Oxidative Addition, Transmetalation, and Reductive Elimination at a 2,2′-Bipyridyl-Ligated Gold Center


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ABSTRACT: Three-coordinate bipyridyl complexes of gold, [(κ²-bipy)Au-(η²-C₂H₂)][NTf₂], are readily accessed by direct reaction of 2,2′-bipyridine (bipy), or its derivatives, with the homoletic gold ethylene complex [Au(C₂H₄)][NTf₂]. The cheap and readily available bipyridyl ligands facilitate oxidative addition of aryl iodides to the Au(I) center to give [(κ²-bipy)Au(Ar)][NTf₂], which undergo first aryl-zinc transmetalation and second C–C reductive elimination to produce biaryl products. The products of each distinct step have been characterized. Computational techniques are used to probe the mechanism of the oxidative addition step, offering insight into both the origin of the reversibility of this process and the observation that electron-rich aryl iodides add faster than electron-poor substrates. Thus, for the first time, all steps that are characteristic of a conventional intermolecular Pd(0)-catalyzed biaryl synthesis are demonstrated from a common monometallic Au complex and in the absence of directing groups.

INTRODUCTION

The development of the chemistry of gold has been one of the most striking research themes of recent times. However, despite the promise implied by the “redox gold problem”,2 where the relative reluctance of gold to partake in oxidative addition step is challenging, due to the formally nucleophilic partners;5,6 however, the requirement of a strong external oxidant limits the attractiveness of this strategy. Accordingly, extensive efforts have been devoted to the identification of oxidative addition processes that might allow the routine exploitation of internal oxidants (e.g., aryl halides) in Au catalysis. Three distinct strategies have emerged to facilitate the oxidative addition step: (a) the use of directing groups,7,8 (b) the use of highly electrophilic initiation motifs (e.g., allylic bromides, aryl diazoniums, CF₃I),4,9–13 and (c) modification of the ancillary ligand on Au.14 The latter option is most attractive, as it potentially offers the greatest substrate scope; however, this avenue is also the least developed and most challenging. Of specific relevance is the work of Amgoune, Bourissou, and co-workers, who employed a bulky carboranyl diphosphine ligand that subtends a bite angle of approximately 90° at the Au center.15 This results in Au(I) complexes that express enhanced π-back-donation15 and undergo facile non-directed oxidative addition of both strained C–C bonds12b and aryl iodides (Scheme 1B).14

Clearly, the evolution of redox gold catalysis will be facilitated by gaining an in-depth understanding of fundamental steps that might underpin a possible catalytic cycle.16 Although the process in Scheme 1B is unique in its ability to promote efficient non-directed oxidative addition of aryl iodides,
downstream cross-coupling steps (i.e., transmetalation and C–C reductive elimination) were not achieved.14 Indeed, while several elementary organometallic processes have been substantiated for gold only recently,16 there are no reports where all steps of a possible intermolecular biaryl forming cross-coupling cycle have been demonstrated from a common monometallic Au complex. In this article, we show how manipulation of the ligand environment at gold allows the sequential observation of oxidative addition, transmetalation, and reductive elimination from the same species (Scheme 1C).

At the outset of our studies, we targeted higher (>2) coordinate entry, such that our investigations into downstream reactivity might be facilitated. Ultimately, we found that the target complexes can be accessed readily by addition of bipy or its derivatives to homoleptic Au(I)-alkene complexes prepared in situ. The gold alkene complex [Au(C2H4)3][NTf2] (2a) might be facilitated. Ultimately, we found that the target complexes can be accessed readily by addition of bipy or its derivatives to homoleptic Au(I)-alkene complexes prepared in situ. The gold alkene complex [Au(C2H4)3][NTf2] (1) was prepared in a manner analogous to that reported for [Au(C2H4)3][SbF6] (Scheme 2).19 Complex 1 is extremely fragile, but reacts rapidly with bipy to yield [bipyAu(C2H4)3][NTf2] (2a). This process occurs with similar efficacy for a variety of substituted bipyridines; in particular, exposure of 1 to 5,5′-difluoro-2,2′-bipyridine (F2-bipy) generated ([F2-bipy]Au(C2H4)3)[NTf2] (2b), in which the fluorine substituents provide a convenient 19F NMR spectroscopic handle for further studies. The molecular structure of 2b was determined by single-crystal X-ray diffraction (scXRD), which revealed a distorted trigonal planar gold center with the F2-bipy ligand adopting the symmetric κ2-mode. Most importantly, the Au–C distances are contracted and the alkene C=C bond is elongated significantly in comparison to two-coordinate [Au(n2-alkene)]+ cations (L = PR3, NHC) (see the SI).20 These observations are consistent with enhanced π-back-donation enforced by the F2-bipy ligand system. Significantly, whereas 1 is exceptionally fragile, complexes 2 show impressive stability, being handled readily in air and tolerating nonanhydrous solvents in subsequent reactions.

With ample quantities of 2b in hand, investigations into its behavior toward aryl-halide oxidative addition were undertaken. When 2b was exposed to 4-fluoriodobenzene (2 equiv) at 50 °C in CD3Cl2, the solution changed rapidly from colorless to pale yellow color (Scheme 3). Moreover, the 19F NMR spectrum showed three new multiplets in a 1:1:1 ratio, consistent with oxidative addition to give [(F2-bipy)Au(4-F-C6H4)I][NTf2] (3a). Further confirmation was obtained by analysis of the reaction mixture using high-resolution electrospray ionization mass spectrometry (ESI-HRMS). An ion was observed with m/z 610.9482, which is in agreement with the calculated m/z for the [(κ2-F2-bipy)Au(4-F-C6H4)I]+ (3a−NTf2) cation (610.9501). Subsequently, the molecular structure of 3a was confirmed unequivocally by scXRD, with the Au(III) center adopting a slightly distorted square planar geometry, as expected for a d3 metal (Figure 1). Given subsequent observations (vide infra), it is important to note that the C−I bond has clearly been broken in a formal oxidative addition reaction.

The promise of our initial observation of oxidative addition to afford 3a was tempered by the fact that the conversion was only around 10%. By increasing the aryl iodide loading from 2 to 20 equiv an increased conversion of 35% was observed after...
6 h at 50 °C. Raising the temperature to 80 °C increased the consumption of 2b, but full conversion to 3a could still not be achieved. $^{19}$F NMR spectroscopy revealed that conversion reaches a plateau at 40–60 °C, whereas higher temperatures (70 or 80 °C) lead to decomposition of 3a (see the SI). We hypothesized that 3a may be in equilibrium with Au(I)-ethylene complex 2b (i.e., that oxidative addition may be reversible), and hence we devised experiments to explore this most interesting proposition. We reasoned that if oxidative addition to 2b is reversible, then removal of free ethylene from the reaction mixture should drive the equilibrium to the right. Thus, a solution of 2b and 4-fluoriodobenzene (20 equiv) was heated to 50 °C in a sealed tube under a static vacuum (approximately $10^{-2}$ mbar). Remarkably, using this simple modification, full conversion to 3a was observed ($^{19}$F NMR) after 1 h. To confirm the reversibility of the oxidative addition process, a solution of 3a was pressurized (1 bar) with ethylene, and this resulted in >95% conversion to 2b after 1 h at 60 °C (Scheme 3). This latter result also provides unambiguous confirmation of the feasibility of C(sp$^2$)–I reductive elimination from complex 3a.$^{25}$ That 2b and 3a lie in a finely balanced equilibrium contrasts sharply with both the oxidative addition behavior of Pd(0) complexes toward aryl iodides and the work of Amgoune and Bourissou (Scheme 1B).$^{14}$

The apparent differences in reactivity between 2a/b and Amgoune and Bourissou’s carbonyl diphosphine system (Scheme 1B) prompted us to explore the potential energy surface for the oxidative addition step using density functional theory (Figure 2, black pathway). Starting from the ethylene complex, 2a, initial substitution of C$_2$H$_4$ by a representative electron-deficient aryl iodide, 4-CF$_3$-iodobenzene, to form an η$^2$-arene complex is moderately endothermic ($\Delta E = +17.6$ kcal/mol).$^{22}$ In comparison, Joost et al. computed a value of +3 kcal/mol for the corresponding initiation step in Scheme 1B, where anionic [NTf$_2$]$^-\text{I}$ is displaced by 4-fluoriodobenzene.$^{14}$ The neutral ethylene ligand present in 2a/b clearly stabilizes the Au(I) precursor more effectively than [NTf$_2$]$^-\text{I}$. From the η$^2$-arene intermediate, the oxidative addition step is moderately exothermic ($\Delta E = -13.2$ kcal/mol), with a barrier of only 10.1 kcal/mol for the forward reaction and 23.3 kcal/mol for the microscopic reverse (C–I reductive elimination). The combination of an endothermic ligand displacement step and a moderately exothermic oxidative addition makes the overall reaction very marginally endothermic (+4.4 kcal/mol). This observation, alongside the surmountable barrier for the reverse step, is consistent with the experimental evidence for an equilibrium. Comparing again to the computed surface for Amgoune and Bourissou’s 1,2-bis(diphenylphosphino)-1,2-

dicarbosododecarborane-ligated system,$^{14}$ the most conspicuous difference appears to be the relative stability of 2a/b compared to LAu-NTf$_2$.

With conditions in hand for the efficient oxidative addition of 4-fluoriodobenzene to 2b, we explored the scope of the reaction with respect to the aryl iodide component (Table 1). Within 1–6 h at 50 °C, full conversion to the corresponding Au(III) complex was observed with a range of aryl iodides, as determined by $^{19}$F NMR spectroscopy. Both electron-rich (3f/g) and electron-poor (3d) aryl iodides are tolerated, as well as substrates with bulky groups adjacent to iodine (3i/g/h). Furthermore, heteroaromatic (3j) and halide-containing substrates (3b/c/e) are also compatible. For 3b and 3e, the high selectivity of 2b toward the C–I bond is significant; no competing C–Cl/Br oxidative addition was observed. Oxidative addition products 3a–j were isolated in good to excellent yields and were characterized by ESI-MS, $^1$H NMR, and $^{13}$C NMR spectroscopies. The molecular structures of complexes 3b/c/f/h/j were also confirmed by scXRD. These complexes are air stable for days at room temperature and stable for

Figure 1. Molecular structure of the cation of 3a. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms and the NTf$_2$ anion have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Au–C 2.011(3), Au–I 2.5357(3), Au–N1 2.080(3), Au–N2 2.130(3), N1–Au1–N2 78.92(12), N(2)–Au–I 99.37(8), N(1)–Au–C 95.17(14), C–Au–I 86.54(11).

Figure 2. Computed potential energy surface for the oxidative addition reaction, starting from 2a. Calculations were performed using the oB97-XD functional, a def2-TZVP basis with associated 60-electron pseudopotential on Au, def2-SVP with associated 28-electron pseudopotential on I, def2-SVP on C/N, and def2-SV on H/O/F. The effects of solvent were incorporated using the SMD solvation model (CH$_2$Cl$_2$ solvent). Energies shown include zero-point corrections. The inset compares the transition structure for the reaction with 4-OMe-iodobenzene (L) and 4-CF$_3$-iodobenzene (R).
Table 1. Scope of Aryl Iodide Oxidative Addition to 2b

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<tr>
<th>ArI</th>
<th>Yield (%)</th>
<th>[M]</th>
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<tr>
<td>2a</td>
<td>84%</td>
<td>B(OMe)₂</td>
</tr>
<tr>
<td>2b</td>
<td>79%</td>
<td>B(pin)</td>
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<tr>
<td>2c</td>
<td>68%</td>
<td>SiMe₃</td>
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<tr>
<td>2d</td>
<td>82%</td>
<td><a href="t-Bu">B(pin)</a></td>
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<tr>
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<tr>
<td>2f</td>
<td>72%</td>
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<tr>
<td>2g</td>
<td>74%</td>
<td>Li</td>
</tr>
<tr>
<td>2h</td>
<td>79%</td>
<td>ZnCl</td>
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*Yields were determined by ¹⁹F NMR spectroscopy.

Scheme 4. Reaction Profiles for Oxidative Addition of 4-Substituted Aryl Iodides to 2b

*Reaction progress monitored by ¹⁹F NMR spectroscopy. *Reaction conditions: 2.87 μmol of 2b, 28.7 μmol of aryl iodide, 0.0041 M with respect to 2b in CH₂Cl₂ under N₂.
We were able to form 4 in 24% yield (entries 5, 6). 4-TolylSnBu3 and 4-tolylSnMe3 offered further benefits, generating 4 in 51% and 61% yield, respectively (entries 7, 8); in the case of 4-tolylSnBu3, homocoupling product 5 was also observed. Ultimately, we found that 4-tolylZnCl offered the best reactivity, providing 4 in 72% yield (entry 9). This result demonstrates the feasibility of efficient fragment coupling and C−C bond formation, while also providing the first example of a Negishi cross-coupling at gold, albeit under stoichiometric conditions.

The most probable pathway for the Au-mediated Negishi coupling involves transmetalation of the arylzinc reagent with 3a to give intermediate 6, which undergoes reductive elimination to release 4 and generate complex 7 (Scheme 5A).

To gain further evidence for these steps, we monitored the reaction of 3a with 4-tolylZnCl by variable-temperature 19F NMR spectroscopy (Scheme 5B). This showed complete consumption of 3a at −78 °C to give an intermediate consistent with 6. This species was stable up to approximately −40 °C, at which point it decomposed rapidly to form 4 and a small amount of 5. Aliquots of the reaction mixture were analyzed by ESI mass spectrometry (Scheme SA), and an ion was observed with m/z 575.0997, which agrees with the calculated m/z for the cation of 6 (575.1004). Tandem mass spectrometry showed that this ion fragments to a new ion with m/z 389.0140, which corresponds to the calculated m/z for the cation of 7 (m/z 389.0159). These data amount to the direct observation of reductive elimination from 6 to give 4 and 7.

Despite observing the formation of 7, we have so far been unable to render the overall three-step process catalytic. We speculate that the relative conditions required for the oxidative addition (greater than 50 °C) versus the transmetalation/reductive elimination steps (operating below −30 °C), combined with the fragility of 7 under the reaction conditions, mean that decomposition occurs before subsequent reoxidation.

**CONCLUSION**

In summary, we show that the Au(I) complex ([F2-bipy]Au(C₂H₄)[NTf₂]) undergoes sequential aryl-iodide oxidative addition, aryl-zinc transmetalation, and C−C reductive elimination to provide the first example of a Au-mediated Negishi cross-coupling. Accordingly, elementary steps that are typical of Pd-catalyzed biaryl formations have now been demonstrated from a simple monometallic Au center in the absence of directing groups. The chemistry is switched on by the simple bipyridyl ligand framework, which enhances back-donation from Au to facilitate the key aryl−iodine oxidative addition step. The studies described here underpin our ongoing efforts to devise oxidant-free Au-catalyzed biaryl formations using readily available aryl halides as the electrophilic partner.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01411.

Experimental details and characterization data (PDF)
Crystallographic data (CIF)
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**Notes**
The authors declare no competing financial interest.

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