfoximines 3e and 3d were obtained with s factors of 162 and 140, respectively. The catalytic system was compatible with common functional groups, such as ketone, sulfone and phosphate in the alkene, providing access to 3e (95.6:4.4 er), 3f (94.6:5.4 er) and 3g (97.6:2.4 er).

Notably, the reaction of 1a (1.0 equiv), methyl acrylate 2b (2.0 equiv), in the presence of Pd(OAc)<sub>2</sub> ligand, Ag<sub>2</sub>CO<sub>3</sub> and 2-Cl-BQ led to (S)-3b (96% ee, s factor of 85 with 34% conversion) (eq 1).<sup>10</sup>

The study was initiated with the non-substituted N-Boc-phenyl-2-pyridyl sulfoximine rac-1a-1 and ethyl acrylate 2a (0.6 equiv) in presence of Pd(OAc)<sub>2</sub> (10 mol%), Boc-L-Phe-OH (L1; 30 mol%), Ag<sub>2</sub>CO<sub>3</sub> (2.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1,2-DCE) at 75 °C (Table 1a). The desired C2-alkenylation product (S)-3a-1 (18%, conversion after 3 days) along with precursor (R)-1a-1 were obtained in 75% ee and 17% ee, respectively, exhibiting a low selectivity factor (s) of 8. This encouraging result unfolded our curiosity about examining the effect of other ligands. None of the N-Boc, N-acetyl-, and N-imide-protected commercially available α-amino acid ligands (L2–L6) with distinct side chains were effective. Assuming the additional coordination ability of the easily modifiable OH group in threonine, various N,O-protected threonine ligands were tested. The reaction s factor was improved a little for (S)-3a-1 to 12 and 11 when Boc-L-Thr(Bu)-OH (L7) and Boc-L-Thr(Bn)-OH (L8) were used, respectively. Electronic perturbation in the O-benzyl moiety did not have any impact on the enantioselectivity (L9 and L10). The use of 2a (2.0 equiv) in presence of ligand L8 improved the conversion (50%) with (S)-3a-1 (70% ee). To enhance sulfoximine resolution efficiency while maintaining conversion (~50%; Table 1a), we scrutinized the co-oxidant effect (Table 1b). Chlorobenzoquinone (2-Cl-BQ) was found to be the best, providing (S)-3a-1 in 77% ee with 39% conversion (s factor of 13; entry-2, Table-1b). Upon a thorough D<sup>2</sup>G and reaction parameters screening, 3-methyl pyridyl was found superior.<sup>10</sup> Thus, the reaction of 1a (1.0 equiv), methyl acrylate 2b (2.0 equiv), in presence of Pd(OAc)<sub>2</sub> ligand, Ag<sub>2</sub>CO<sub>3</sub> and 2-Cl-BQ in 1,2-DCE led to (S)-3b (96% ee, s factor of 85 with 34% conversion) (eq 1).<sup>10</sup>
We next probed sulfoximines KR via enantioselective C–H arylation with arylpinacol boronate esters (Table 4). The reaction of 1b with various arylpinacol boronate esters having electron withdrawing groups [p-CF3 (4a), m-CF3 (4b), m-COME (4c) and p-F (4d)], electron donating groups [p-Me (4e), and p-OMe-m-OrEt (4f)] at the aryl motif independently led to the arylative resolution products 5a (96.1:3.9 er, 42%), 5b (96.5:3.5 er, 43%), 5c (97.5:2.5 er, 41%), 5d (98.4:1.6 er, 40%), 5e (97.2:2.8 er, 41%), and 5f (96.4:3.6 er, 44%), respectively, with s factor of 69–171 and conversion 46–49%. Moreover, the precursor (R)-1b was isolated in 41–46% yield with good enantioselectivity. The labile (−)Cl group was tolerated under the Pd-catalytic system, making 5g (97.8:2.2 er, 39%) with an s factor of 117. Notably, π-conjugated naphthyl-enabled sulfoximine resolution product 5h (99.5:1.0 er, s factor of >200) was reliably accessed. Next, the arylative of m-OrEt-phenyl bearing sulfoximines 5i with 4a provided 5l (>99% ee) with s factor of >200. Likewise, 5j (97.2:2.8 er, s factor of 112) was made from the arylation of 2-naphthyl containing sulfoximines 1j with 4e. The sterically bulky o-tolyl enabled sulfoximines, 1k and 1l, were successful in undergoing arylation with 4a/4c/4e to afford 5k–n in good enantioselectivity; the moderate s factor of 19–24 and conversion (c = 29–38%) is considered suitable.

The synthetic potential of chiral sulfoximine was next probed (Scheme 1). The trifluoroacetic acid (TFA) mediated N-Boc deprotection of (R)-1b provided chiral sulfoximine 5c (95% ee). Next, reduction of 5c to chiral sulfide 7 (90% ee) when exposed to t-BuLi at rt for 2 h; chiral integrity of S-motif is preserved. The N-Boc deprotection and intramolecular Michael cyclization to the activated olefin-moiety of (S)-3c smoothly delivered 8 (as a single diastereomer) in 95% ee. A TFA assisted N-Boc deprotection and oxidative intramolecular C–N bond formation of (S)-5d furnished (S)-9 (93% ee, 62% yield).

We performed a theoretical study to unveil the reaction mechanism (Fig. 2 and Fig. 3).10–12 The MPAA ligand coordination to the metal center lowers the energy barrier of the CMD step, forming a semi planar five membered ring.13 We believe the CMD step could be the main responsible for the kinetic resolution. This hypothesis has been previously validated by Cheng et al, who also focused their study on the CMD as determining step.14 Based on their findings, and considering the plane defined by the coordination of MPAA to the Pd, the bulky α–side chain of the ligand...
Table 4. Scope of C–H Arylative Kinetic Resolution of Sulfoximines\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Ar\textsuperscript{1} (4a–h)</th>
<th>R</th>
<th>Conv (%)</th>
<th>5 (yield, %)</th>
<th>5 (yield, %)</th>
<th>5 (yield, %)</th>
<th>5 (yield, %)</th>
<th>5 (yield, %)</th>
<th>5 (yield, %)</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-F\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>49</td>
<td>42 (5a)</td>
<td>96.1:3.9</td>
<td>44 (1b)</td>
<td>94.3:5.7</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-F\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>49</td>
<td>43 (5b)</td>
<td>96.5:3.5</td>
<td>41 (1b)</td>
<td>94.9:5.1</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Ac-C\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>46</td>
<td>41 (5c)</td>
<td>97.5:2.5</td>
<td>42 (1b)</td>
<td>90.9:9.1</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-F\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>47</td>
<td>40 (5d)</td>
<td>98.4:1.6</td>
<td>42 (1b)</td>
<td>92.6:7.4</td>
<td>171</td>
<td></td>
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<tr>
<td>4-Me-C\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>47</td>
<td>41 (5e)</td>
<td>97.2:2.8</td>
<td>46 (1b)</td>
<td>89.9:10.1</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Cl-C\textsubscript{6}H\textsubscript{4}</td>
<td>Me</td>
<td>46</td>
<td>39 (5g)</td>
<td>97.8:2.2</td>
<td>44 (1b)</td>
<td>91.4:8.6</td>
<td>117</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-naphthyl</td>
<td>Me</td>
<td>42</td>
<td>38 (5h)</td>
<td>99.0:1.0</td>
<td>51 (1b)</td>
<td>85.5:14.5</td>
<td>&gt;200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: rac–1 (0.2 mmol), 4 (2.0 equiv), Pd(OAc\textsubscript{2}) (10 mol%), L8 (20 mol%), Ag\textsubscript{2}O (2.0 equiv), 2-Cl-BQ (0.5 equiv), TFT (3.0 mL), 60 °C, 3 days. \textsuperscript{b}Yield of the isolated arylation product.

Scheme 1: Derivatization of Chiral Products

A. synthesis of N-free sulfoximine:

B. synthesis of chiral sulfoxide:

C. synthesis of five-membered cyclic sulfoximine:

D. synthesis of thiazine:

\begin{itemize}
\item \textsuperscript{1}Bu group from N-Boc removed from all models to simplify visualization.
\item Relative free energies in parentheses (\textDelta G\textsuperscript{f}), distances in Å.
\end{itemize}

Figure 2. Transition structures for each CMD\textsubscript{Pyr} approach.

In case of upward phenyl group linkage (CMD\textsubscript{Pyr-UR} and CMD\textsubscript{Pyr-US}), the sulfur atom and its substituents are located above the plane; while these substituents are below the plane for CMD\textsubscript{Pyr-DR} and CMD\textsubscript{Pyr-DS}. In agreement with Cheng’s observations,\textsuperscript{11} the C1-N2-Pd-O3 dihedral angle for CMD\textsubscript{Pyr-UR} and CMD\textsubscript{Pyr-US} is ca 170°, which generates a high steric interaction when compared with the ca 140° for CMD\textsubscript{Pyr-DR} and CMD\textsubscript{Pyr-DS}. These latter are favored by hydrogen bond interactions, making the combination of steric and electronic effects accounting for a difference of nearly 10 kcal/mol in each enantiomer.
The preference for the S configuration by ~2.5 kcal/mol over the R isomer, lies in a steric clash of the NBOc group with the methyl group from the pyridine moiety and in consequence with the phenyl group, causing an energetically demanding arrangement. The coordination of both ‘N’ atoms in sulfoximine 1a forms int-0 with the displacement of acetic acid, where the S-configuration at sulfur is 1.0 kcal/mol more stable than the R one (Fig. 3). Prior to deprotonation, a cis coordination of aryl group to the N-protected moiety of the MPAA-ligated intermediate occurs. This assists the CMD process by establishing the absolute configuration of the sulfur motif. This calculation fully complies with the experimental observations of the resolution selectivity (calc. 98:2, exp. 98:2; Fig 3-III). Notably, the experimentally observed S-int-2py is thermodynamically favored over R-int-2py isomer by 6 kcal/mol. In respect, the CMD transition states of int-1sac (Fig 3-I) and int-1sac (Fig 3-II) lie much higher than int-1py (Fig 3-III), and their respective $\Delta AG^\circ$ do not coincide with the experimental findings. Further studies confirms that the CMD process is irreversible.  

In summary, a Pd(II)-catalyzed pyridyl substituted KR of sulfoxamines through C(aryl)–H alkenylation and arylation has been revealed for the first time. The transformation addresses the inherent challenges in the KR of coordinatively active pyridyl-enabled sulfoxamines (highly susceptible to TM-catalyst quenching) with no prochiral center in the presence of chiral amino acid MPAA ligands and Pd(II)-catalyst. The common functional groups were tolerated under Pd-catalysis exhibiting good substrate scope for C–H alkenylative and arylative sulfoximines KR products in high enantioselectivity with $s$ factor up to >200. In-depth DFT studies uncover the salient features of coordination selectivity of pyridyl group over sulfoximine imine.

ASSOCIATED CONTENT

Supporting Information

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Author Contributions
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Catalyzed Iminodative Kinetic Resolution of Racemic Sulfoxides. Chem.-
S-centred kinetic resolution
Alkenylation and Arylation
up to >99% ee
30 examples

FG = Alkanyl/Aryl

S-isomer

R-isomer