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# Distal Functionalization via Transition Metal Catalysis †

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**Abstract:** The ubiquitous presence of $sp^3$ C−H bonds in natural feedstock makes them inexpensive, easily accessible, and attractive synthons for the preparation of common and/or complex molecular frameworks in biologically active natural products, pharmaceutics, agrochemicals, and materials. However, the inertness of these bonds due to the high bond dissociation energies and low polarity difference between the carbon and hydrogen atoms makes them challenging reaction partners. Moreover, the desired site-selectivity is often an issue in reactions with multiple analogous $sp^3$ C−H bonds. To overcome these problems, transition metal-catalyzed C−H functionalization has been developed with the assistance of various well-designed directing groups which can coordinate to a metal center to deliver it on a targeted C−H bond through an appropriate spatial arrangement, enabling C−H activation via the formation of a cyclometalated species. However, the frequent requirement of additional steps for the construction of the directing groups and their subsequent removal after the desired operation severely hampers the efficacy and compatibility of the reactions. A promising solution would be the utilization of a transient ligand which can bind to the substrate and coordinate to the metal center in a reversible fashion. In this way, the directing group is installed, $sp^3$ C−H functionalization occurs, and the directing group is then removed in situ without affecting the substrate function after the catalysis is finished. Overall, the whole process occurs in a single reaction pot. Herein, we are presenting our studies on transition metal-catalyzed transient directing group-enabled C−H functionalization reaction.

**Keywords:** C−H bond functionalization; transition metal; catalysis



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Transition metal-catalyzed C−H bond functionalization reactions have been playing a vital role in modern organic synthesis [1–25]. The rhodium-catalyzed chelation-assisted intermolecular hydroacylation developed in 1997 was the first example of transient directing group-enabled C−H functionalization processes [26]. Considerable efforts have been devoted to this area since then, and a variety of transition metal-catalyzed coupling reactions have been reported via an $sp^2$ C−H functionalization process [20–25]. Moreover, palladium-catalyzed site-selective functionalization of $sp^3$ C−H bonds has also been established recently by Yu, Dong, and the current authors via a transient imine-based strategy [27–31]. Furthermore, the enantioselective version of this transformation was also demonstrated on *o*-alkylbenzadehydes by Yu in the presence of a chiral ligand [27,32]. Mechanistically, a substituted imine moiety is formed in situ via the condensation of an amine and carbonyl compound, which then serves as a bidentate ligand to coordinate to a palladium center, and thus site-selectively activates a C−H bond. Despite being a powerful approach, the current development has several limitations. First, linear aldehydes are not effective substrates, and functionalization on remote positions, such as the γ-C−H bonds of aliphatic aldehydes and δ-C−H bonds of aliphatic amines, has not been achieved. Thus, the substrate scope of this approach is limited. Second, intermolecular arylation was the only reported reaction on unactivated $sp^3$ carbons via a catalytic $Pd^{II}/Pd^{IV}$ pathway, although acetoxylation and fluorination were demonstrated on *o*-alkylbenzadehydes. Thus, the reaction scope of this approach is limited. Third, site- and enantio-selective functionalization of unactivated $sp^3$ C−H bonds has not been developed.

Our original study of direct arylation of primary amines suffers from the limited substrate scope. Amines bearing a quaternary carbon on the α- or β-position were the only effective substrates with glyoxylic acid as a ligand [31]. Furthermore, δ-C−H functionalization of aliphatic primary amines has not been demonstrated. To overcome these limitations, a series of α-keto acids have been initially screened for arylation of butan-2-amine. Gratifyingly, pyruvic acid was identified as an effective ligand, and amine was site-selectively arylated on the terminal γ-$sp^3$ carbon in 61% yield. Compared with glyoxylic acid, which gave no product, the presence of the methyl group in 2-pyruvic acid may provide two beneficial effects for the process: (1) it favors the formation of the cyclic intermediate by relieving the steric compression in imine which is created by the methyl group. (2) It increases stability of the palladacycle 30c and thus favors formation of this key intermediate. Moreover, with the same ligand, δ-C−H arylation of commercially available 3-methylbutan-1-amine was also achieved to provide the mono- and di-arylated products and in 64% yield with a 2.4:1 ratio.

In our initial study of C–H arylation of aliphatic aldehydes, the β-secondary $sp^3$ C−H bond of a linear aliphatic aldehyde remained as a challenging reaction site. To solve this issue, intensive studies on modifications of reaction conditions have been carried out with arylation of pentanal. Delightfully, the product could be obtained in 51% yield with catalytic $Pd(C_6H_5CN)_2Cl_2$ in the presence of m-toluic acid by using by using 3-amino-3-methylbutanoic acid as a transient ligand. It is believed that the sterically incumbent gem-methyl groups will have two-fold advantages: (1) It will effectively favor the 'Thorpe–Ingold effect', which might allow close proximity to the target β-$sp^3$ C−H bond. (2) It will diminish the possibility of oxidation at the α-carbon of amines.

Direct C−H functionalization of aliphatic aldehydes on β-carbons has been achieved in recent years via a radical, oxidative conjugated addition or transient directing group-promoted C−H functionalization pathway. However, direct γ-C−H functionalization of aliphatic aldehydes has not been achieved so far. To overcome this hurdle and improve the synthetic application of the transient directing group-promoted C−H functionalization process, site-selective arylation of 2-benzyl-2-ethylpentanal was explored with a variety of ligands. Delightfully, acetohydrazide turned out to be a unique ligand which predominantly favors functionalization of the terminal γ-C−H bond to the relatively reactive secondary benzylic β-C−H bond. There are two possible reasons for this observation: (1) Cyclopalladation via a 6-membered ring transition state is more favorable than a 5-membered ring transition state due to the relative rigidity of the cyclic system and the steric effect in the latter case. (2) The formation of a 5,5-bicyclic palladium intermediate is favorable and reversible, but the following step, oxidation by iodobezene, requires a higher activation energy compared with a 5,6-palladacycle.

To broaden the reaction scope of the transient directing group-promoted C−H functionalization process, development of novel pathways other than the reported $Pd^{II}/Pd^{IV}$ catalytic cycle is highly desirable. Towards this goal, site-selective C−H cyanomethylation of aliphatic ketones was investigated based on our success in palladium-catalyzed dehydrogenative coupling of aliphatic amides and acetonitrile. To our delight, cyanomethylation of 2-pentanone was achieved on the β-secondary carbon with β-alanine as a transient ligand in the presence of a silver and copper salt. It is noteworthy that the formation of (cyanomethyl)copper by acetonitrile and a silver and copper salt has been proposed in the previous study, based on a series of control experiments. On the basis of these results, a plausible catalytic cycle is proposed. Imine formation of 2-pentanone and β-alanine followed by ligand exchange on the palladium center provides the intermediate, which undergoes site-selective C−H bond cleavage to generate a palladacycle. Transmetalation with (cyanomethyl)copper takes place to generate the dialkyl Pd(II) intermediate, which provides the product via a sequential reductive elimination and ligand dissociation process.

In our study of β-selective arylation of aliphatic aldehydes, it was noticed that reaction yields were dramatically decreased with butylamine as a ligand, indicating that a bidentate directing group is preferred in this process. Furthermore, a pyridine derivative of a potential

palladacycle was obtained, and this species underwent arylation smoothly to provide the corresponding aldehyde in a decent yield. These results suggest that a palladacycle should be involved in the catalytic cycle, which provides direct support for the asymmetric process. As an initial exploration for the asymmetric version of the transient directing group strategy, site- and enantio-selective arylation of 2-pentanone was attempted. A series of chiral β-amino acids was initially screened, and a moderate enantiomeric excess value has been achieved in our studies.

In summary, for the first time, palladium-catalyzed δ-selective arylation of aliphatic primary amines and γ-selective arylation of aliphatic aldehydes have been demonstrated via a transient directing group-promoted $sp^3$ C−H functionalization process. Furthermore, β-selective cyanomethylation of aliphatic ketones was developed via a different catalytic pathway from present-day reports. Moreover, an asymmetric version of the palladium-catalyzed transient directing group-promoted C−H functionalization process has been demonstrated on unactivated $sp^3$ carbons with a chiral ligand.

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