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

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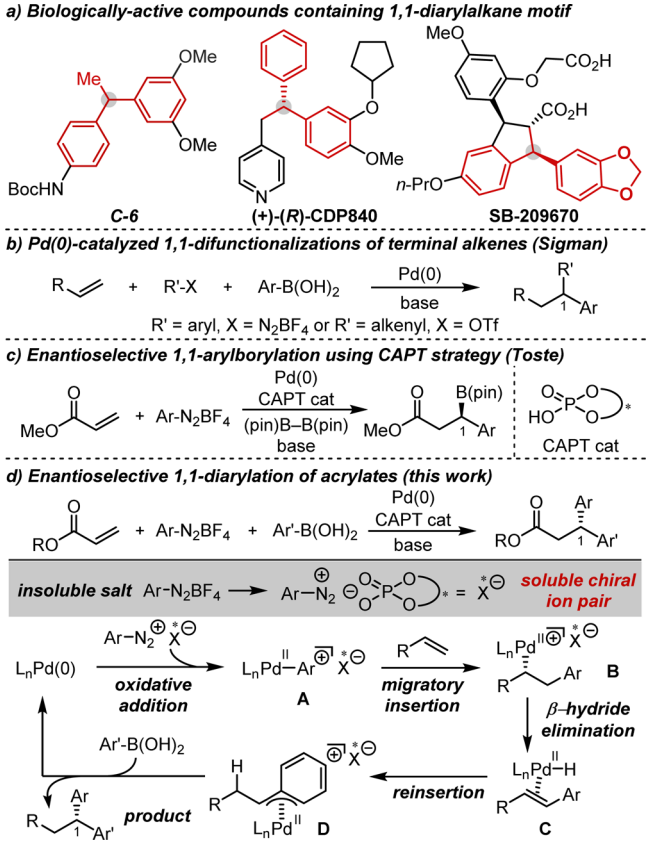
Supporting Information

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 aryldiazonium salts and arylboronic acids gave the corresponding 3,3-diarylpropanoates in moderate to good yields with high enantioselectivies (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,[1] providing rapid access to complex building blocks, such as the 1,1-diarylalkane motif that is widespread in numerous natural products and pharmaceuticals.[2] 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).[3] In addition, compounds containing a 1,1-diarylmethine stereogenic center are present in a number of drug targets, like CDP840[2b] 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 aryldiazonium salts or alkenyl triflates to construct 1,1-difunctionalized products (Scheme 1b).[4] Despite the significance of enantioenriched 1,1-diarylalkanes, 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).[5] 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 arylboronic acids in place of B_2pin_2 was projected to involve several additional complications, including solubility issues as well as the potential for direct interactions with the chiral anion.[6]

Scheme 1. Relevance and Overview of Enantioselective 1,1-Difunctionalization of Alkenes



Mechanistically, the crucial step in the CAPT approach is the formation of a soluble chiral ion pair between the chiral phosphate anion and an aryldiazonium 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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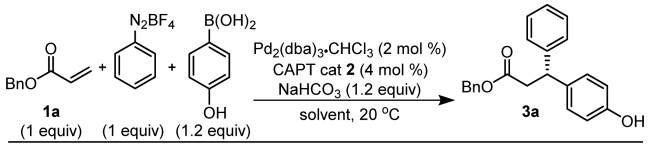
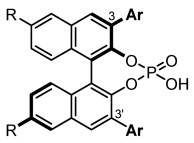
C followed by reinsertion to give **D**. Stabilized as a π-benzyl species, **D** undergoes transmetalation with the second coupling partner and reductive elimination, releasing the product. Herein we present the development of an enantioselective 1,1-diarylation of benzyl acrylates that provides 3,3-diarylpropanates[7] with high enantioselectivity using a CAPT approach (Scheme 1d). The best chiral anion and substrate combination was determined using a multidimensional parametrization[8] tactic, revealing key insight 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[9] (**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

Table 1. Evaluation of CAPT Catalysts[a]





(*R*)-**2a**, R= H, Ar = Ph
(*R*)-**2b**, R= H, Ar = 4-OMe-C_6H_4
(*R*)-**2c**, R= H, Ar = 4-*i*Pr-C_6H_4
(*R*)-**2d**, R= H, Ar = 4-NO_2-C_6H_4
(*R*)-**2e**, R= H, Ar = 3,5-$(Me)_2$-C_6H_4
(*R*)-**2f**, R= H, Ar = 3,5-$(CF_3)_2$-C_6H_4
(*R*)-**2g**, R= H, Ar = 2-*i*Pr-C_6H_4
(*R*)-**2h**, R= H, Ar = 2,6-$(i$Pr$)_2$-C_6H_4
(*R*)-**2i**, R= H, Ar = Mes
(*R*)-**2j**, R= C_8H_{17}, Ar = 2,4,6-$(i$Pr$)_3C_6H_2$
(*R*)-**2k**, R= C_8H_{17}, Ar = 2,4,6-$(Cy)_3C_6H_2$
(*R*)-**2l**, R= C_8H_{17}, Ar = 9-anthracenyl

entry	CAPT cat	% yield **3a**[b]	er[c]	entry	CAPT cat	% yield **3a**[b]	er[c]
1	**2a**	18	42.5 : 57.5	7	**2g**	27	60.5 : 39.5
2	**2b**	12	35 : 65	8	**2h**	47	75.5 : 24.5
3	**2c**	9	37.5 : 62.5	9	**2i**	40	79 : 21
4	**2d**	19	44 : 56	10	**2j**	67	81 : 19
5	**2e**	27	51.5 : 48.5	11	**2k**	52	84 : 16
6	**2f**	14	56.5 : 43.5	12	**2l**	47	87.5 : 12.5

[a]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. [b]Determined by ^{1}H NMR analysis of the crude reaction mixtures using an internal standard. [c]Determined by supercritical fluid chromatography (SFC).

groups in **2** with substituents at the 2- and 2,6-positions resulted in a significant increase in er compared with 3,5- or 4-substituted catalysts (**2a**–**f**), all of which also returned low yields of the desired product (**3a**). In agreement with this observation, increasing the size of the substituents at the 2,4,6-positions from methyl (**2i**) to isopropyl (**2j**) to cyclohexyl (**2k**) led to increasing er values as well as increased yields. Finally, the extended 9-anthracenyl π system (**2l**) afforded the highest enantioselectivity, although slightly lower yields were observed because of a higher percentage of traditional Heck product formation. Control experiments demonstrated that no desired product was observed when hexane was used as the solvent, and lower enantioselectivity resulted when the reaction was conducted in THF, in which the diazonium salt is soluble (Table S1).

In order to gain further insight into the effect of the chiral anion substitution pattern on the enantioselectivity and perhaps predict a more selective CAPT catalyst, we applied our multidimensional parametrization technique, which correlates relevant molecular descriptors to the reaction outcome.[8] As a result, an excellent correlation was established, relating the measured enantioselectivity to three parameters derived from a phosphate model system (**4**, Figure 1). As mentioned previously, chiral anions with 2,6-disubstituted aryl groups resulted in

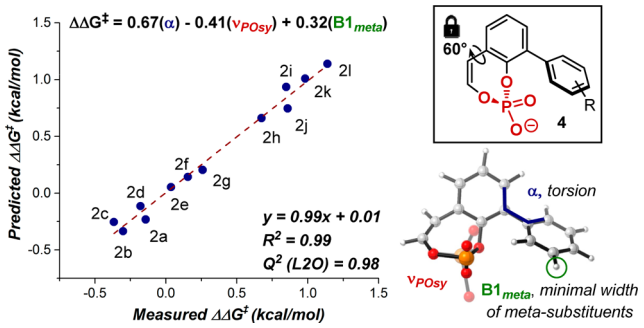


Figure 1. Effect of CAPT catalyst on enantioselectivity.

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 (ν_{POsy}) 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 $\mathbf{B1}_{meta}$ represents the minimum width of the meta substituents of the arenes, suggesting that the size of the substituent at this position impacts the enantioselectivity.[10] 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 stereodefining 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-Naph; **1i**, 3-OMe; **1k**, 1-Naph; **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),

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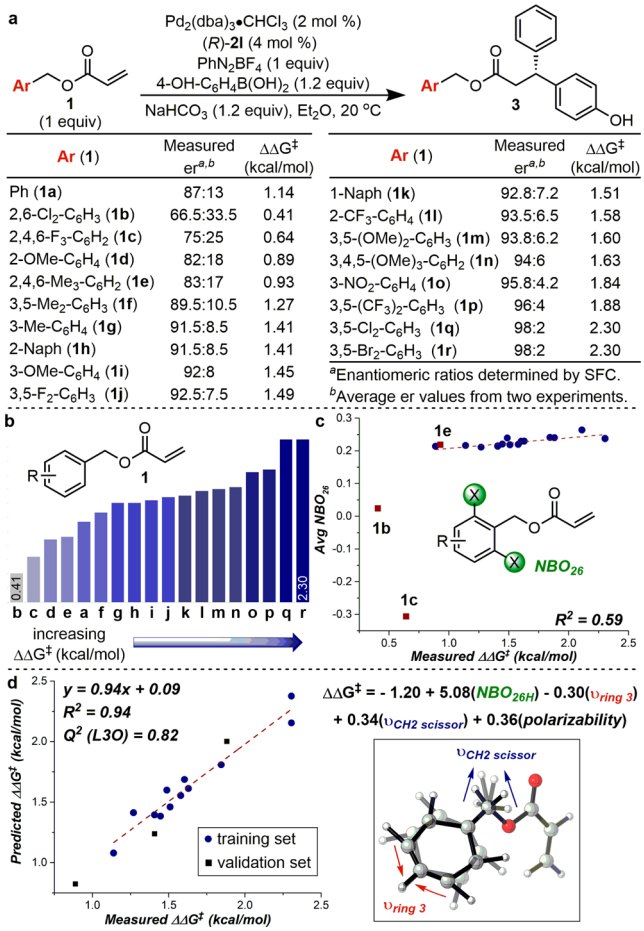


Ar (1)	Measured er[a,b]	ΔΔG‡ (kcal/mol)	Ar (1)	Measured er[a,b]	ΔΔG‡ (kcal/mol)
Ph (**1a**)	87:13	1.14	1-Naph (**1k**)	92.8:7.2	1.51
2,6-Cl_2-C_6H_3 (**1b**)	66.5:33.5	0.41	2-CF_3-C_6H_4 (**1l**)	93.5:6.5	1.58
2,4,6-F_3-C_6H_2 (**1c**)	75:25	0.64	3,5-$(OMe)_2$-C_6H_3 (**1m**)	93.8:6.2	1.60
2-OMe-C_6H_4 (**1d**)	82:18	0.89	3,4,5-$(OMe)_3$-C_6H_2 (**1n**)	94:6	1.63
2,4,6-Me_3-C_6H_2 (**1e**)	83:17	0.93	3-NO_2-C_6H_4 (**1o**)	95.8:4.2	1.84
3,5-Me_2-C_6H_3 (**1f**)	89.5:10.5	1.27	3,5-$(CF_3)_2$-C_6H_3 (**1p**)	96:4	1.88
3-Me-C_6H_4 (**1g**)	91.5:8.5	1.41	3,5-Cl_2-C_6H_3 (**1q**)	98:2	2.30
2-Naph (**1h**)	91.5:8.5	1.41	3,5-Br_2-C_6H_3 (**1r**)	98:2	2.30
3-OMe-C_6H_4 (**1i**)	92:8	1.45	[a]Enantiomeric ratios determined by SFC.		
3,5-F_2-C_6H_3 (**1j**)	92.5:7.5	1.49	[b]Average er values from two experiments.		

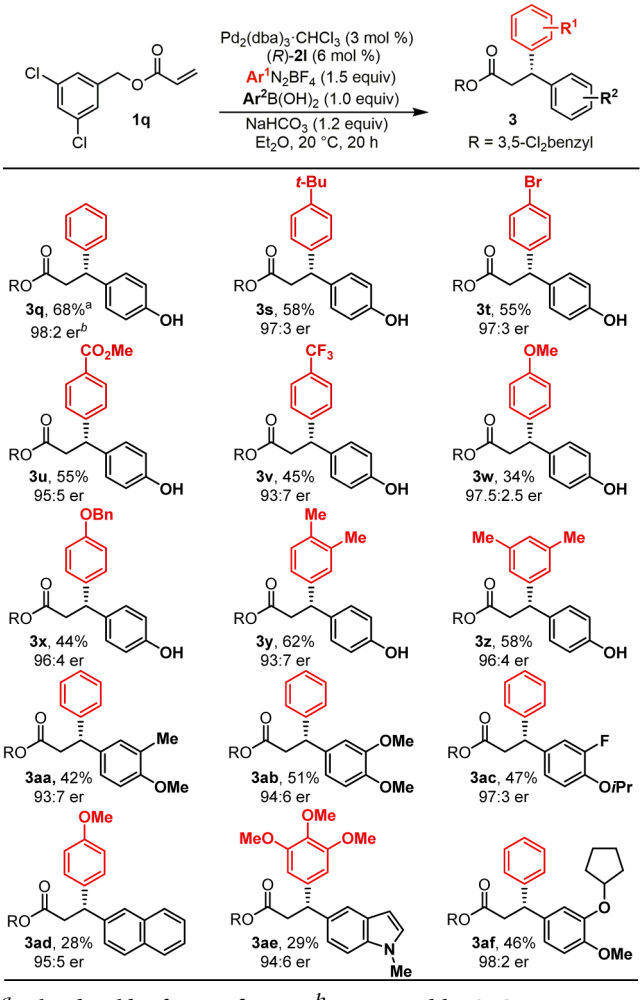
Figure 2. Effect of benzyl group substitutions on enantioselectivity.

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 $\mathbf{NBO_{26H}}$ (the average NBO charge of the 2,6-hydrogens[11]) 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, ν_{ring3} and $\nu_{CH_2scissor}$ 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−π 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., π-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 the

Table 2. Aryldiazonium Salt and Boronic Acid Scope



[a]Isolated yields after purification. [b]Determined by SFC.

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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),[2b] 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, aryldiazonium 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., π-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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