C–H Activation Using Organophosphorus Compounds

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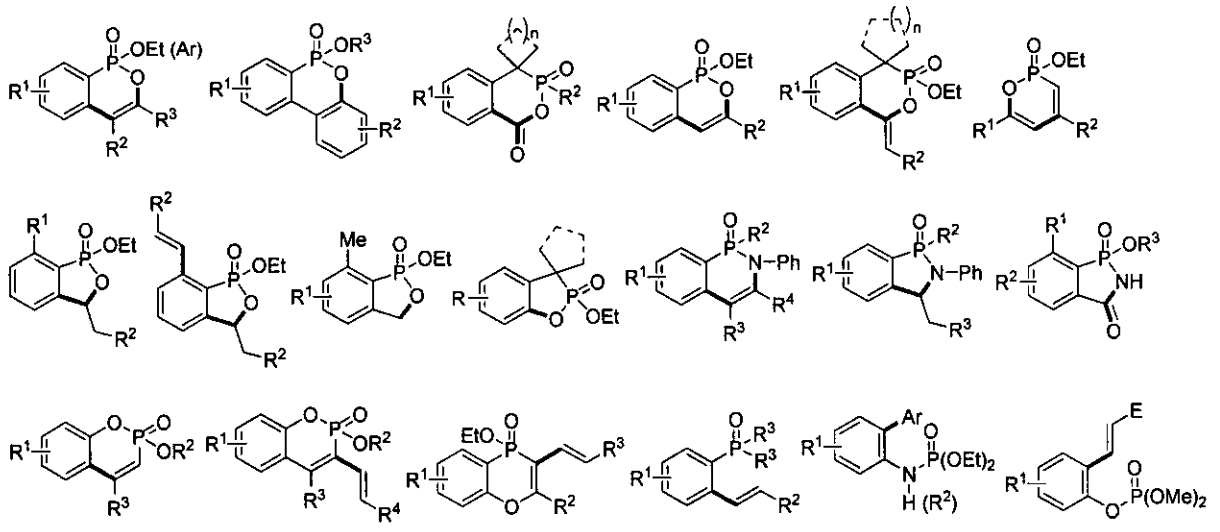
C–H bond functionalizations catalyzed by transition metals are interesting since these procedures permit for a more clear-cut synthetic strategy to products devoid of demanding prefunctionalization of starting materials, thus avoiding byproducts in step-economical manner. In order to have a broad synthetic strategy in a C–H functionalization, the desired C–H bond in the starting material should be selectively activated over all the C–H bonds existing in the substrate. In particular, since there is a trivial difference in the reactivity between the C–H bonds in aromatic compounds, a selective C–H bond functionalization is very crucial. Recently, a series of examples of C–C and C–heteroatom bond formation have been described by introducing directing groups. As a consequcnce, a number of coordinating directing groups have been employed for atom- and step-economical C–H bond functionalization. Among those, imines, amides and heterocyclic compounds bearing nitrogen are most frequently utilized as directing groups. In addition, C–H functionalization using hydroxyl and carboxyl as directing groups through weak coordination has been studied to a great extent. However, there is still a need to develop useful functional groups for direct *ortho*-selective C–H bond cleavage, which will provide a significant effect in synthetic applications. Encouraged by a number of transition metal-catalyzed cyclizations using a carboxylic acid group, we imagined that C–H bond functionalization with phosphonic acid monoesters would perform as a desirable platform for the preparation of phosphaisocoumarins, which may be phosphorus heterocycles exhibiting effective biological activity. Moreover, to date, phosphaisocoumarin scaffolds have been synthesized through intramolecular cyclization. Although alkynylarylphosphates or their monoesters have been used in the cyclization, as far as we know, Rh-catalyzed cyclization using alkynes and arylphosphonic acid monoesters has not been utilized for the synthesis of phosphaisocoumarins. Furthermore, to the best of our knowledge, methods using phosphorus compound as a directing group is few. Inspired by recent our interests in organophosphorus compounds, we decided to examine C–H bond functionalization with phosphonic acid monoester. Rh-catalyzed cyclization of phosphinic acids and phosphonic monoesters with alkynes has been developed. The oxidative annulations proceeds with complete conversion of phosphinic acid derivatives and allowed the atom-economic preparation of useful phosphaisocoumarins with high yield and selectivity. The reaction is tolerant of extensive substitution on the phosphinic acid, phosphonic monoester and alkyne, including halides, ketone, and hydroxyl groups as substituents. Furthermore, we found that alkenylphosphonic monoesters proceed to give a wide range of phosphorus 2-pyrones through oxidative annulations with alkynes. Mechanistic studies revealed that C–H bond metalation was the rate-limiting step. An efficient and cost-effective Ru-catalyzed oxidative cyclization of phosphonic acid monoesters or phosphinic acids with alkynes has been developed for the synthesis of a wide range of phosphaisocoumarins in good to excellent yields under aerobic conditions. A multitude of arylphosphonic acid monoesters and arylphosphinic acids having electron-donating and -withdrawing groups were oxidatively cyclized. Various diarylacetylenes, dialkylacetylenes, and alkylarylacetylenes effectively underwent Ru-catalyzed oxidative cyclization. A substrate possessing benzoic acid as well as a phenylphosphonic monoester moiety was smoothly cyclized with hex-3-yne to afford a compound having both isocoumarin and phosphaisocoumarin moieties. Alkenylphosphonic monoester afforded phosphorus

2-pyrone through oxidative cyclization with alkyne. Competition experiments between diaryl- and dialkylalkynes and between diarylacetylenes having 4-methoxy and 4-chloro groups gave results which showed that the present oxidative cyclizations were not affected by the electronic effects of alkynes. Mechanistic studies revealed C–H bond metalation to be the rate-limiting step.



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