Synthesis of Phosphaisocoumarins via Ruthenium Catalysis

Significance: Presented is the ruthenium-catalyzed C–H activation–cyclization of aryl phosphonic monoester and phosphinic acids resulting in phosphaisocoumarins. An extensive screening identified the mixture of Ag₂CO₃–AgOAc–KPF₆ to be ideal. The reason for the effectiveness of the mixture of Ag₂CO₃–AgOAc–KPF₆ is not identified. However, it was shown that in the absence of KPF₆ the reaction does proceed, albeit with lower yields (63% vs. 97%). AgOAc alone affords a comparable yield to the Ag₂CO₃–AgOAc mixture, although this was established early in the optimization study with only 2 mol% ruthenium catalyst. AgOAc alone was not used with a higher catalyst loading, leading to the extrapolation that the reaction may be successful without additional KPF₆ and Ag₂CO₃. The scope of the reaction was well studied and the yields range from moderate to good.

Comment: Heterocyclic phosphorus-containing compounds can have significant biological and pharmaceutical properties. The synthesis of phosphaisocoumarins has recently been reported using rhodium-catalyzed C–H activation–cyclization of alkynes with organophosphorus compounds (Y. Unoh et al. Org. Lett. 2013, 15, 3258). The current report uses similar conditions, but with a less expensive ruthenium catalyst, albeit in a more complex overall reaction system. The reaction seems tolerant to electron-withdrawing and -donating groups on both alkyne and aryl phosphorus starting materials, although alkynes with strong electron-withdrawing groups were not tested. Some mechanistic studies were conducted using deuterium-labelled organophosphorus compounds, and a kinetic isotope effect (k_H/k_D = 5.67) was observed, indicating that C2–H bond cleavage is most likely involved in the rate-limiting step. A plausible mechanism was proposed, which does not include rationalization of the effect of the mixture of reagents involved in the reaction.