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Electrostatic Control of Regioselectivity via Ion Pairing in a Au(I)–Catalyzed Rearrangement†

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The rearrangement of 3-substituted aryl alkynyl sulfoxides catalyzed by cationic Au(I) complexes was studied with different counterions in solvents spanning a range of dielectric constants (ε). Pulsed-gradient diffusion NMR experiments demonstrated strong ion pairing in low-ε solvents. The regioselectivity of the reaction was insensitive to ε when ion pairing was weak but increased monotonically as ε was decreased in the regime of strong ion pairing. DFT calculations of putative product-determining transition states indicated that the product resulting from the more polar transition state is favored due to electrostatic stabilization in the presence of strong ion pairing.

Introduction

Ion pairing has been widely exploited to control the rate and selectivity of reactions that involve charged species.1-5 In the strategies that have been developed to date, counterions have been used to promote phase transfer, create new steric and chemical environments, bind weakly to reactive centers, participate directly in chemical reactions, or a combination of the above. Because of its proximity to a reactive species in an ion pair, a counterion could in principle affect the selectivity of a reaction through electrostatic interactions that differentiate competing transition states. Although the major electrostatic interaction is the charge–charge attraction that holds an ion pair together, transition states that have significantly different charge distributions could be (de)stabilized to different extents by the local electric field generated by a counterion.6-9 Here we show that ion pairing changes the regioselectivity of a Au(I)-catalyzed aryl alkynyl sulfoxide rearrangement by favoring the product resulting from a more polar transition state through electrostatic interactions.

Results and discussion

Previous studies have shown that Au(I) complexes catalyze a rearrangement of aryl alkynyl sulfoxides to dihydrobenzothiepinones, a transformation that replaces an aryl C–H bond with a C–C bond.10-12 To study regioselectivity for this reaction, we prepared 3-Cl aryl alkynyl sulfoxide 1a, for which C–H functionalization can occur at the 2- or 6-position. We first assessed the effects of ligand structure on selectivity using a series of common phosphine (R₃P) and N-heterocyclic carbene (NHC) ligands (Table 1). 1a was reacted with 2 mol% R₃PAuCl or NHCAuCl precatalyst and 2 mol%...
NaBArF₄ (ArF = 3,5-(CF₃)₂C₆H₃) in CH₂Cl₂ at room temperature for 17 h. NaBArF₄ serves as a Cl⁻ abstractor to generate an active cationic R₃PAu(I) or NHCAu(I) catalyst. These conditions gave clean conversion to the two expected regiosomeric products 2a and 3a in moderate to good yields and recovery of the starting material. For NHCAu(I) catalysts, increasing the steric demand of the NHC (IMes < IPr < SIPr) increased the 3a:2a ratio from 0.7:1.0 to 1.9:1.0, favoring functionalization at the more accessible C–H bond (Table 1, entries 1–3). For the R₃PAu(I) catalysts with R₃P = Ph₃P, (o-tol)P, SPhos, or XPhos, the selectivity was completely insensitive to ligand structure. The ratio of 3a:2a was 0.6:1.0 with all of these catalysts despite their substantially different steric and electronic properties (Table 1, entries 4–7).

Overall, the ligand screen highlights the difficulty of controlling regioselectivity for this aryl C–H functionalization by changing the ligand structure.

To test whether ion pairing could affect selectivity, we performed the reaction with different counterions in solvents that span a range of dielectric constants (ε). Nitrile complexes [NHCAu(NCR)]X and [R₃PAu(NCR)]X (X = anion) were used as pre-catalysts in these experiments to obviate Cl⁻ abstraction. Spontaneous dissociation of NCR generates the catalytically active cationic Au(I) complex. The reactions were performed with 2.5 mM 1a and 2 mol% catalyst loading at room temperature. The reactions were stopped after 4 h to determine the product ratio using ¹H NMR. Unoptimized yields varied from 22% to 88% depending on the ligand (Table S2). Recovered substrate 1a accounted for essentially all of the remaining material.

The dielectric constant of the solvent affected the regioselectivity obtained with each of the Au(I)-catalysts in a counterion-dependent manner. The results for NHCAu(I) complexes are shown in Figure 1a. With [IPrAu(NCMe)]BArF₄, the solvent had little effect on selectivity. The 3a:2a ratio ranged from 0.8:1.0 to 1.2:1.0 across seven solvents with ε ranging from 2.4 (toluene) to 20.7 (acetone). With [IPrAu(NCMe)]SbF₆, however, a significant solvent dependence was observed. For solvents with ε ≥ 8.9 (CH₂Cl₂, (CH₂Cl)₂, acetone), the 3a:2a ratio was similar to the ratio with the BArF₄⁻ complex. For solvents with ε ≤ 6.0, the ratio increased monotonically as ε decreased, reaching 2.7:1.0 in toluene. The same trend was observed with [IPrAu(NCMe)]BF₄, but the increase in the ratio for ε ≤ 6.0 was attenuated. Thus, the counterion determined the dependence of the selectivity on ε, with the magnitude given by the order SbF₆⁻ > BF₄⁻ > BArF₄⁻ ≈ 0. The same solvent and counterion dependencies were observed with the IMes and SIPr complexes (Figure 1a and Table S2). These effects added to the effects of the steric properties of the ligand such that the largest 3a:2a ratio, 4.5:1.0, was obtained with [SIPrAu(NCMe)]SbF₆ in toluene.

Larger counterion-dependent responses to ε were obtained with phosphine complexes. Since BArF₄⁻ complexes proved to be unstable in solution, we compared complexes with SbF₆⁻, PF₆⁻, and BF₄⁻ counterions. The same trends were observed in all cases: the 3a:2a ratio showed essentially no dependence on ε for solvents with an ε > 8, but increased monotonically as ε.

![Figure 1. Effect of solvent dielectric on product ratio for substrate 1a, catalyzed by [NHCAu(NCR)]X (a) and [R₃PAu(NCMe)]X (b). Magnitude of the dielectric response is dependent on the ligand and identity of counterion X⁻.](chart)
was decreased below 8 (Figure 1b). The changes were significantly larger with SbF$_6^-$ than with PF$_6^-$ or BF$_4^-$ and they varied with the phosphine structure in the order XPhos $\approx$ (o-tol)P $>$ Ph$_2$P (Table S2). With XPhos and (o-tol)P ligands and SbF$_6^-$ counterion, the 3a:2a ratio increased by a factor of 4.3–5.0 in going from $\varepsilon$ = 8.9 (CH$_3$Cl)$_2$ to $\varepsilon$ = 2.4 (toluene). Only the solvent’s $\varepsilon$ impacted selectivity and not its molecular properties (dipole moment, coordinating ability, etc.) The product ratios obtained in solvent mixtures matched the expected value for their calculated $\varepsilon$.

The dependence of the product ratio on $\varepsilon$ and the choice of counterion suggests that the selectivity-determining step proceeds from an ion-paired intermediate in low-$\varepsilon$ solvents. Previous diffusion NMR studies of many organometallic complexes have shown that ion pairing is strongly favoured in CDCl$_3$ complexes have shown that ion pairing is strongly favored in CDCl$_3$. Previous diffusion NMR studies of many organometallic complexes have shown that ion pairing is strongly favored in CDCl$_3$ and less polar solvents.

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To assess the extent of ion pairing for the catalysts used here, we performed pulsed gradient spin echo (PGSE) diffusion $^1$H NMR measurements using 5 mM solutions of [IPrAu(NCPh)]BAr$_4^-$, and [IPrAu(NCMe)]SbF$_6$ in CD$_2$Cl$_2$ and CDCl$_3$ at 25 °C. The diffusion coefficients ($D$) of the ions were obtained from Stejskal-Tanner plots (Figure S1). To compare between CD$_2$Cl$_2$ and CDCl$_3$, the hydrodynamic radii ($r_H$) of the ions were calculated using the Stokes–Einstein equation (see Supporting Information). An increase in the $r_H$ value from one solvent to another indicates an increase in the extent of ion pairing.$^{14}$

$^1$H PGSE NMR measurements of [IPrAu(NCPh)]BAr$_4^-$ yielded an $r_H$ value for the cation that increased from 6.6 Å in CD$_2$Cl$_2$ to 7.2 Å in CDCl$_3$, and an $r_H$ for the anion that increased from 6.6 Å to 7.3 Å (Table 2). Since the molecular radius of [IPrAu(NCPh)]BAr$_4^+$ estimated from the crystallographic cell volume is 7.3 Å,$^{19}$ the $r_H$ values in CDCl$_3$ are consistent with complete ion pairing in this solvent. This result also suggests that ion pairing is likely strongly favored in CDCl$_3$ for all complexes studied here because BAr$_4^+$ is larger and much more lipophilic than the other counterions. The smaller $r_H$ values for BAr$_4^-$ and [IPrAu(NCPh)]$^+$ in CD$_2$Cl$_2$ indicate much weaker ion pairing in this solvent.$^{14}$ $^1$H PGSE measurements of additional complexes indicated that the hydrodynamic radii for unpaired [IPrAu(NCPh)]$^+$ and BAr$_4^-$ were ∼6.3 Å and ∼6.4 Å, respectively (Table S1). For [IPrAu(NCPh)]SbF$_6^-$ only the cation $r_H$ values could be obtained because the quadrupole moment of Sb renders the SbF$_6^-$ species $^{19}$F NMR-silent. The cation $r_H$ for this complex increased from 5.8 Å in CD$_2$Cl$_2$ to 6.3 Å in CDCl$_3$, again indicating much stronger ion pairing in CDCl$_3$.

The diffusion NMR results, combined with extensive data from other organometallic complexes,$^{14, 15, 17, 18}$ indicates that the equilibria strongly favor the ion paired forms for the NHCAtAu(I) and R$_3$PAu(I) complexes in CDCl$_3$ and all less polar solvents. The monotonic increase of the 3a:2a ratio as $\varepsilon$ is decreased below 8 for all complexes therefore is not likely the result of a significant increase in the extent of ion pairing but instead reflects an increased strength of the effect of the counterion on the product-determining transition states (see below).

To gain further insight into the origin of the ion pairing effect, we explored its dependence on the aryl substituent. Additional 3-substituted aryl alkynyl sulfoxides 1b – 1f were reacted with [(o-tol)PAu(NCMe)]SbF$_6$ to yield regioisomeric products 2b – 2f and 3b – 3f. Figure 2 shows the product ratios, 3x:2x, in CH$_3$Cl, CHCl$_3$, and toluene. The magnitude of the change in product ratio from high $\varepsilon$ (CH$_3$Cl$_2$) to low $\varepsilon$ (toluene) exhibited a strong dependence on the substituent. Substituent 1b showed essentially no response to the change in $\varepsilon$. For the rest of the substrates, the 3x:2x ratio increased from high $\varepsilon$ to low $\varepsilon$, with the magnitude of the change given by the order OMe < Br < F < Cl < CF$_3$ (Table 3). For CF$_3$-substituted 1f, the ratio increased by a factor of 6.3. In all of these cases, a smaller increase was obtained in CHCl$_3$ compared to toluene, consistent with the trend evident in Figure 1.

The absence of a correlation between the size of the substituent and the magnitude of the selectivity change from high-$\varepsilon$ to low-$\varepsilon$ solvent indicates that ion pairing does not principally affect selectivity via steric interaction. The results in

### Table 2. Solvent dependence of the diffusion coefficient $D$ (10$^{-10}$ m$^2$/s) and hydrodynamic radius $r_H$ (Å) of representative Au(I) complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Solvent</th>
<th>$D$</th>
<th>$r_H$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[IPrAu(NCPh)]BAr$_4^+$</td>
<td>CDCl$_3$</td>
<td>6.0</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>Anion</td>
<td>5.9</td>
<td>7.3</td>
</tr>
<tr>
<td>[IPrAu(NCPh)]BAr$_4^+$</td>
<td>CD$_2$Cl$_2$</td>
<td>8.7</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>Anion</td>
<td>8.7</td>
<td>6.6</td>
</tr>
<tr>
<td>[IPrAu(NCMe)]SbF$_6$</td>
<td>CDCl$_3$</td>
<td>7.0</td>
<td>6.3</td>
</tr>
<tr>
<td>[IPrAu(NCMe)]SbF$_6$</td>
<td>CD$_2$Cl$_2$</td>
<td>10.3</td>
<td>5.8</td>
</tr>
</tbody>
</table>

CD$_2$Cl$_2$ to 7.2 Å in CDCl$_3$, and an $r_H$ for the anion that increased from 6.6 Å to 7.3 Å (Table 2). Since the molecular radius of [IPrAu(NCPh)]BAr$_4^+$ estimated from the crystallographic cell volume is 7.3 Å,$^{19}$ the $r_H$ values in CDCl$_3$ are consistent with complete ion pairing in this solvent. This result also suggests that ion pairing is likely strongly favored in CDCl$_3$ for all complexes studied here because BAr$_4^+$ is larger and much more lipophilic than the other counterions. The smaller $r_H$ values for BAr$_4^-$ and [IPrAu(NCPh)]$^+$ in CD$_2$Cl$_2$ indicate much weaker ion pairing in this solvent.$^{14}$ $^1$H PGSE measurements of additional complexes indicated that the hydrodynamic radii for unpaired [IPrAu(NCPh)]$^+$ and BAr$_4^-$ were ∼6.3 Å and ∼6.4 Å, respectively (Table S1). For [IPrAu(NCPh)]SbF$_6^-$ only the cation $r_H$ values could be obtained because the quadrupole moment of Sb renders the SbF$_6^-$ species $^{19}$F NMR-silent. The cation $r_H$ for this complex increased from 5.8 Å in CD$_2$Cl$_2$ to 6.3 Å in CDCl$_3$, again indicating much stronger ion pairing in CDCl$_3$.

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![Figure 2. Substrate-dependent change in regioselectivity in CH$_3$Cl$_2$, CHCl$_3$ and toluene. Catalyst = [(o-tol)PAu(NCMe)]SbF$_6$.](image-url)
Figures 1 and 2 instead implicate an electrostatic effect of the counterion on the energy barriers leading to the two products.

To probe electrostatic differences between the reactions with different substrates, DFT calculations were performed for putative product-determining transition states for each substrate. Recent experimental and computational studies provide strong evidence that C–C bond formation occurs through an irreversible \([3,3]\)-sigmatropic rearrangement of a cationic vinyl Au intermediate \(I\) (Table 3).\(^{12, 20, 21}\) We calculated the \([3,3]\) transition state leading to each regioisomer for the substrates in Figure 2 with a model Me,P-Au(I) catalyst. We then calculated a dipole moment \((\rho)\) for each transition state using the center of nuclear charge as the origin. Figure 3 shows the charge density maps for the regioisomeric transition states for substrates \(1b\) and \(1f\). The difference in the magnitude of the dipole moments \((\Delta |\rho|)\) indicates the extent to which the transition states differ in their charge distributions. The calculations revealed a strong correlation between \(\Delta |\rho|\) and the magnitude of the change in the product ratio upon switching from \(\text{CH}_2\text{Cl}_2\) to toluene: \(\Delta |\rho| \approx 0\) with \(\text{CH}_3\)-substituted sulfoxide and increased in the order \(\text{OMe} < \text{F} < \text{Cl} < \text{Br} < \text{CF}_3\) (Table 3).

Table 3. Calculated dipole moments of isomeric transition states leading to products \(2x\) and \(3x\).

| R          | Transition state dipole moment | \(\Delta |\rho|\) (D) | \(P\) \(\text{toluene}\) |
|------------|-------------------------------|---------------------|-------------------------|
| Me (1b)    | 4.1                           | 0.7                 | 1.3                     |
| MeO (1e)   | 4.1                           | 0.7                 | 1.3                     |
| F (1e)     | 2.9                           | 2.5                 | 3.1                     |
| Cl (1a)    | 2.6                           | 3.3                 | 5.0                     |
| Br (1d)    | 2.5                           | 5.0                 | 2.7                     |
| CF\(_3\) (1f) | 2.4                          | 6.6                 | 6.3                     |

\(P\) \(\text{toluene}\) and \(P\) \(\text{CH}_2\text{Cl}_2\) are the product ratios \((3x/2x)\) in toluene and \(\text{CH}_2\text{Cl}_2\).

\(\Delta |\rho|\) and \(|\rho|\) are the product ratios \((3x/2x)\) in toluene and \(\text{CH}_2\text{Cl}_2\).

To probe electrostatic differences between the reactions with...
transition states. This strategy may be applicable to diverse synthetic challenges because many reactions involve competing pathways with significantly different charge distributions.

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Notes and references

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