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Toward anti-Markovnikov 1-Alkyne *O*-Phosphoramidation: Exploiting Metal−Ligand Cooperativity in a 1,3-*N*,*O*-Chelated Cp*Ir(III) Complex

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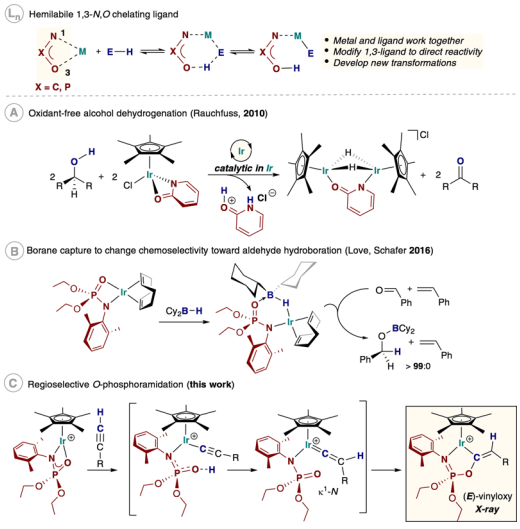
Supporting Information

ABSTRACT: Metal−ligand cooperation between iridium(III) and a 1,3-*N*,*O*-chelating phosphoramidate ligand has been used to develop a protocol for the intermolecular *O*-phosphoramidation of 1-alkynes. This selective C−O bond-forming reaction differs from that of standard amidation reactions, highlighting the ability to control *N*- or *O*-functionalization based on judicious choice of *N*,*O*-chelating ligand and metal center. Advances toward the development of catalytic anti-Markovnikov *O*-phosphoramidation using iridium(III), including characterization of rare reactive intermediates that invoke 1,3-bidentate donor ligand hemilability, are disclosed.

It is well understood that ligands are indispensable to many catalytic processes, offering control of selectivity, reactivity, and often reaction mechanism. In the context of enzymatic and homogeneous catalysis, metal complexes having 1,3-bidentate donor ligands have been shown to facilitate a broad range of important chemical transformations (Scheme 1). In some instances, these metal-ligated systems have been shown to act cooperatively via a change in ligand denticity to carry out a key bond cleavage and/or formation step.[1] For instance, the active site of monoiron hydrogenase comprises a 2-hydroxypyridonate (2-hp) cofactor that is proposed to aid the Fe center in H_2 cleavage.[2] In related work, Yamaguchi showed that a Cp*Ir(III) 2-hp complex could be employed for the oxidant-free metal/ligand-promoted dehydrogenation of alcohols,[3] and Rauchfuss later showed that the 2-hp ligand was critical for achieving turnover.[4] In addition, platinum-group metals having 1,3-donor acetate coligands have found widespread applicability for C−H bond activation of hydrocarbons via ambiphilic metal−ligand activation (AMLA), for example.[5] Likewise, we recently reported that the 1,3-*N*,*O*-chelated phosphoramidate complex, [Ir{κ^2-*N*,O-Xyl(N)P(O)(OEt)$_2$}(η^4-COD)] (COD = 1,5-cyclooctadiene) could be employed for the activation of dicyclohexylborane ($HBCy_2$), to realize chemoselective hydroboration of aldehydes in the presence of alkenes, thereby reversing the known reactivity profile for free $HBCy_2$.[6] These examples illustrate how understanding and harnessing the hemilability of a 1,3-bidentate donor ligand provide a route for the development of new transformations via metal−ligand cooperativity (MLC; Scheme 1).

Scheme 1. Examples of MLC Using 1,3-*N*,*O*-Chelated Complexes



Pursuant to this goal, we aimed to utilize cooperation between Ir(III) and a hemilable phosphoramidate ligand to develop a new chemical transformation: 1-alkyne *O*-phosphoramidation. Notably, realizing regioselective and diastereoselective *O*-phosphoramidation of alkynes would provide an alternative route into vinyloxy organophosphates. Vinyl organophosphates such as Mevinphos, Dichlorovos, and Tetrachlorphos, for example, are acetylcholinesterase inhibitors and are commercial agrochemicals that have been used for insect control.[7] Related catalytic alkyne hydroamidation reactions have been employed by Gooßen and Niedner-Schatteburg using [Ru(1,5-COD)(met)$_2$] (met = methylallyl) as the precatalyst. In their study, the authors propose that vinylidene rearrangement of a terminal acetylide, followed by intramolecular attack by the nitrogen of a κ^1-*N* amidate coligand provides the *N*-functionalized anti-Markovnikov addition product.[8] Notably, such proposed metal-containing intermediates were characterized using mass spectrometry (ESI-MS) alone and were not isolated (Scheme 2).[8a] As far as we are aware, exclusive *N*-amidation regioselectivity has always been encountered with primary or secondary amide substrates. Furthermore, phosphoramidate nucleophiles also prefer *N*-functionalization,[9] owing in part to the thermodynamic penalty associated with reduction of the

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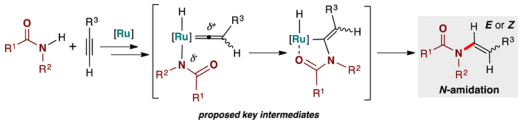
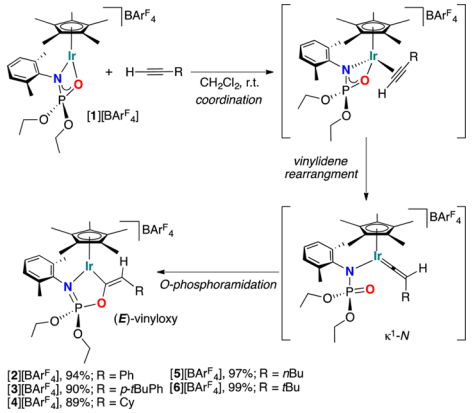
Scheme 2. [Ru]-Mediated *N*-Hydroamidation



phosphine oxide (P═O) double bond (148 kcal·mol^{-1}) to that of a (P−O) single bond (88 kcal·mol^{-1}).[10] Though intriguingly, we have shown that the Cp*Ir(III) phosphoramidate complex [Cp*Ir(κ^2-*N*,*O*-Xyl(N)P(O)(OEt)$_2$)][BAr$^F_4$] (Ar^F = 3,5-(CF$_3$)$_2$C$_6$H$_3$), Xyl = 2,6-Me$_2$C$_6$H$_3$, [**1**][BAr$^F_4$]) preferentially affords κ^1-*N* phosphoramidate complexes allowing the P═O group to serve as a pendant Lewis base.[11] This observation provides foundation for the development of a κ^2-*N*,*O* phosphoramidate Cp*Ir(III) complex that invokes MLC to access unprecedented anti-Markovnikov 1-alkyne *O*-phosphoramidation. Herein key reactive intermediates adopting a hemilabile κ^1-*N* bound motif have been structurally characterized. Insights into these 1,3-*N*,*O*-chelated complexes rationalize the observed regioselectivity and diastereoselectivity of the resulting (*Z*)-vinyloxyorganophosphate products, providing new opportunities in metal-mediated amidation.

We began our study by combining a $CDCl_3$ solution of [**1**][BAr$^F_4$][11a] with a terminal alkyne, phenylacetylene, which results in an intense color change from red-orange to dark green in <5 min. This reaction results in a change from a four- to a five-membered metallacycle to give the 16-electron (*E*)-vinyloxy iridium(III) complex, [Cp*Ir(κ^2-*N*,*C*-(*E*)-Xyl(N)P(O-C═C(H)(Ph))(OEt)$_2$)][BAr$^F_4$] [**2**][BAr$^F_4$] as a green oil in 94% isolated yield following workup (Scheme 3). ^{1}H NMR

Scheme 3. Generation of Five-Membered Irida(III)cycles



spectroscopy provides clear evidence for incorporation of 1 equiv of phenylacetylene, providing a new downfield-shifted alkene signal at δ = 6.84 [d, $^4J_{H,P}$ = 5.1 Hz, 1H]. The observed long-range $^4J_{H,P}$ coupling between hydrogen and phosphorus reflects the partial multiple bond character between these atoms.[12] Furthermore, a ^{1}H−^{1}H NOESY NMR experiment provides a NOE cross-peak between the vinyl CH group (H2) and the Cp*(CH$_3$) ring protons, providing irrefutable evidence for assignment of (*E*)-vinyl geometry. Consistent with expansion of the parent four-membered metallacycle [**1**][BAr$^F_4$] and loss of ring strain, the ^{31}P{^{1}H} NMR spectrum of [**2**][BAr$^F_4$] provides a signal at δ_P = 33.9 from 41.5 in [**1**][BAr$^F_4$].[11a] For the Ir alkenyl group, ^{13}C{^{1}H} NMR spectroscopy displays downfield shifted signals at δ = 178.1 [$^2J_{P,C}$ = 13.4 Hz] and 128.1 [$^3J_{P,C}$ = 13.6 Hz] for the [Ir]-C(R)═CH(Ph) and [Ir]-C(R)═CH(Ph) carbon atoms. Large values of $^nJ_{P,C}$ for the vinyl group: $^2J_{P,C}$ = 13.4 Hz and $^3J_{P,C}$ = 13.6 Hz compared to $^2J_{P,C}$ ~ 9.0 Hz and $^3J_{P,C}$ ~ 6.0 Hz for the ligand P−O−CH$_2$−CH$_3$ unit, for example, are consistent with the cyclic, multiple bond character within these irida(III)-cycles.[13] Furthermore, the scope of this transformation could be extended to other aryl- and alkyl-substituted 1-alkynes, giving analogous five-membered irida(III)cycles [**3**][BAr$^F_4$]−[**6**]-[BAr$^F_4$], which were isolated as green oils.

X-ray quality crystals of [**3**][BAr$^F_4$] and [**5**][BAr$^F_4$] could be reliably obtained from a saturated hexanes solution at −35 °C ([**3**][BAr$^F_4$]; Figure 1) and confirm (1) (*E*)-vinyl stereo-

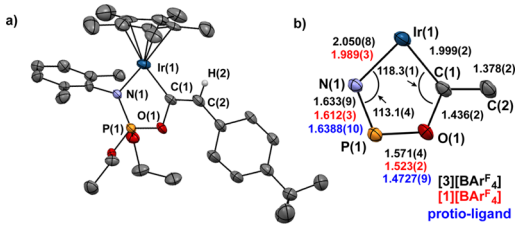


Figure 1. ORTEP depiction of the solid-state molecular structure of (a) [Cp*Ir(κ^2-*N*,*C*-(*E*)-Xyl(N)P(O-C═C(H)(*p*tBuPh))(OEt)$_2$)]-[BAr$^F_4$]; [**3**][BAr$^F_4$]. (b) Front view of irida(III)cyclic core of [**3**][BAr$^F_4$]. Bond lengths (Å) and angles (°).

chemistry and, more importantly, (2) regioselective *O*-phosphoramidation. As inferred from NMR spectroscopic data, the structures feature a genuine five-membered irida(III)cycle[14] comprised of a near planar Ir−N−P−O−C core. Given that crystals of [**2**][BAr$^F_4$] were unattainable, the structure of [**3**][BAr$^F_4$] will be discussed as a representative example; the Ir(1)−N(1) contact [2.050(8) Å] is similar to that observed in [**1**][BAr$^F_4$] [1.989(3) Å], while Ir(1)−C(1) and C(1)−C(2) bond lengths of 1.999(2) and 1.378(2) Å are in good agreement [1.9886(18) and 1.334(3) Å] to those reported for a related Ir(III) phenylvinyl complex, formed through 1-alkyne dimerization.[15] For the ligand scaffold, an elongated P(1)−O(1) bond length of 1.571(4) Å, compared to the P═O bond for the protio ligand[16] (1.4727(9) Å), suggests significantly increased single bond character [cf. 1.555 Å for the average P−O bond length for the two P−OCH$_2$CH$_3$ groups in [**3**][BAr$^F_4$]] (Figure 1). The isolation and characterization of these irida(III)cyclic intermediates, which result from C−O bond formation, arise from the propensity of [**1**][BAr$^F_4$] to adopt a κ^1-*N* bonding motif. To date the related Ir κ^1-*O* structural variant has not been observed. This is in contrast to hydroamidation using a Ru amidate complex (Scheme 2), which is proposed to proceed via a similar five-membered metallacylic intermediate, but instead results in selective C−N bond formation.[8]

We propose that the anti-Markovnikov addition complexes [**2**][BAr$^F_4$]−[**6**][BAr$^F_4$] result from the intermediacy of a cationic π-alkyne adduct, which rearranges to form an iridium-(III) vinylidene complex (Scheme 3) through ligand-assisted proton shuttling (LAPS).[17] To test this hypothesis, coordination of an alternative weak Lewis base to the cationic metal center could prevent the requisite π-alkyne complex formation. Indeed, combination of [**1**][BAr$^F_4$] with excess phenylacetylene in a coordinating solvent (MeCN-d_3) provides an equilibrium mixture of the κ^2-*N*,*O* mono- and κ^1-*N* bis(acetonitrile) adducts,[11a] but not the targeted five-membered ring product, [**2**][BAr$^F_4$]. These results show that a weak Lewis base (MeCN)

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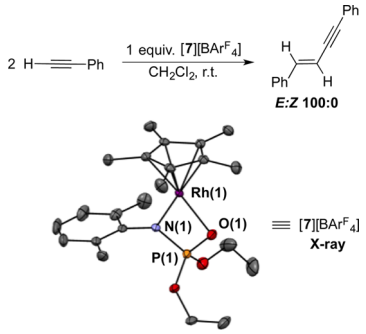
prevents vinylidene formation that is necessary for intramolecular *O*-nucleophilic attack.

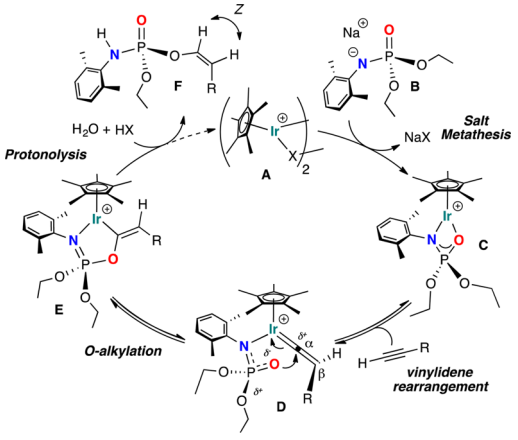
In an effort to highlight the importance of pairing the phosphoramidate ligand with an Ir(III) center to realize the regioselective *O*-phosphoramidation of 1-alkynes, a related rhodium(III) phosphoramidate complex, [Cp*Rh{κ^2-*N*,*O*-Xyl-(N)P(O)(OEt)$_2$}][BAr$^F_4$][**7**][BAr$^F_4$] was prepared (Scheme 4; see SI). Reaction of [**7**][BAr$^F_4$] with phenylacetylene did not produce the related five-membered rhoda(III) cycle, and instead, head-to-head alkyne dimerization, giving the corresponding (*E*)-enyne, was observed along with regeneration of [**7**][BAr$^F_4$]. This experiment suggests that insertion of another alkyne equivalent into a transiently formed rhodium(III) acetylide outcompetes LAPS.[17]

Scheme 4. Reaction of Phenylacetylene with [7][BAr$^F_4$]



The development of a high-yielding, stoichiometric synthesis of such complexes related to previously proposed key catalytic intermediates pointed toward the possibility of accessing an iridium-mediated synthetic cycle for the intermolecular *O*-phosphoramidation of 1-alkynes (Scheme 5). We have shown

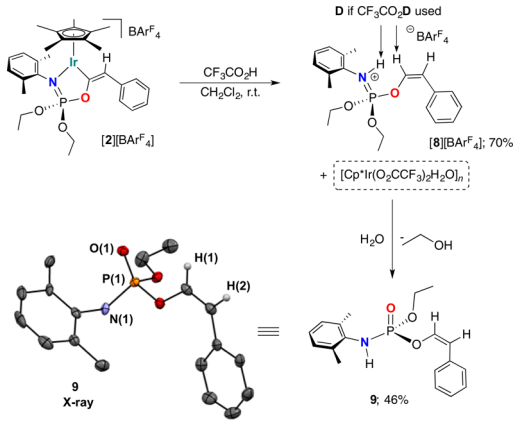
Scheme 5. Proposed Cycle for Catalytic *O*-Phosphoramidation Using 1-Alkynes



that treatment of precursor complex [Cp*Ir(μ-Cl)]$_2$[BAr$^F_4$]$_2$ (**A**) with a sodiated phosphoramidate, Na[R(N)P(O)(OR′)$_2$] (**B**) yields an unsaturated iridium(III) phosphoramidate complex **C** through salt elimination.[11a] The above experiments suggest that treatment of **C** with a 1-alkyne provides an 18-electron η^2-alkyne complex, which upon rearrangement provides vinylidene **D**. Finally, intramolecular *O*-attack by the hemilabile phosphoramidate coligand affords the five-membered irida(III)-cycle **E**. Thus, by using a suitable proton source (HX) to achieve Ir−C bond cleavage of irida(III)cycles [**2**][BAr$^F_4$]−[**6**][BAr$^F_4$] (**E**), we would regenerate precursor complex **A** and the organic *O*-substituted (*Z*)-phosphoramidate product **F** (Scheme 5).

In an effort to realize catalytic turnover, the isolated metallacycle [**2**][BAr$^F_4$] was treated with protio phosphoramidate, [(XylNH)P(O)(OEt)$_2$] [pK_a = 18.3 (DMSO) for (PhNH)P(O)(OEt)$_2$],[18] but failed to produce the vinyloxy iminophosphorane (*Z*)-[Xyl(NH)═P(O-CH═CHPh)-(OEt)$_2$][BAr$^F_4$][**8**][BAr$^F_4$]. Next, we envisaged that (HO)P-(O)(OEt)$_2$ [pK_a = 1.4 (H$_2$O)][19] might serve as a suitable proton source, however at room-temperature, no reaction with [**2**]-[BAr$^F_4$] was observed. Gratifyingly, treatment of [**2**][BAr$^F_4$] with 5 equiv of CF$_3$CO$_2$H [pK_a = 0.52 (H$_2$O)][20] in CDCl$_3$ at ambient temperature provided the protonated (*Z*)-vinyloxy iminophosphorane [**8**][BAr$^F_4$] (Scheme 6). Consistent with the observation that a highly acidic reagent is required for Ir−C bond cleavage, CH$_3$CO$_2$H [pK_a = 4.76 (H$_2$O)][20] also did not affect protonolysis.

Scheme 6. Protonolysis of [2][BAr$^F_4$] with CF$_3$CO$_2$H



The desired organic vinyl phosphate product [**8**][BAr$^F_4$] can be compared with previously reported compounds having similar structural motifs.[21] By using ^{1}H{^{31}P} NMR spectroscopy, two vinylic signals are apparent at δ_H 6.46 and 6.12 as two mutually coupled doublets [$^3J_{H,H}$ = 6.2 Hz], consistent with formation of the thermodynamically less stable (*Z*)-geometric isomer. In addition, a broad doublet at δ = 5.65 [$^2J_{H,P}$ = 17.4 Hz] results from protonation of the iminophosphorane (P═N) functionality under acidic conditions.[22] To further substantiate these assignments, complex [**2**][BAr$^F_4$] was treated with CF$_3$CO$_2$D (>99% d_1) to deliver the (*Z*)-vinyloxy iminophosphorane [**8**][BAr$^F_4$]-d_2, deuterated specifically at the C(1) and N(1) positions (>99% *d*). Under aqueous workup conditions, the P−O(vinyl) and P−OEt groups were notably susceptible to hydrolysis, providing trace amounts of phenylacetaldehyde (<5%) (resulting from tautomerization of the released (*Z*)-enol). Nonetheless, the desired (*Z*)-vinyloxy phosphoramidate **9** could be cleanly isolated in 46% yield following column chromatography (Scheme 6). Single crystals of **9** obtained from a saturated hexanes/toluene solution at 0 °C corroborate the (*Z*)-vinyloxy stereochemistry resulting from protonolysis of the Ir−C bond in [**2**][BAr$^F_4$] (Scheme 6).

In addition to these organic products, the fate of the Ir can be accounted for in the identification of the known aggregate [Cp*Ir(O$_2$CCF$_3$)$_2$(H$_2$O)]$_n$ with its diagnostic Cp* signal at δ_H = 1.57.[23] Consistent with the established reactivity trends of this trifluoroacetate adduct, a small amount (<5%) of the Ir(III) π-

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arene complex of the protio phosphoramidate ligand, $[Cp^*Ir\{\eta^6\text{-}2,6\text{-}Me_2C_6H_3(NH)P(O)(OEt)_2\}][BAr^F{}_4]_2$ [**10**][$BAr^F{}_4$]$_2$ [δ_P = −1.10][24] was also observed. Thus far, the near quantitative formation of $[Cp^*Ir(O_2CCF_3)_2(H_2O)]_n$ has thwarted attempts to render the synthesis of (*Z*)-vinyloxy phosphoramidates catalytic.

In summary, we have been able to exploit established trends in 1,3-bidentate donor coordination chemistry to access a coordinatively unsaturated Ir(III) phosphoramidate complex as a system capable of MLC. The known preference for adopting a hemilabile κ^1-*N* bonding mode could be exploited to develop regioselective and diastereoselective 1-alkyne *O*-phosphoramidation with both aryl and alkyl alkynes. The fully characterized (*E*)-vinyloxy Cp*Ir(III) phosphoramidate complexes provide models and mechanistic insight for the previously proposed metallacylic intermediates for catalytic alkyne hydroamidation chemistry. Similar MLC may be invoked in related transformations involving *N*,*O*-chelated nucleophiles. Release of the desired (*Z*)-vinyloxy organophosphates could be achieved by treatment with strong acid and ongoing efforts focus on developing modified reaction conditions suitable for catalytic turnover.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05143.

^{1}H, ^{13}C, ^{31}P{^{1}H} NMR spectra for all complexes as well as crystallographic data for [**3**][$BAr^F{}_4$], [**5**][$BAr^F{}_4$], [**7**][$BAr^F{}_4$], and **9**. CCDC 1479417−1479420 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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