

Expanding Structural Diversity; Removable and Manipulable Directing Groups for C–H Activation

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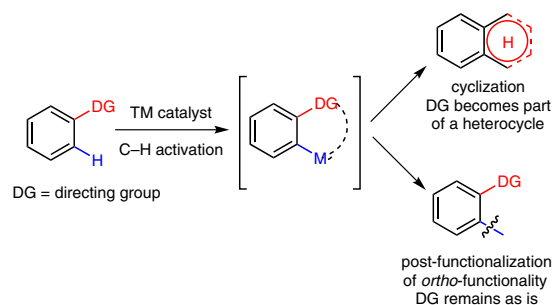
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Abstract: The need to use a static directing group represents a major limitation for the emerging field of *ortho*-selective C–H activation and functionalization. Chemistry was recently developed that allowed partial removal or minor transformations for certain directing groups. Our recent work demonstrated that triazenes were a class of excellent directing groups for C–H activation/functionalization, and subsequent chemical manipulations generated key compounds with synthetic versatility.

Key words: C–H activation, directing groups, transition metals, catalysis, protecting groups

Selective C–H functionalization represents a recent leap for transition-metal catalysis.¹ Compared to traditional cross-coupling reactions,² the ability to avoid substrate pre-activation greatly expands the synthetic toolbox for organic chemists by allowing direct use of hydrocarbon feedstock that was previously considered chemically inert. Heteroatom-directed *ortho*-selective C–H activations of aromatics are among the most intensively studied reactions due to strong industrial demand for highly functionalized benzenes and heteroaromatics. Towards this goal, a number of directing groups and oxidative coupling reactions have been developed over the past decade.^{1b,3}



Scheme 1 Limitations of classical *ortho*-selective C–H activation

However, a fundamental limitation of this approach involves the directing groups themselves. Almost always, such groups contain heteroatoms, enabling coordination to transition metals and delivering these catalysts towards the *ortho*-C–H bond. Chemically stable C–C or C=C bonds are present within virtually all directing groups.

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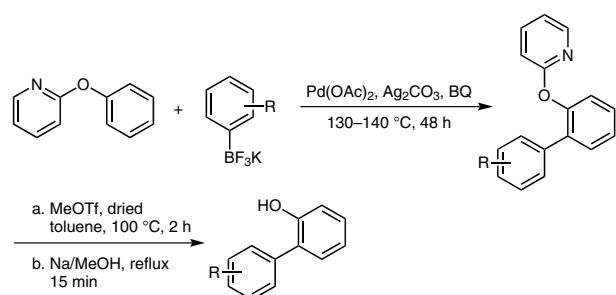
Chengming Wang (left), originally from Weifang, Shandong Province, China, received his BS degree in applied chemistry at Yantai University in 2008 and MS degree in organic chemistry at Shanghai University in 2011. He is now a research associate in Prof. Yong Huang's lab. His research interests are focused on novel transition-metal-catalyzed processes.

Professor Yong Huang (right), born in Jinan, Shandong Province, China, obtained his BS degree in chemistry at Peking University in 1997. He received his MS and PhD degree at the University of Chicago under the mentorship of Prof. Viresh H. Rawal. In 2002–2004, he was a postdoctoral fellow with Prof. David W. C. MacMillan at Caltech. He subsequently worked as a senior medicinal chemist at Merck Research Laboratories at Rahway, NJ, USA until 2009. He started his independent academic career as a Pengcheng Professor in 2009 at Peking University, Shenzhen Graduate School.

This posts a formidable challenge for removal of these groups or for further use in direct versatile chemical transformations. Indeed, the vast majority of directing groups either remain on the products as auxiliaries, or can only undergo limited heterocyclization reactions with the newly installed functionalities (Scheme 1).^{1b,3,4} This inadequacy severely restricts product structural diversity for C–H functionalization. There has been an urgent demand for directing groups that can be conveniently removed or are amenable to a wide range of chemical manipulations. This spurred intense structure design and related chemistry development in recent years.

There have been several reports that common heterocyclic ethers or amines could be deprotected to reveal the corresponding alcohols or amines.⁵ In 2010 Wu et al. reported a 2-phenoxy pyridine directed *ortho*-arylation reaction catalyzed by palladium (Scheme 2).^{5a} The arylation product was treated with MeOTf followed by Na/MeOH under reflux conditions. The pyridine directing group was

removed and a biphenyl-2-ol product was revealed. Similar results were later reported by Ackermann using a ruthenium catalyst.^{5b}



Scheme 2 Removal of pyridine to reveal a hydroxyl group

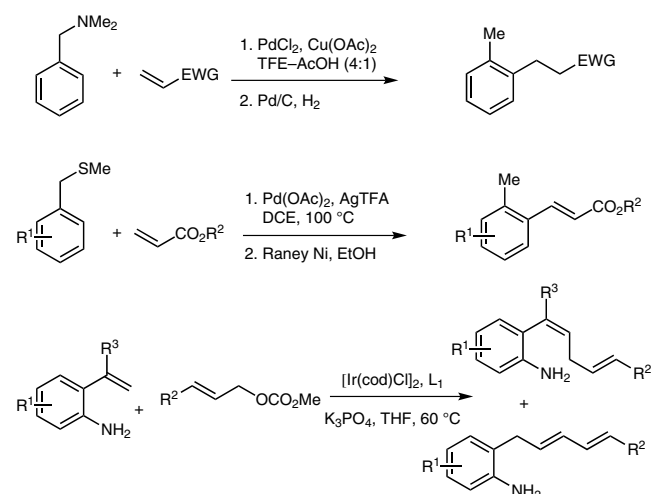
Arrayas and Carretero jointly reported a 2-PySO₂ directed indole alkenylation reaction (Scheme 3).^{5c} After the oxidative Heck reaction, the directing 2-PySO₂ group could be removed under reductive conditions to reveal unprotected indoles. Subsequently, the authors showed that 2-PySO was also an effective directing group for C–H alkenylation and could be removed by using *n*-BuLi at low temperature.^{5d–f}

In 2011, Ackermann et al. reported Ru-catalyzed pyrimidine directed indole arylation (Scheme 4, equation 1).^{5g} By exposing the arylated products to hot NaOEt in dimethyl sulfoxide (DMSO),^{5g,h} the pyrimidine was cleaved to afford N–H indole products. Subsequently, similar methods were utilized by Xu,⁵ⁱ Zhu,^{5j} and Miura^{5k} for their Pd-catalyzed cyanation of indoles and Cu-catalyzed

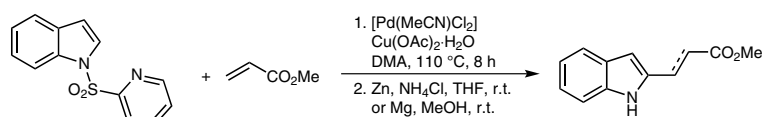
cross-coupling reactions between indoles and 1,3-azoles (Scheme 4, equations 2 and 3).

Me₂N-CH₂ was reported by Shi et al. to be able to direct *ortho*-alkenylation (Scheme 5).^{5l} The *N,N*-dimethyl amino group was cleaved under standard hydrogenation conditions and, simultaneously, the electron-deficient olefin was hydrogenated. A similar strategy was employed by Zhang et al. to convert a thioether directing group into a methyl group by using Raney Nickel,^{5m} in this case, the double bond remained intact. You et al. reported that free NH₂ can also act as an unmasked directing group for vinyl alkylation reactions.^{5n–o}

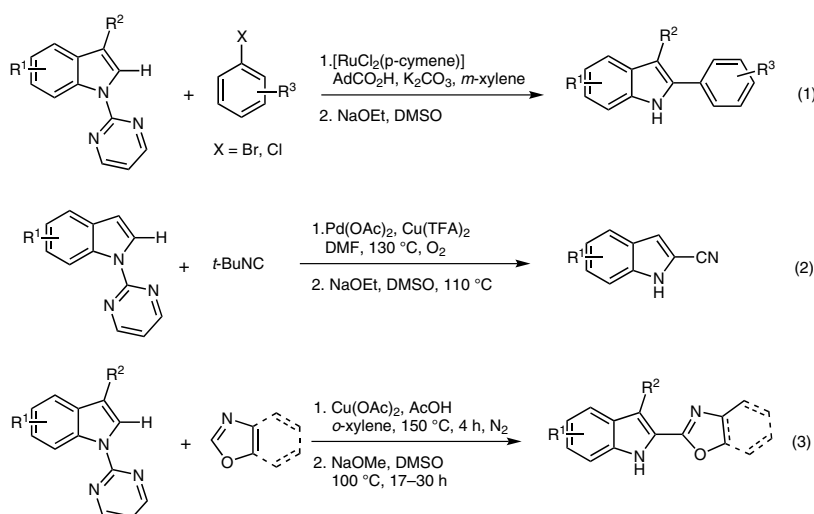
Amides are among the most versatile directing groups for C–H functionalization.⁶ The carboxylic portion of an am-



Scheme 5 Deamination following oxidative C–H Heck coupling

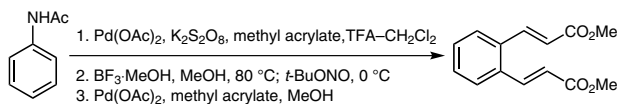


Scheme 3 Reductive cleavage of 2-PySO₂



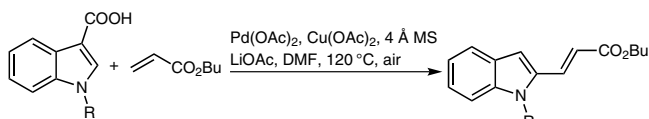
Scheme 4 Removal of pyrimidine to generate unprotected indoles

ide could be removed by heating to reflux with water or in basic solution.^{6a,b} Significantly, Schmidt and co-workers disclosed a two-step sequence, allowing complete replacement of the acetamide moiety with an electron-deficient olefin.^{6c} Post C–H functionalization, the acetamide was first converted into a diazonium intermediate, which underwent a second Heck coupling reaction (Scheme 6).



Scheme 6 Two-step conversion of acetamide into olefins

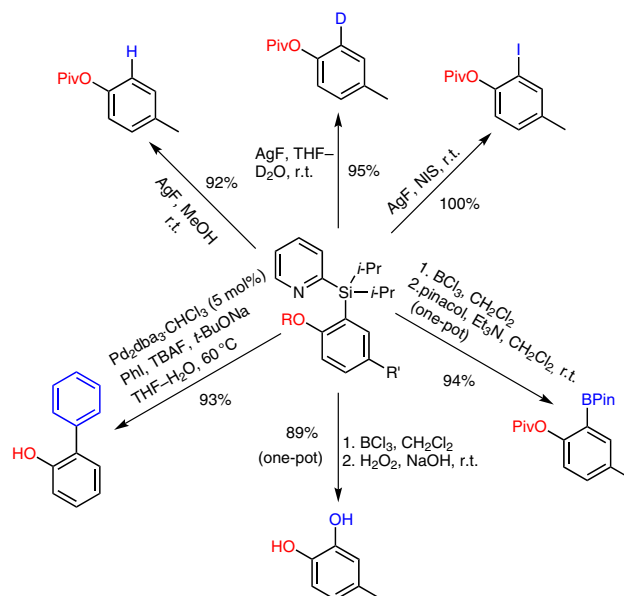
Carboxylic acids and their salts were first discovered as a highly effective directing group for both Pd and Rh-catalyzed C–H activation by Yu and Miura.⁷ Concurrent decarboxylation was observed by Satoh and Miura during a palladium-catalyzed indole 2-alkenylation (Scheme 7).^{7b}



Scheme 7 The carboxyl group acts as a removable directing group

A major advance for directing group removal and manipulation was made by Gevorgyan et al.^{8a–d} They demonstrated that a silicon-based PyDipSi group not only permitted several *ortho*-selective C–H functionalization opportunities, but could also be removed by treatment with fluoride under mild conditions or undergo several useful transformations (Scheme 8 and Scheme 9).^{8b} The pyridine residue within this directing group was essential to deliver metal binding and directing capabilities. Subsequently, silanol ethers were reported by Gevorgyan^{8c} and Ge^{8e} as masked phenol surrogates for directed C–H functionalization (Scheme 8). Again, F[–] was utilized to achieve mild silyl removal.

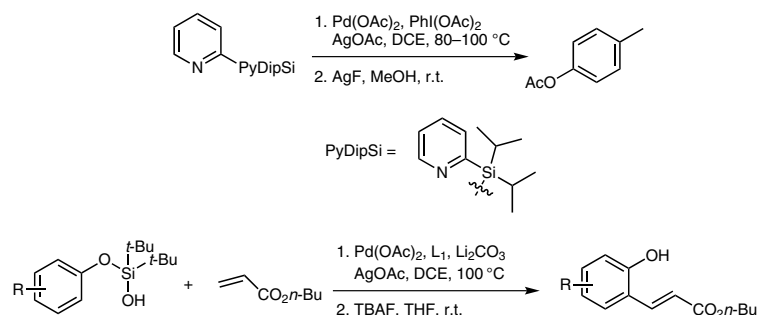
In-depth analysis of directing group structures indicated that most directing groups for *ortho*-selective C–H activation reactions possess a quite stable C–C, C–O or C–N bond, therefore prohibiting bond cleavage and subsequent chemical modifications. Recently, we reported that tri-



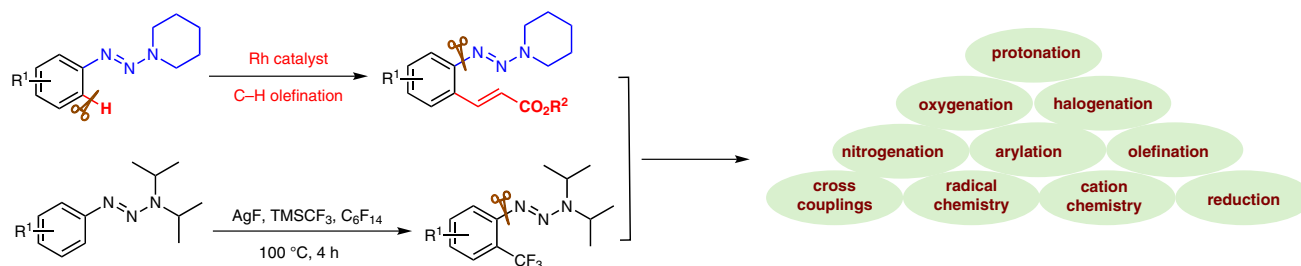
Scheme 9 Further transformations of the PyDipSi group

azenes were a class of effective directing groups for oxidative Heck coupling reactions (Scheme 10).^{9a} By introducing two electronegative nitrogen atoms to the C–N bond attached to arenes, we were able to significantly attenuate DG–substrate bonding, allowing quantitative ambient removal and enabling a number of important synthetic manipulations. Independently, Bräse et al. reported an *ortho*-selective trifluoromethylation reaction of phenyl triazenes promoted by ‘AgCF₃’ (Scheme 10).^{9b} Preliminary data supported a radical pathway as opposed to classical ‘directed’ metal insertion into inert C–H bond mechanism.

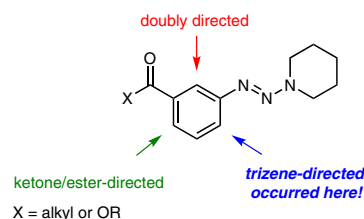
Triazenes were found to assist rhodium insertion into *ortho*-Ar–H bonds of various electronic natures under ambient or gentle heating conditions. In particular, arenes bearing strong electron-withdrawn groups were well tolerated, thus expanding substrate scope beyond earlier directing groups. Interestingly, when another directing group was present, complete selectivity was achieved for the less hindered triazene *ortho*-C–H (Scheme 11). The doubly activated C–H bond remained inert, since both steric factors and ligand chelation diminished reactivity at this location.



Scheme 8 PyDipSi and silanols as removable and versatile directing groups



Scheme 10 Triazenes as a new generation of directing groups capable of synthetic versatility



Scheme 11 Unique chemoselectivity of triazenes

The post-modification flexibility was underscored by several key features of triazenes.^{9c–l} Removal of this directing group was conveniently accomplished at room temperature by using $\text{BF}_3 \cdot \text{OEt}_2$ to yield the corresponding Ar–H product in quantitative yields. Treatment with acids or other electrophiles generates either the diazonium, the phenyl cation, or a phenyl radical species, which could further react with transition metals, electrophiles and SOMophiles to access a wide spectrum of functionalities (Scheme 12). Very recently, we discovered that clipping 1, 2 and 3 nitrogen atoms off the triazene group could be achieved by modulating the metal species and other reaction conditions. This achievement opens the door to a variety of novel scaffold syntheses using triazene-directed selective C–H functionalization reactions.

Activation of inert C–H, C–H, C–O and C–N bonds has emerged as a new paradigm for chemical functionalization of molecular architecture. Despite recent advances

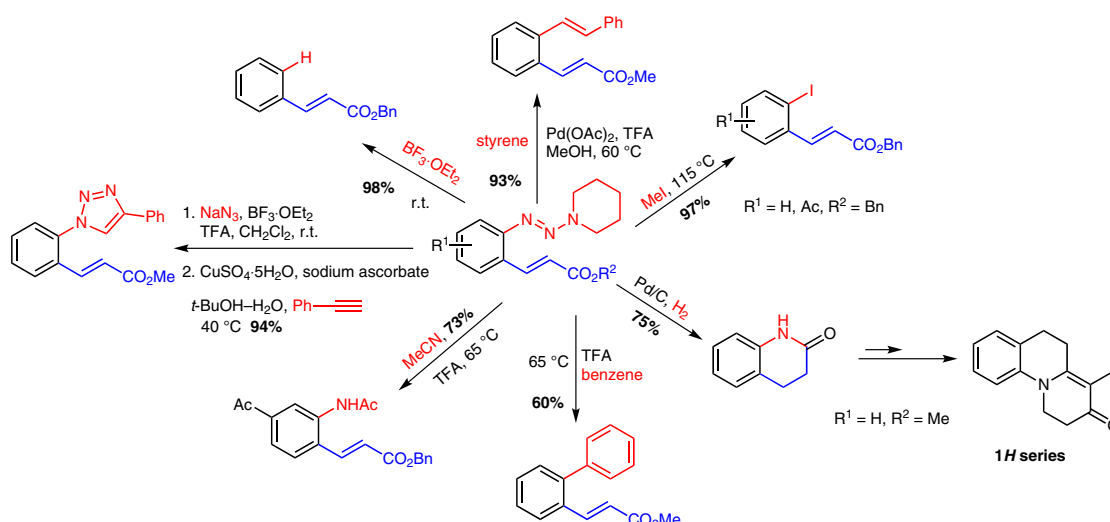
for selective C–H functionalization, the use of a directing group often leaves a trace in the product that curbs structural diversity. Developing novel directing groups to overcome this hurdle is urgently needed. Our recent work in this area validated the existence of such groups. In addition, cascade reactions using this strategy should deliver previously unattainable transformations in one pot. We expect further in-depth studies and novel design in this area will surface in the near future.

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Scheme 12 Chemical manipulation of triazenes post-C–H functionalization

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