

Chapter 9

C-H Bond Functionalization in Complex Organic Synthesis

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Activation and functionalization of unactivated sp^3 C-H bonds have been demonstrated in complex substrates containing multiple reactive groups. These reactions were designed as key steps in syntheses of natural products (rhazinilam, teleocidins) as well as in direct hydroxylation of α -amino acids. Both stoichiometric and catalytic C-H bond functionalization methods are discussed in this chapter.

Introduction

C-H bond activation represents a chemical process of broad synthetic potential. The ability to activate ubiquitous, but often inert C-H bonds has far-reaching implications ranging from oxidation of simple hydrocarbons to the synthesis of complex organic molecules. Although C-H bond functionalization of alkanes has historically relied on radical chemistry, homogeneous transition metal complexes capable of activating C-H bonds in arenes and alkanes unlocked a new era in this field (1).

The inorganic and organometallic communities have generated a body of fundamental knowledge related to the feasibility and mechanistic issues of this transformation (see other chapters in this volume). However, most of these pioneering studies have been focused on simple hydrocarbons. Thus, we set out to address the considerable challenge of whether C-H functionalization could be realized in complex substrates and in a selective manner. In other words, we have been searching for new types of reagents and catalysts that are compatible with reactive functionalities. It is well-recognized that functional groups present in substrates strongly influence the reactivity of proximal C-H bonds, a fact that has been extensively studied in arene systems (e.g. *ortho*-metallation, electrophilic substitution) (2). Similarly, sp^3 C-H bonds adjacent to a heteroatom or a functional group (activated C-H bonds) are often (but not always) more reactive toward functionalization (Figure 1). At the same time, functional groups of the substrate affect the reactivity of metal catalysts (coordination chemistry). All of these issues must be considered and studied in a systematic fashion in order to develop new catalysts capable of selective functionalization of different types of C-H bonds in the presence of reactive functionalities. Such systems, applicable to a broad range of substrates, will unlock unprecedented synthetic possibilities, on both conceptual and practical level.

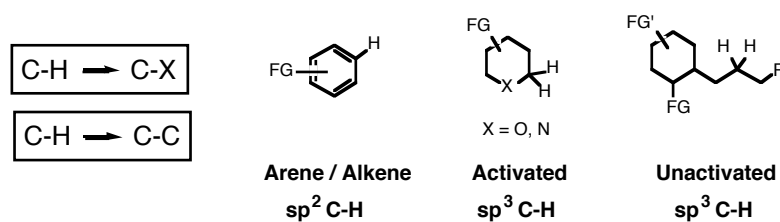


Figure 1. C-H bond functionalization in complex organic substrates. Different types of C-H bonds.

Alkane C-H Bonds: Coordination-Directed C-H Bond Activation of Alkyl Groups

As a part of our initial goals, we have focused on the possibility of functionalizing alkane segments in complex organic substrates, perhaps the most challenging aspect of this area. As a first approach we proposed to achieve this goal via *coordination-directed C-H bond activation* (3, 4). Following this strategy, a suitable heteroatomic function is utilized to activate and direct a metal complex to a specific alkane segment of the

substrate in such a way as to prevent interference by other functional groups. We set out to explore the formation and reactivity of metallacycle intermediates with the view of developing new functionalization reactions, and possibly catalytic systems (Figure 2).

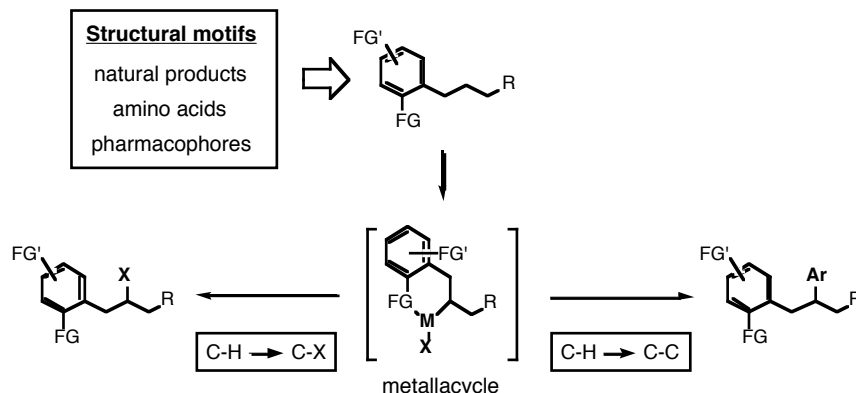


Figure 2. Selective C-H Bond functionalization via coordination-directed approach

We have demonstrated the feasibility of this approach in the context of the synthesis of the antitumor agent rhazinilam (Figure 3) (5). The pivotal step in rhazinilam assembly involved a selective functionalization of the diethyl segment in intermediate **1** via the attachment of a platinum complex. The proximity of the amino group to the ethyl groups augured well for directed C-H activation. This was achieved *via* the intermediacy of platinum complex **4** (Figure 4). Remarkably, thermolysis of complex **4** provided platinum hydride **5** as a single product in excellent yield (>90%) as determined by proton NMR spectroscopy. Indeed, activation of the desired ethyl group took place with concomitant loss of methane, followed by β -H-elimination affording alkene-hydride platinum (II) complex **5**. Decomplexation of the platinum metal *via* treatment with aqueous potassium cyanide, followed by the Schiff base hydrolysis, provided alkene **2**. Noteworthy is the fact that selective dehydrogenation of one of the ethyl groups was achieved in the presence of a variety of functional groups including an ester, pyrrole and arene rings. Furthermore, we have recently demonstrated that the platinum chemistry described above could be adapted to chiral oxazoline ligands ultimately affording alkene **2** in an optically pure form (6).

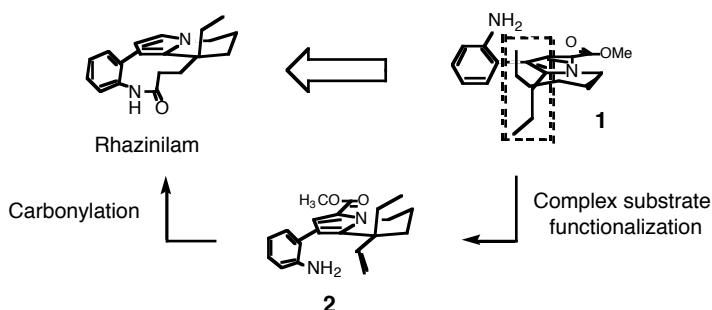


Figure 3. The total synthesis of rhazinilam was achieved via selective C-H activation (dehydrogenation)

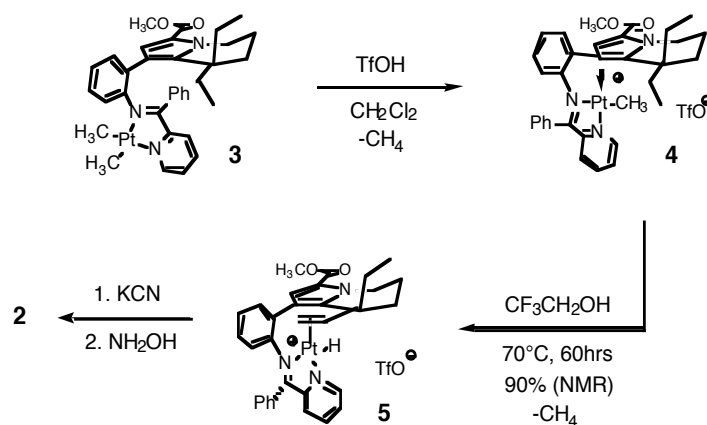


Figure 4. Selective dehydrogenation of one ethyl group was accomplished in the presence of many functional groups via coordination-directed C-H bond activation.

We have also demonstrated that the directed cyclometallation reaction may be extended to other substrates with a promising degree of generality. At the same time, we began to focus on the development of catalytic systems wherein the transition metal, following the C-H activation and functionalization step, could be recycled. In this context we became interested in the possibility of functionalizing free amino acids in water.

We found that L-valine was converted to γ -lactone **6** in water in the presence of K₂PtCl₄ (1-5 mol%) as the catalyst and CuCl₂ (5-7eq.) as the oxidant (Figure 5A). The highest turnover number achieved to date is twenty (1 mol% K₂PtCl₄, 5 eq. CuCl₂) (7). A number of substrates have been investigated including norvaline, leucine, isoleucine, proline, n-butylamine and valeric acid. The results generated in this study uncovered regioselectivity trends for α -amino acids that were distinctly different from those for simple aliphatic amines and carboxylic acids.

In the case of α -amino acids, γ -hydroxylation was the favored process over δ -oxidation. Thus, the direct functionalization of natural amino acids afforded valuable intermediates (γ -lactones) in one step without the use of organic solvents. We proposed that the reaction proceeds via coordination directed C-H bond activation yielding a putative platinacycle intermediate **8** or **9**, which collapses to afford a lactone and the regenerates platinum catalyst (Figure 5B).

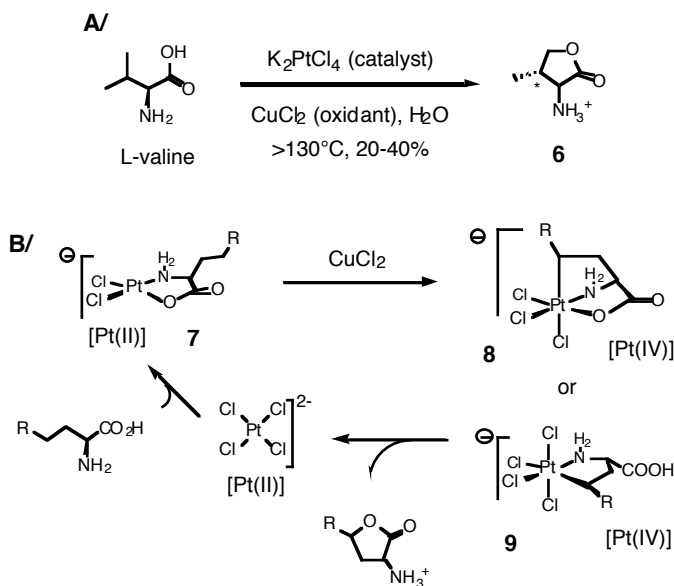


Figure 5. A/ Selective hydroxylation of α -amino acids in water via catalytic C-H bond activation. B/ Proposed catalytic cycle. Mechanistic work suggests that the reaction proceeds through a Pt(IV)-platinacycle (**8** or **9**).

Mechanistic studies (unpublished data) revealed important insights which may have broader applicability in the context of C-H bond functionalization of complex substrates. Namely, our data is consistent with the mechanistic outline wherein the exchange of the product for starting material at the metal center is slow. Perhaps surprisingly, both C-H activation and functionalization steps are facile transformations, whereas the catalyst regeneration step is slow. In order to achieve a practical turnover rate, the reaction must be heated to $>130^\circ\text{C}$. Thus, in the process of designing catalytic systems for C-H functionalization of complex substrates, the character and strength of the coordination bond between the functional groups and the metal catalyst must be taken into account.

Having demonstrated the feasibility of the coordination-directed activation both in stoichiometric and catalytic functionalization of alkyl groups, we subsequently turned to the development of methods for direct formation of C-C bonds from C-H bonds. In this context we were inspired by a class of natural products known as teleocidins. We envisioned that the teleocidin core, a complex fragment of a natural product containing two quaternary stereocenters and a pentasubstituted benzene ring, would be made via a series of non-traditional disconnections, serving as the platform for new reaction discovery (Figure 6) (8).

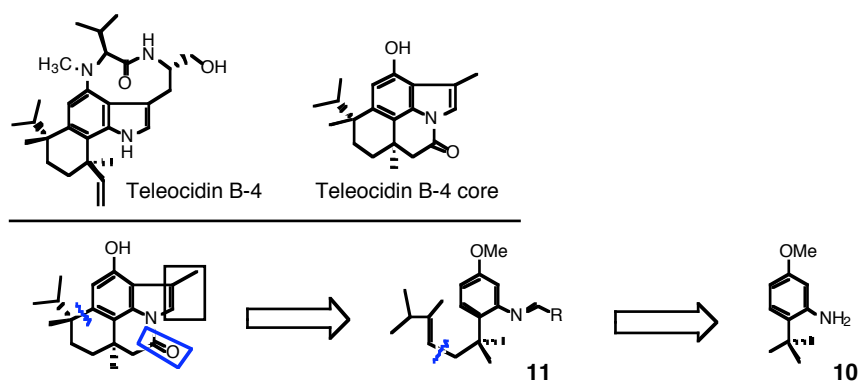


Figure 6. Retrosynthetic analysis of teleocidin natural products. Proposed non-traditional disconnections stimulated the development of new C-H activation/C-C bond forming processes.

According to the synthetic plan outlined above, we set out to prepare intermediate **11** through alkenylation of *t*-butyl aniline **10** (Figure 6). We envisioned that a new transformation of this type might be accomplished *via* sequential cyclometallation and transmetalation. Consequently, Schiff base **12** was prepared and submitted to a systematic screening of metal salts in the context of directed C-H bond activation (cyclometallation). We found that Pd(II) salts were the only reagents capable of furnishing desirable and stable metallacycle products (*cf.* **13**, Figure 7). We were delighted to find that palladacycle **13** and vinyl boronic acid **14** yielded desired alkene **15** in 86% yield in the presence of Ag₂O as the reagent of choice. This two-step sequence (**12**→**13**→**15**) provided not only the desired alkenylation product **15**, but moreover set the stage for the development of a new catalytic transformation (see below).

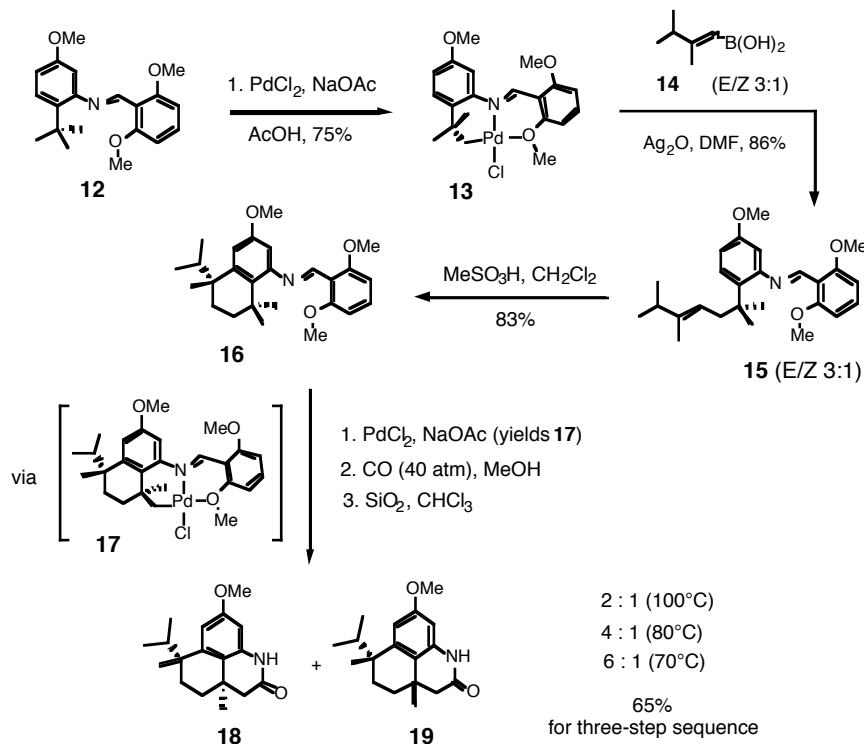


Figure 7. Two tandem cycles of C-H bond functionalization render two quaternary centers of the teleocidin core.

The subsequent step in the route centered on the closure of the cyclohexane ring through a formal hydroarylation process. In this instance, the presence of the methoxy group *meta*- to the amine facilitated the Friedel-Crafts reaction in the presence of methanesulfonic acid, providing racemic compound **16** in 83% yield. At this stage of the synthesis a diastereoselective one-carbon homologation of the methyl group that is *anti* to the isopropyl group (1,4-chiral transfer) was required (Figure 7). Thus, intermediate **16** was again treated with PdCl_2 and NaOAc to yield a mixture of diastereomeric palladacycles (cf. **17**), followed by addition of CO(g) and methanol. The resulting methyl esters were not isolated, but instead acidic hydrolysis of the Schiff base, accompanied by spontaneous cyclization, furnished lactams **18** and **19** (6:1 ratio at 70 °C). This three-step sequence converted compound **16** to the desired lactam without isolation of a single intermediate. Lactam **18** was subsequently converted to the final product (the teleocidin B4 core) in three steps (not shown, ref. 8)

In summary, the core of teleocidin B4 was synthesized in four C-C bond forming steps starting from *t*-butyl derivative **12** (9 steps in total). The key sequence of the synthesis consisted of two C-H bond functionalization cycles, namely alkenylation and oxidative carbonylation of a *t*-butyl group. This work demonstrated that the consideration of non-traditional disconnections in the context of synthetic strategy has significant consequences, in that not only new perspectives on organic compounds emerge, but the development of new chemical transformations is further inspired.

As the previous study led to the development of stoichiometric alkenylation and arylation methodology, the stage was set to address the next central question of whether a new catalytic system could be generated. We have put forth a mechanistic proposal of a putative catalytic cycle, which served well as a design blueprint and guide for our explorations (Figure 8).

Based on our preliminary results we focused on the possibility of generating a phenylpalladium species (*cf.* **22**), followed by the C-H activation step (Figure 9). Phenylboronates (10), phenylstannanes (11), and phenylsilanols (11,12) have been suggested to undergo transmetallation with Pd(OAc)₂ in polar solvents. Consequently, through a systematic search of reaction conditions (Pd²⁺ salts, arene donors, solvents) we uncovered an exciting lead. While PhB(OH)₂ and PhSnBu₃ failed, Schiff base **20** was transformed to compound **21** in 53% isolated yield via *direct arylation of the t-butyl group in the presence of PhSi(OH)Me₂ and Pd(OAc)₂* (Figure 9). Note that the phenyl ring is attached at the *neo*-alkyl position (13) and that no *bis*-arylation products were identified. Thus, the first three steps of the cycle have been synchronized and direct arylation of compound **20** in the presence of a stoichiometric amount of Pd(OAc)₂ was developed.

The next critical question centered on the compatibility of this system with an oxidant. Following an extensive study we were delighted to find that *the direct arylation of substrate 26 proceeded under conditions catalytic in palladium in the presence of Cu(OAc)₂ as the oxidant and phenyldimethylsilanol as the phenyl ring donor* (Table 1).

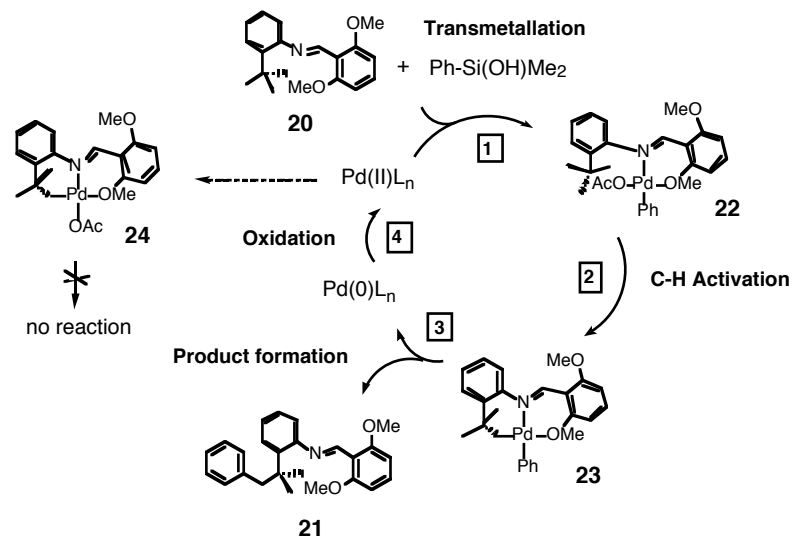


Figure 8. Proposed catalytic cycle for arylation of *t*-butyl group.

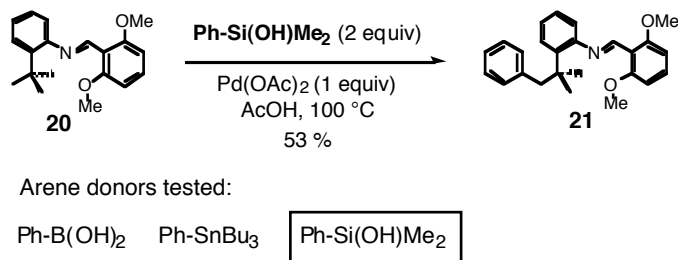


Figure 9. Development of one-pot arylation protocol

A systematic mapping of the system included examining the Schiff base-directing element of the substrate, metal salts, oxidants and solvents. 2-Thiomethoxybenzylidene Schiff base **25** afforded consistently higher yields than the dimethoxy substrate **20**, while Pd(OAc)₂ proved to be a catalyst of choice and DMF the best solvent. Out of the oxidants tested, Cu(OAc)₂ was the most efficient. We rapidly discovered that Ph₂Si(OH)Me was a superior phenyl donor affording the highest yield of product **26**, with only traces of biphenyl and phenyl acetate side products (14).

Further optimization showed that the highest isolated yield of **26** (73%) was achieved in the presence of 4 mol% of Pd(OAc)₂ and

Table 1. Catalytic arylation. Optimization Studies.

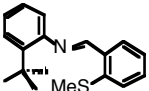
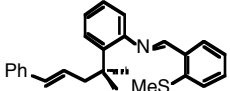
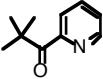
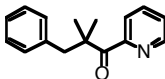
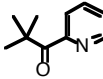
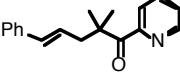
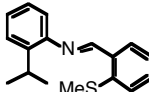
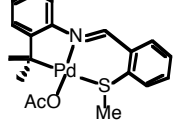
silanol	Pd(OAc) ₂ mol %	Yield (w/BQ) ^a %	TON	Ph-Ph (%)	PhOAc (%)
PhSi(OH)Me ₂	1	17	17	8	7
	2.5	33	13	5	5
	4	37 (52)	9 (13)	5 (12)	5 (7)
	5	42 (49)	8 (10)	7 (12)	4 (8)
Ph ₂ Si(OH)Me	1	26	26	<1	<1
	2.5	51	20	<1	<1
	⇒ 4	58 (73)	15 (18)	<1	<1
	5	61 (68)	12 (15)	<1	<1
PhSi(OMe) ₃	2.5	31	12	4	<1

(a) isolated yields. The value in parentheses represents the isolated yield in the presence of a catalytic amount of benzoquinone (1:1 ratio of Pd to BQ).

benzoquinone (1:1), and two equivalents of Cu(OAc)₂ (Table 2). The new arylation methodology was also extended to alkenylation, as documented by the transfer of styrenyl group to substrate **25** furnishing compound **27** in 64% yield (Table 2). In addition to the *t*-butylaniline substrate, 2-pivaloylpyridine also proved to be a good substrate for both arylation and alkenylation reactions. As in the previous case, substrate **28** underwent single arylation/alkenylation at the *t*-butyl group. However, the Schiff base derived from *ortho-i*-propylaniline **31** yielded no desired material, biphenyl (22%) being the major detected product.

A concise synthesis of compound **36**, depicted in Figure 10, demonstrated the synthetic power of the new methodology, and simultaneously revealed both the remarkable selectivity as well as limitations of this system. Substrate **33** was converted to complex product **36** in three steps via catalytic alkenylation of **33**, Friedel-Crafts cyclization, and finally catalytic arylation to furnish substance **36**. Thus, tandem alkenylation-arylation of the *t*-butyl group provided a product of considerable complexity via a novel bond construction strategy (14).

Table 2. Catalytic arylation and alkenylation of selected substrates

entry	substrate	conditions	product
1	 25	$\text{Ph}-\text{CH}=\text{CH}-\text{Si}(\text{OH})\text{Me}_2$ a, 64%	 27
2	 28	$\text{Ph}_2\text{Si}(\text{OH})\text{Me}$ a, 78%	 29
3	 28	$\text{Ph}-\text{CH}=\text{CH}-\text{Si}(\text{OH})\text{Me}_2$ a, 63%	 30
4 ^b	 31	$\text{Ph}_2\text{Si}(\text{OH})\text{Me}$ a, trace	 32

(a) substrate ($c = 0.02 \text{ M}$) in DMF, silanol (2 equiv), $\text{Pd}(\text{OAc})_2$ (4 mol %), benzoquinone (4 mol %), $\text{Cu}(\text{OAc})_2$ (2 equiv), 100°C . The alkenylation reactions also yielded a side product ($\text{PhCH}=\text{CH}_2$)₂ in 10% yield.

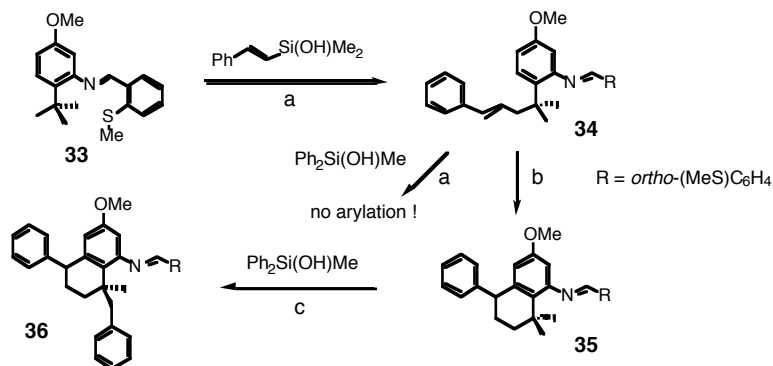


Figure 10. Tandem alkenylation-arylation of *t*-butyl group. Cond: (a) $\text{Pd}(\text{OAc})_2$ (4 mol %), benzoquinone (4 mol %), $\text{Cu}(\text{OAc})_2$ (2 equiv), 100°C , 66 %. (b) MeSO_3H , CH_2Cl_2 , 52 %. (c) $\text{Pd}(\text{OAc})_2$ (8 mol %), BQ (8 mol %), $\text{Cu}(\text{OAc})_2$ (2 equiv), 100°C , 45 % (4:1 ratio of diastereomers).

In summary, a new system for the catalytic arylation and alkenylation of alkane segments has been developed. The *ortho-t*-butylaniline substrates and 2-pivaloylpyridine may be arylated and alkenylated on the *t*-butyl group while no functionalization occurred at more reactive C-H and other bonds. We hypothesize that the high selectivity of this system stems from the confluence of the directing effect of the Schiff base or pyridine moiety and the unique reactivity properties of a phenyl-palladium acetate species (Ph-Pd-OAc•L_n). Formation of palladacycle **24** represents a competitive and unproductive route as this intermediate did not undergo transmetalation (or conversion to the product) under reaction conditions (Figure 8). *ortho-i*-Propylaniline **31** appeared to favor this pathway which may in part explain the negative results with this substrate.

Summary and Future Directions.

We are currently exploring this remarkable transformation (catalytic arylation) in terms of scope and mechanism. Furthermore, this system serves as an encouraging starting point for a broad program. We plan to study the reactivity of a range of aryl-metal systems (Ar-M-X_n•L_n) in the context of arylation of diverse substrates. The key issue that we intend to address is the possibility for discerning different types of C-H bonds in the presence of other reactive bonds (e.g. N-H, O-H). In addition to natural products, pharmacophore motifs will be included as substrate candidates. The selection of substrates provides the important context for a methodological program.

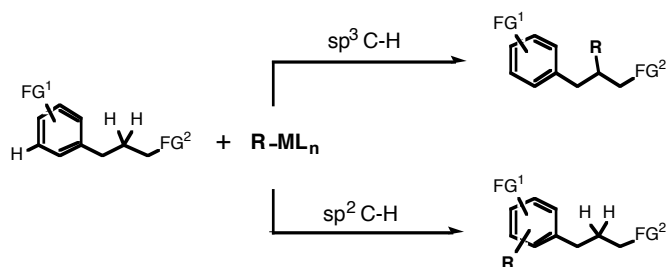


Figure 11. Future directions. Programmable targeting of different types of C-H bonds.

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