Development and Analysis of a Pd(0)-Catalyzed Enantioselective 1,1-Diarylation of Acrylates Enabled by Chiral Anion Phase Transfer

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Supporting Information

ABSTRACT: Enantioselective 1,1-diarylation of terminal alkenes enabled by the combination of Pd catalysis with a chiral anion phase transfer (CAPT) strategy is reported herein. The reaction of substituted benzyl acrylates with aryl diazonium salts and arylboronic acids gave the corresponding 3,3-diarylpropanoates in moderate to good yields with high enantioselectivities (up to 98:2 er). Substituents on the benzyl acrylate and CAPT catalyst significantly affect the enantioselectivity, and multidimensional parametrization identified correlations suggesting structural origins for the high stereocontrol.

From the perspective of molecular diversity and step economy, palladium-catalyzed difunctionalization reactions of alkenes are a powerful synthetic tool,† providing rapid access to complex building blocks, such as the 1,1-diarylkane motif that is widespread in numerous natural products and pharmaceuticals.‡ In fact, a high-throughput screen of 1,1-diarylmethines synthesized in our group led to the identification of a compound, C-6, that is selectively active against chemoresistant breast cancers (Scheme 1a).§ In addition, compounds containing a 1,1-diarylmethine stereogenic center are present in a number of drug targets, like CDP840‡b and SB-209670 2c (Scheme 1a). Thus, developing synthetic methods to access these compounds in a modular and stereocontrolled manner is of great importance, particularly to accelerate the screening process and structure–activity relationship studies in drug discovery.

In this context, our group has focused on the development of Pd(0)-catalyzed three-component coupling of terminal alkenes, arylboronic acids, and aryl diazonium salts or alkanyl triflates to construct 1,1-difunctionalized products (Scheme 1b).§ Despite the significance of enantioenriched 1,1-diarylkanes, the enantioselective three-component coupling reaction has remained elusive since the desired process is suppressed in the presence of common P- or N-based chiral ligands.4b To address this problem, the Toste group recently reported the Pd(0)-catalyzed enantioselective 1,1-arylborylation of terminal alkenes using a chiral anion phase transfer (CAPT) strategy (Scheme 1c).† We envisioned that this approach would translate well to the enantioselective 1,1-diarylation of alkenes because of the similarity in the proposed mechanisms. However, the use of aryl diazonium in place of Bpin was projected to involve several additional complications, including solubility issues as well as the potential for direct interactions with the chiral anion.6

Mechanistically, the crucial step in the CAPT approach is the formation of a soluble chiral ion pair between the chiral phosphate anion and an aryl diazonium cation from the corresponding tetrafluoroborate salt that is insoluble under the reaction conditions (Scheme 1d). Oxidative addition of this chiral ion pair by Pd(0) generates cationic Pd−aryl intermediate A that, assuming the chiral anion remains associated, undergoes an enantioselective migratory insertion of the acrylate alkene, generating Pd−alkyl B. To form the 1,1-diarylated product, the catalyst migrates to C1 via β-hydride elimination to form alkene.

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C followed by reinsertion to give D. Stabilized as a π-benzyl species, D undergoes transmetalation with the second coupling partner and reductive elimination, releasing the product. Herein we present the development of an enantioselective 1,1-diarylation of benzyl acrylates that provides 3,3-diarylpropionates with high enantioselectivity using a CAPT approach (Scheme 1d). The best chiral anion and substrate combination was determined using a multidimensional parametrization tactic, revealing key insights into potential remote non-covalent interactions responsible for effective asymmetric catalysis. Our efforts toward applying this CAPT strategy in an enantioselective 1,1-diarylation reaction were initiated with the examination of several common BINOL-based chiral phosphoric acids (2) in addition to benzyl acrylate (1a) as the substrate and phenyldiazonium salt and 4-hydroxyphenylboronic acid as coupling partners (Table 1). Increasing the torsion of the aryl phosphate model system (4, Figure 1). As mentioned previously, chiral anions with 2,6-disubstituted aryl groups resulted in enhanced enantioselectivity, and in general, larger dihedral angles (α) correlate with higher enantioselectivity ($R^2 = 0.78$; Figure S4). The appearance of α in the multivariate model reinforces the significance of the arene’s orientation toward the phosphate group, conceivably allowing for stabilizing non-covalent interactions with the substrates. Additionally, the symmetric $P=O$ stretch ($\nu_{PO}$) could describe the effect of the aryl ring substituents on the phosphate’s interaction with the diazonium and/or palladium counterions. Finally, the Sterimol parameter $B_{1meta}$ represents the minimum width of the meta substituents of the arenes, suggesting that the size of the substituent at this position impacts the enantioselectivity. While this strategy revealed a potentially predictive model that could identify a more selective CAPT catalyst, an inherent limitation concerns the synthetic effort and accessibility required to examine any predictions. Therefore, we selected the best-performing chiral anion (2l) in terms of $er$ and redirected our efforts toward evaluating the benzyl acrylate substrate.

Aligning with our goals to not only optimize this reaction but also understand the influences on the enantioselectivity, benzyl acrylates provided an exciting advantage in that a diverse library could easily be generated from the corresponding benzyl alcohols for a broad survey of substituent effects. Therefore, a set of substituted benzyl acrylates was designed to include electron-withdrawing and -donating substitutions at single, multiple, and varying positions (Figure 2a,b). After evaluating a number of these benzyl acrylates in combination with phosphate 2l, a significant effect of both the substituents’ identity and position on the arene was revealed (a range of ∼2 kcal/mol). As the benzyl group is distal from the site of reaction, these nonintuitive observations support our hypothesis that attractive non-covalent interactions between the benzyl group and the chiral anion are controlling elements in the stereodirecting step. The use of substrates 1d (2-Ome), 1f (3,5-Me$_2$), and 1g (3-Me) with electron-donating substituents resulted in enantioselectivities similar to that with 1a. Conversely, several additional electron-donating substitutions and two extended π systems (1h, 2-Nph; 1i, 3-Ome; 1k, 1-Nph; 1m, 3,5-(OMe)$_2$; 1n, 3,4,5-(OMe)$_3$) exhibited higher enantioselectivities compared with 1a. Adding a substituent at the 4-position did not have a significant effect on the enantiodetermining step (compare 1m and 1n). Finally, good to excellent enantioselectivities were observed when electron-deficient substrates were used (1j, 3,5-F$_2$; 1l, 2-CF$_3$; 1o, 3-NO$_2$; 1p, 3,5-(CF$_3$)$_2$; 1q, 3,5-Cl$_2$; 1r, 3,5-Br$_2$). Serendipitously, both 1q and 1r resulted in the highest enantioselectivity (98:2 er). In contrast, substrates 1b (2,6-Cl$_2$) and 1c (2,4,6-F$_3$),

![Figure 1. Effect of CAPT catalyst on enantioselectivity.](image-url)

Table 1. Evaluation of CAPT Catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>CAPT cat</th>
<th>% yield 3a</th>
<th>$er$</th>
<th>entry</th>
<th>CAPT cat</th>
<th>% yield 3a</th>
<th>$er$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>18</td>
<td>42.5</td>
<td>2</td>
<td>3c</td>
<td>9</td>
<td>37.5</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>12</td>
<td>35.6</td>
<td>2</td>
<td>2h</td>
<td>47</td>
<td>75.5</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>9</td>
<td>37.5</td>
<td>2</td>
<td>2i</td>
<td>40</td>
<td>79.2</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>19</td>
<td>44.6</td>
<td>2</td>
<td>2j</td>
<td>67</td>
<td>81.9</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>27</td>
<td>51.5</td>
<td>2</td>
<td>12</td>
<td>47</td>
<td>87.5</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>14</td>
<td>56.5</td>
<td>2</td>
<td>11</td>
<td>52</td>
<td>84.6</td>
</tr>
</tbody>
</table>

Reactions were performed on a 0.1 mmol scale of 1a in solvent (2 mL) at 20 °C for 20 h and were repeated twice. Determined by $^1$H-NMR analysis of the crude reaction mixtures using an internal standard. Determined by supercritical fluid chromatography (SFC).
which contain electronegative atoms at the 2,6-positions, provided the desired product with the lowest er values, emphasizing the positional requirement of an electron-withdrawing group for the enantioselectivity and thus highlighting the potential for non-covalent interactions between the benzyl group and the CAPT catalyst. To understand these diverse effects, additional studies were initiated, focusing on relating the substituent effects to the observed enantioselectivities. The same multidimensional parametrization technique was applied to correlate various molecular descriptors of the benzyl acrylates to the measured enantioselectivity. During this process, we observed a trend between the average natural bond orbital (NBO) charge of the atoms at the 2,6-positions and the measured $\Delta \Delta G^\ddagger$ values (Figure 2c).\(^{11}\) Because of the significant difference in charge between a halogen and a hydrogen, we were not surprised to observe that substrates 1b and 1c are outliers in this simple relationship. Nonetheless, this insight could suggest that the 2,6-hydrogens themselves play a role in catalyst recognition and that electron-deficient hydrogens lead to a more selective process.\(^{12}\) Although this parameter could solely represent the electronic contribution from the benzyl acrylates' substituents, it was also a significant term in the multivariate model, supporting its descriptive power of the benzyl acrylate's effect on the enantioselectivity (1b, 1c, and 1e were removed from the training set; Figure 2d). Combining NBO\(^{26}\)H (the average NBO charge of the 2,6-hydrogens) with three additional terms (two stretching frequencies and the acrylate's mean polarizability) provided an excellent correlation between the measured and predicted $\Delta \Delta G^\ddagger$ values. As IR vibrations are sensitive to changes in electronic nature and mass, $\nu_{ring}$ and $\nu_{CH2}$ likely account for these effects resulting from the various benzyl groups' substituents.\(^{13}\) We previously used polarizability as a parameter to propose a substrate—ligand lone pair–$\pi$ interaction in a Pd-catalyzed redox relay Heck reaction,\(^{14}\) and we interpret this variable similarly here. The results of this multidimensional correlation are consistent with our hypothesis that there are non-covalent interactions between the benzyl acrylate and the anthracenyl group on the phosphate (e.g., $\pi$-stacking).\(^{15}\) Additional detailed studies are underway to elucidate the subtle effects on the enantioselectivity in this complex system and to identify specific attractive interactions.

Finally, the scope of the reaction was evaluated using the optimal chiral anion 2l and 3,5-dichlorobenzyl acrylate (1q) (Table 2). Overall, excellent enantiomeric ratios are observed in moderate yields. Lower yields are observed because of the competitive formation of the traditional Heck product. Nonetheless, both electron-rich and -poor aryldiazonium salts are well-tolerated under the optimized reaction conditions, with electron-withdrawing substituents (3u and 3v) leading to slightly lower enantioselectivities. As boronic acids are known to interact directly with phosphates,\(^{6}\) it was hypothesized that compatibility between these two components may be an issue for the boronic acid scope. This was not foreseen as a detriment since

![Figure 2. Effect of benzyl group substitutions on enantioselectivity.](image-url)

**Table 2. Aryldiazonium Salt and Boronic Acid Scope**

<table>
<thead>
<tr>
<th>Aryldiazonium Salt</th>
<th>Boronic Acid</th>
<th>Isolated yield</th>
<th>Enantiomeric ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q</td>
<td>ArN2BF(_4) (1.5 equiv)</td>
<td>96.2%(^a)</td>
<td>97.3:93.0</td>
</tr>
<tr>
<td>3q</td>
<td>ArN2BF(_4) (1.5 equiv)</td>
<td>93.7%(^a)</td>
<td>97.5:92.5</td>
</tr>
<tr>
<td>3e</td>
<td>ArN2BF(_4) (1.5 equiv)</td>
<td>97.3%(^a)</td>
<td>97.3:93.0</td>
</tr>
</tbody>
</table>

\(^{a}\)Isolated yields after purification. \(^b\)Determined by SFC.
boronic acid could easily be exchanged with the corresponding diazonium salt. In general, we observed that electron-rich arylboronic acids performed best in this chemistry, leading to higher yields, likely because of the increased rate of transmetalation compared with electron-poor arenes. Of note, 2-naphthyl (3ad) and 5-indole (3ae) groups were incorporated with 95:5 and 94:6 er, respectively, albeit in low yields. Additionally, 3af, which is a relevant building block en route to the drug target CDP840 (Scheme 1a), was synthesized with high enantioselectivity (98:2 er). Although a limitation of this methodology lies in the reaction yield, the modularity of the coupling partners and step economy in this three-component coupling reaction can compensate for this limitation. Additional studies aim to overcome the competitive Heck reaction via exploration of different combinations of benzyl acrylates and chiral phosphoric acids, as this pathway is also sensitive to the identity of these two species (Table S1).

In conclusion, we have developed an enantioselective three-component coupling reaction of benzyl acrylates, arildiazonium salts, and arylboronic acids that provides a modular approach to the synthesis of 1,1-diarylated products with high enantioselectivity. The key to a highly selective process was realized by utilizing a chiral anion phase transfer strategy, wherein the enantioselectivity is closely tied to the identity of the CAPT catalyst. Additionally, the er values are surprisingly sensitive to the electronic and steric nature as well as the position of substituents on the benzyl acrylate substrate. We applied a multidimensional modeling technique to reveal specific properties of the CAPT catalyst and the acrylate that may be responsible for the observed range of enantioselectivity. These results suggest that attractive non-covalent interactions between the two components (e.g., \( \pi-\pi \) stacking) are controlling elements in the enantiodetermining step. Future studies include further exploration of these putative interactions in order to understand the origin of the enantioselectivity and facilitate the improvement and expansion of this and other reactions in development.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11367.

Experimental procedures, additional data, and complete refs 2b and 2c (PDF)

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Notes
The authors declare no competing financial interest.

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REFERENCES


(11) For substrates 1d, 1k, and 11, only the NBO charge of the 2-hydrogen was used. For 1e, the average NBO charge of the methyl hydrogens was included.

