C–H ACTIVATION USING TRANSIENT DIRECTING GROUPS

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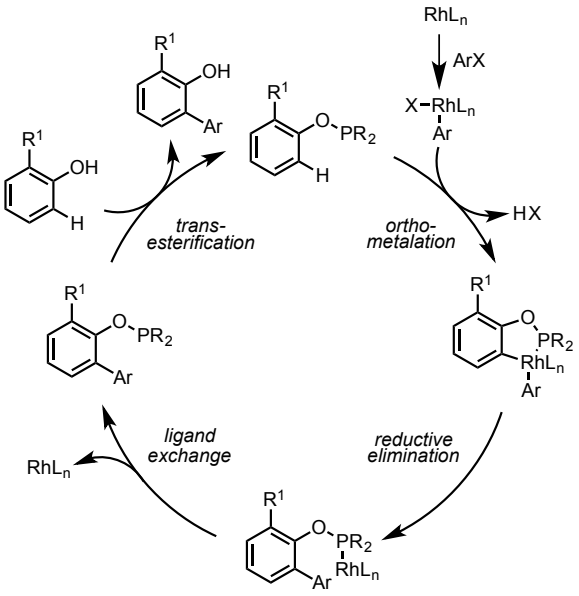
BACKGROUND

The ability to directly transform unactivated C–H bonds into more complex motifs using C–H activation is a powerful strategy in organic synthesis because it allows for the elaboration of structures without requiring prefunctionalization at the reaction site. C–H activation involves the transformation of an unactivated C–H bond into a carbon-metal bond that can then be used for further coupling. In order for it to be properly utilized, however, specific challenges must be addressed, namely how to activate an inert bond in a selective and controlled fashion. To meet these challenges, chemists often utilize directing groups (DG), groups already installed on the substrate molecule that can precoordinate to the metal and bring it into close proximity to the C–H bond. Although powerful, DG strategies present significant drawbacks that inhibit their widespread use in complex molecule synthesis. Even when installation or removal is facile, stoichiometric DGs can still suffer from issues of atom economy. Furthermore, they can often be just as large as the substrate, generating a large amount of waste byproducts when removed. To address these drawbacks, small organic molecules have been developed that bind to the substrate in a reversible fashion and can be use to catalytically direct C–H activation, acting as a transient DG.

PHOSPHITES AND PHOSPHINITES

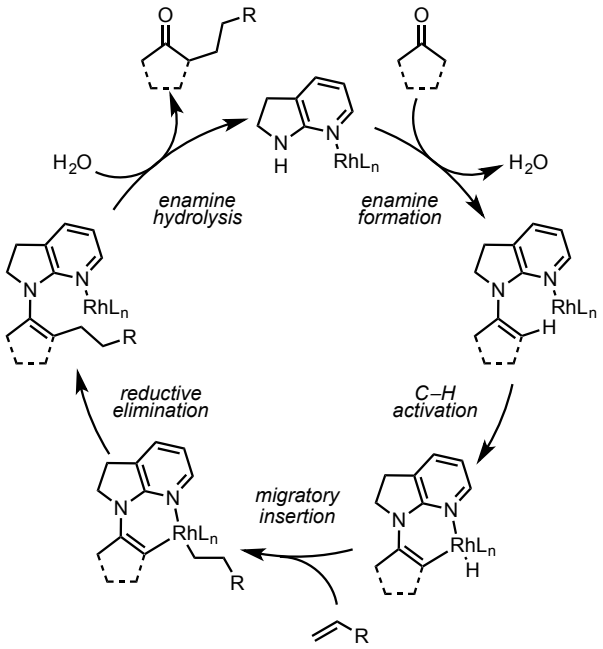
Parshall demonstrated in 1969 that triphenylphosphite complexes of ruthenium form metallacylic species by insertion into the *ortho* position of one phenoxy group, and also noted that these complexes could catalyze *ortho*-deuteration of phenol under an atmosphere of D_2, presumably by exchange of the phenoxy groups on the phosphite.[1] With these results in mind, Lewis explored the ability of catalytic phosphite DGs to direct C–C bond formation by utilizing a similar catalytic system under a pressure of ethylene, and demonstrated that high yields of the bis-alkylated phenols could be obtained.[3] Bedford then went on to show that rhodium-based complexes with phosphinites as a catalytic DG could be used for the *ortho*-arylation of phenols with aryl halides.[4]



Scheme 1. Catalytic cycle for phenol *ortho*-arylation using a phosphinite as a transient directing group.

The DG is able to undergo trans-esterification between substrate and product, directing *ortho*-metalation and subsequent cross coupling, as demonstrated in Scheme 1.

IMMINES AND ENAMINES



Scheme 2. Catalytic cycle for ketone α–alkylation using 7-azaindole as a transient directing group.

In addition to phosphorus-based transient DGs, research has also been performed using amine-derived catalytic DGs, reversibly forming imines or enamines *in situ*. In 1997, Jun demonstrated that aminopyridines could be used as a transient DG with aldehydes, which directed their alkylation with alkenes *via* reversible imine formation.[5] Dong went on to demonstrate that ketones could be α–alkylated with terminal olefins by using 7-azaindoline as a catalytic DG. This reversibly forms an enamine that is activated for C–H activation at the α–position, as demonstrated in Scheme 2.[6] Most recently, Yu reported that amino acids could act as transient DGs to direct the palladium catalyzed β– or γ–arylation of aldehydes and ketones using aryl iodides.[7] In this context, the use of chiral amino acids allowed for the synthesis of chiral products with high entantioselectivity.

CONCLUSION

The use of a transient DG allows for the application of directed C–H activation strategies without prefunctionalization of the substrate. Transient DGs can be used catalytically, reversibly forming species that can undergo the desired coupling reaction and then releasing the DG after the reaction has taken place. Applications of such strategies could be used in the future to develop more expedient synthetic routes in organic synthesis and medicinal chemistry.

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