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Highlight

Recent advances of remote selective C–H activation: Ligand and template design

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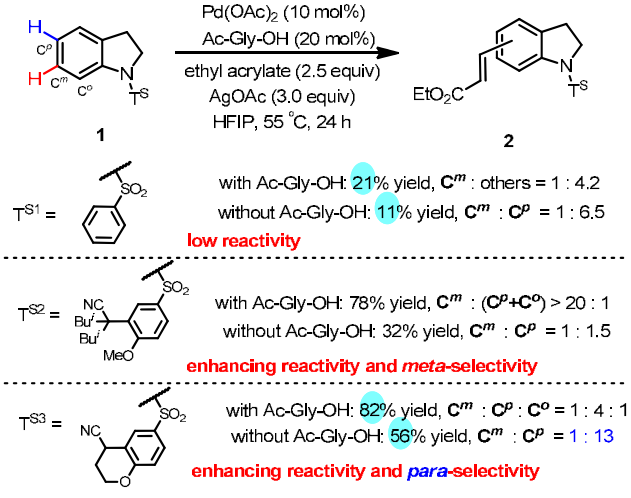
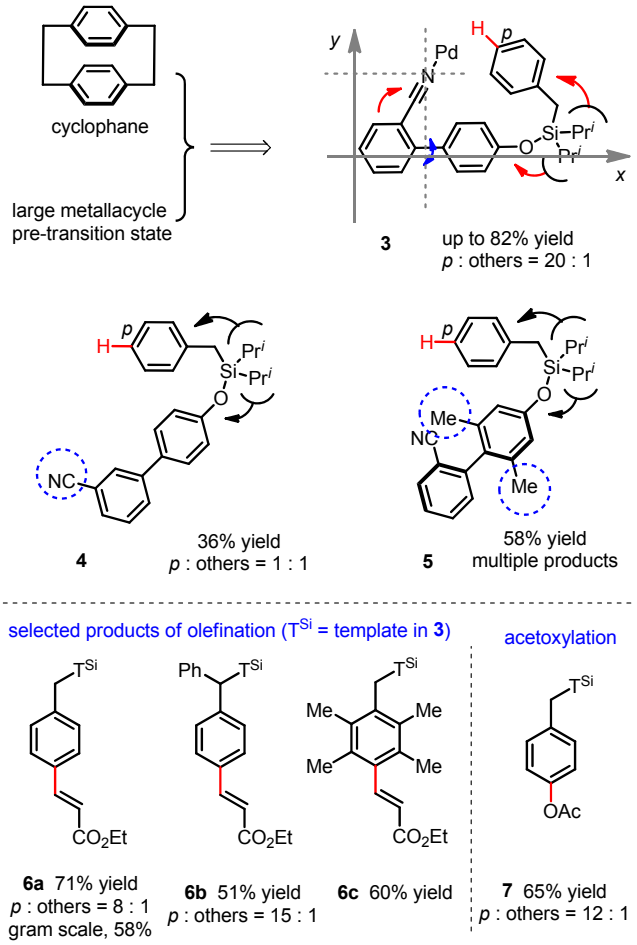
Regioselective (site selective) control is one of the major aims of research directed towards the development of novel organic methodologies. Regioselective control is especially important for C–H activation reactions because most organic compounds contain a large number of C–H bonds and it can therefore be difficult to differentiate between similarly reactive C–H bonds. Traditional approaches for controlling the regioselectivity of C–H activation reactions involve the use of an *ortho* directing group, which results in an *ortho*-selective functionalization process, and *ortho*-C–H functionalization reactions of this type have been studied extensively [1–7]. In contrast, reports pertaining to remote selective C–H activation using an existing functional group remain scarce because of the inability of functional groups to strongly direct the activation of a single remote C–H bond. Many examples have been reported for *meta*-selective C–H functionalization reactions by virtue of the steric or electronically biased properties of the arene substrates, however these usually suffer from limited substrate types and scope [8–22]. In contrast, remote C–H bond activation reactions that override the intrinsic electronic and steric properties of the substrate as well as the *ortho*-directing effects via a more general method, are less-well developed. Yu's pioneering work towards the use of an end-on template strategy for the activation of C–H bonds has inspired research involving template- and ligand-controlled (mono-protected amino acid ligands) remote site selective activation of C–H bonds [23–28]. A variety of different nitrile templates have been developed to promote the *meta*-selective C–H functionalization reactions of a wide range of substrates, including toluenes, phenols, anilines and carboxylic acids etc. [23–32]. In addition, the research groups of Yu and Dong recently described the development of a novel and elegant *meta*-C–H activation strategy using a ligand and norbornene-type transient mediator (not discussed in this highlight) [33–35]. Herein, we provide a brief overview of recent developments in the design and application of ligands and templates for the remote site selective C–H activation of aromatic compounds.

Yu/Movassaghi and co-workers [27] have developed several sulfonyl-type templates for the *meta*-selective C–H functionalization of indoline and indole derivatives (Scheme 1). The focus of this particular study was to develop a robust method for the preparation of the T^{S2} template for the *meta*-selective C–H activation of indoline and indole substrates. Interestingly, however, they also discovered that the T^{S3} template exhibited enhanced *para*-selectivity towards indoline compared with control experiments using the T^{S1} template. Although the selective *para* C–H functionalization of indolines is not particularly challenging, Yu's results show that template-directed *para*-C–H bond activation is possible and that this strategy could potentially be used for the activation of *para*-C–H bonds in other systems.

The regioselective *para*-C–H activation of toluene can be difficult compared with indole and indoline substrates. Maiti's group [36] recently reported the preparation of an interesting template that could direct the Pd-catalyzed *para*-C–H activation of toluene-type substrates with excellent selectivity. Maiti's template design strategy differed from Yu's in the sense that it was dependent on the occurrence of a larger metallacycle pre-transition state (Scheme 2). Inspired by the cyclophane structure, Maiti's group employed a biphenyl skeleton for the



Scheme 1. Template-improved *para*-selective C–H activation of indoline.



Scheme 2. Template-design for *para*-selective C–H activation of toluene.

template backbone. Control experiments revealed that the nitrile group had to be fixed to a specific position on the *x* axis, and that it must possess a certain degree of flexibility along the *y* axis (**3** vs **4** and **5**). With the assistance of mono-protected amino acid (MPAA), this newly developed template was successfully used for a series of *para*-selective C–H olefination and acetoxylation reactions with tolerance for variation in substrate scope. It is noteworthy that this template strategy allowed for the olefination of a sterically encumbered substrate. Furthermore, the C–Si and O–Si bonds could both be readily cleaved after the *para*-functionalization reaction. We believe that these developments will lead to the discovery of additional templates for the *para*-selective C–H activation of numerous substrates, especially some of the more challenging substrates, such as benzoic acid derivatives.

In most of the published cases, Yu's template strategy required the addition of a MPAA to enhance the level of *meta*-selectivity through its tendency towards a concerted deprotonation/metalaton C–H activation mechanism [37]. In contrast, Kanai's group [38] introduced a new methodology involving the use of a secondary interaction from a directing ligand. In this way, the assistance of a secondary interaction between the functional groups of the ligand and the substrate allowed for the metal center coordinated to the ligand to become fixed to a certain C–H bond. This secondary interaction therefore led to the selective activation of the C–H bond nearest the metal center (Fig. 1).

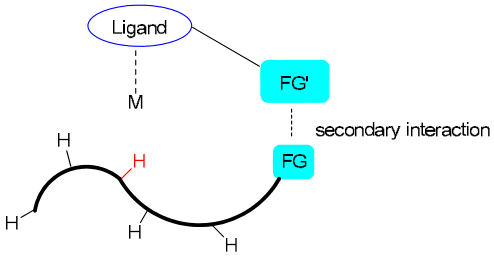
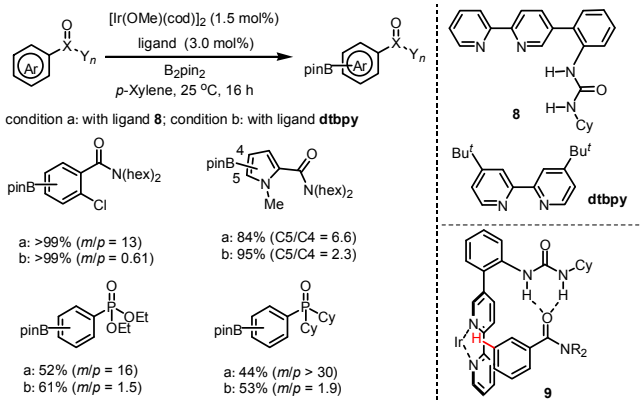


Fig. 1. Bifunctional ligand design concept for remote selective C–H activation.

The iridium-catalyzed C–H borylation of aromatic compounds is a powerful methodology for the preparation of aryl boronic esters because of its simplicity and mild reaction conditions. Furthermore, the newly created C–B bond can be readily transformed to a variety of different functional groups. However, the regioselectivity of this reaction is usually dependent on the intrinsic electronic and steric properties of the substrate. Kanai and co-workers used this reaction to examine their new design concept, which was based on the use of a hydrogen bonding interaction as the secondary interaction (Scheme 3). A series of bipyridine ligands bearing urea or thiourea functionalities were screened with ligand **8**, providing access to the desired products with a variety of different *meta*/*para* ratios. Structure **9** clearly shows that the *meta*-C–H bond was fixed to the Ir metal center. The *meta*-selective C–H borylation of aromatic amides, esters, phosphonates, phosphonic diamides and phosphine oxides was therefore controlled by the hydrogen bonding interaction formed between the ligand and the substrate. One of the problems associated with a hydrogen bond is that it is too weak to be formed at high reaction temperatures. However, this concept still provides a potential solution for controlling the outcome of remote selective C–H activation reactions. It is envisaged that this strategy could also be used to overcome the challenges associated with the *para*-C–H activation of benzoic acid derivatives.

In summary, several different approaches have been developed to overcome the challenges associated with remote site-selective C–H bond functionalization reactions. The *meta*-



Scheme 3. Ligand-improved *meta*-selective C–H borylation.