/ Review

Palladium(0)-Catalyzed Benzylic C(sp³)-H Functionalization for the Concise Synthesis of Heterocycles and Its Applications

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C–H functionalization reactions involve the activation of otherwise unreactive C–H bonds, and represent atom economical methods for the direct transformation of simple substrates to complex molecules. While transition metal-catalyzed C(sp²)-H functionalization reactions are regularly used in synthesis, C(sp³)-H functionalization is rarely applied to the synthesis of complex natural products because of the difficulties associated with controlling selectivity. With this in mind, we focused on the development of new palladium (Pd)(0)-catalyzed C(sp³)-H functionalization reactions for the synthesis of complex molecules, resulting in several new methods capable of solving these problems. We initially developed a concise synthetic method for the facile construction of oxindoles and spirooxindoles *via* a Pd-catalyzed benzylic C(sp³)-H functionalization reaction. This method was subsequently extended to the synthesis of various heterocycles, including 2-arylindoles, benzocarbazole, indolocarbazole, indoloquinazolinone, and indoloquinazolinone, as well as the total synthesis of several pyrrolophenanthridine alkaloids without the need for any protecting groups. This method was also successfully applied to the synthesis of the right-hand fragment of benzohopane from tetrahydro-2H-fluorene, which was constructed by a Pd-catalyzed benzylic C(sp³)-H functionalization. In this review, we provide a detailed discussion of our most recent investigations pertaining to Pd(0)-catalyzed benzylic C(sp³)-H functionalization.

Key words C–H functionalization; palladium (Pd); oxindole; heterocycle; total synthesis

1. Introduction

During the synthesis of a target compound, reactive functional groups such as halogen and triflate substituents are traditionally employed to access intermediates bearing the desired functional groups. A wide variety of reliable functional group transformations has been developed to date, and these reactions have paved the way for the total synthesis of numerous complex natural products.^{1–3)} However, the introduction of a desired functional group invariably requires the application of a stepwise synthetic route starting from a reactive intermediate, which can lead to higher and higher costs depending on the number of synthetic steps required. To solve this problem, C–H functionalization,⁴⁾ which involves the activation of an otherwise unreactive C–H bond, has attracted considerable attention as an atom economical method for the direct transformation of a simple substrate to a complex molecule.

C–H functionalization reactions can be roughly classified into C(sp²)-H and C(sp³)-H functionalizations.⁴⁾ C(sp²)-H functionalization dates to the work of Murahashi's group⁵⁾ in 1955, when they reported the co-catalyzed carbonylation of *N*-benzylideneaniline *via* C(sp²)-H bond activation.

In 1993, Murai *et al.* reported an Ru-catalyzed C(sp²)-H functionalization⁶⁾ as a practical and precise method for the introduction of alkyl groups at the ortho position. Following on from these early works, many other chemists have developed an academic interest in the efficiency of C(sp²)-H functionalization, and developed various new reactions. In contrast, the development of practical C(sp³)-H functionalization reactions has lagged because of the low reactivity of C(sp³)-H bonds compared with C(sp²)-H bond. In 2000, Hartwig and colleagues reported the selective borylation of the C–H bonds of methyl groups.⁷⁾ In the same year, Chatani *et al.* reported an acylation reaction involving C(sp³)-H functionalization.⁸⁾ Based on these reports, C(sp³)-H functionalization attracted considerable attention from many synthetic chemists.

Palladium (Pd) is one of the most commonly used catalysts in transition-metal-catalyzed C–H functionalization reactions.^{9–20)} Under Pd catalysis, there are two main approaches for activating unreactive C(sp²)-H and C(sp³)-H bonds, including: i) an intramolecular approach; and ii) a directing group approach. A variety of different directing groups and reaction conditions involving Pd catalysts have been developed for extending the substrate scope of C–H functionalization reactions.^{21–29)} However, very little progress has been made towards controlling the selectivity of C(sp³)-H

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Fig. 1. Spirooxindole Natural Products and Related Complex Indole Alkaloids

functionalization in the presence of $C(sp^2)$ –H bonds. This issue is further confounded by the lack of suitable methods for distinguishing between the different $C(sp^3)$ –H bonds found in complex molecules. The application of $C(sp^3)$ –H functionalization to the total synthesis of complex natural products therefore remains a big challenge in synthetic chemistry, whereas $C(sp^2)$ –H functionalization is employed routinely.^{30–32} We recently became interested in the development of Pd(0)-catalyzed $C(sp^3)$ –H functionalization reactions for the synthesis of complex molecules, and developed several new methods that addressed some of the problems described above. In this review, we provide a summary of our recent research on the Pd(0)-catalyzed benzylic $C(sp^3)$ –H functionalization reaction and its application.^{33–43}

2. Pd-Catalyzed Benzylic $C(sp^3)$ –H Functionalization as a Strategy for the Synthesis of Oxindoles and Spirooxindoles

Spirooxindole natural products, which are characterized by the fused *spiro*-structure of their oxindole core bearing various rings at its C3 position, have attracted considerable attention from numerous synthetic chemistry groups because of their complex structures and their pronounced biological

activities^{44–53} (Fig. 1). The spirooxindole skeleton could be used as a valuable synthetic intermediate for the construction of complex indole alkaloids. The development of efficient methods for the construction of this structure is therefore particularly important. A variety of different methods have been reported for the synthesis of spirooxindoles, including an intramolecular Heck,⁵⁴ oxidative rearrangement,⁵⁵ intramolecular Mannich,⁵⁶ and ring expansion reactions.⁵⁷ We previously developed a novel method for the construction of oxindole skeletons from carbamoyl chlorides, as well as a spirooxindole synthesis that proceeded *via* the bismetallation of 1,3-dienes.^{58–61} Furthermore, this method was subsequently applied to a formal synthesis of elacomine.⁶⁰ Although these synthetic methods represent efficient strategies for the construction of spirooxindole moieties, their application has been limited by their requirement for the preparation of the carbamoyl chloride precursors. For example, the treatment of *N*-[2-(1,3-butenyl)aryl]carbamoyl chloride **2** with hexamethyldisilane and a catalytic amount of $[Pd(\eta^3\text{-allyl})Cl]_2$ resulted in an intramolecular carbosilylation reaction to give oxindoles **3** in good yield bearing an allylsilane functional group⁶¹ (Chart 1). The subsequent Sakurai-type cyclization of **3** provided the tricyclic spirooxindoles **4** and **5** by controlling

Biography

Chihiro Tsukano studied chemistry at the Department of Chemistry, the University of Tokyo, under the guidance of Prof. Kazuo Tachibana. After receiving B.Sc. and M.Sc. degrees, he moved to Tohoku University, where he was awarded a Ph.D. in 2006 under the guidance of Prof. Makoto Sasaki. After postdoctoral studies (2006–2008 under Prof. Samuel J. Danishefsky, Memorial Sloan-Kettering Cancer Center, New York), he joined the Department of Chemistry, Tohoku University, and worked in the laboratory of Prof. Masahiro Hirama as an assistant professor. In 2009, he moved to the Graduate School of Pharmaceutical Sciences, Kyoto University, and worked with Prof. Yoshiji Takemoto as an assistant professor. In 2014, he was promoted to lecturer in the same group. His research interests center on the development of novel synthetic methods involving transition-metal catalysts as well as natural product synthesis. He received the Young Scientist's Research Award in Natural Product Chemistry (2012), the Pharmaceutical Society of Japan Award for Young Scientists (2016), and the Asian Core Program Lectureship Award (2016, from Taiwan).

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Chart 1. Stepwise Synthesis of Spirooxindoles *via* a Pd(0)-Catalyzed Carbosilylation Chart 2. Retrosynthesis of Spirooxindoles According to the Pd(0)-Catalyzed Carbosilylation and $C(sp^3)\text{-H}$ Functionalization Strategies Chart 3. $Pd(0)$ -Catalyzed $C(sp^3)\text{-H}$ Arylation⁶³⁾

the stereochemistry of the three contiguous stereogenic centers. Although this strategy provided facile access to several spirooxindoles, *N*-[2-(1,3-butenyl)aryl]carbamoyl chloride **2** ($R = CH_2CH_2OTBS$) had to be synthesized from the corresponding *tert*-butoxycarbonyl (Boc)-protected iodoaniline **1** *via* the construction of the diene moiety (5 steps), followed by the introduction of the carbamoyl chloride group (1 step). To establish a much simpler synthetic strategy for the construction of these spirooxindole systems, we switched our focus to the use of $C\text{-H}$ functionalization chemistry because $C\text{-H}$ bonds can be used directly, thereby avoiding the need for the introduction of an olefin moiety. We therefore planned the intramolecular $C(sp^3)\text{-H}$ functionalization of carbamoyl chloride **6** according to a benzylic $C(sp^3)\text{-H}$ bond activation strategy (Chart 2).

When we started this project, there were very few reports on intramolecular Pd -catalyzed $C(sp^3)\text{-H}$ bond activation followed by a $C\text{-C}$ bond forming reaction. For example, Fagnou and colleagues described the synthesis of dihydrobenzofuran **8** using a Pd -catalyzed $C(sp^3)\text{-H}$ functionalization strategy⁶³⁾ (Chart 3). The authors of this report found that the addition of pivalic acid ($PivOH$) promoted the $C\text{-H}$ bond activation process. Although several reports were available at the time describing the activation of the $C(sp^3)\text{-H}$ bonds of methyl groups for the synthesis of cyclobutene⁶²⁾ and five membered rings,^{63–68)} there were no reports pertaining to Pd -catalyzed $C(sp^3)\text{-H}$ activation followed by a $C\text{-C}$ bond forming reaction to give a methylene or methine moiety. For this reason, several groups became interested in the development of $C(sp^3)\text{-H}$ functionalization chemistries.

We initially investigated the development of a new method for the synthesis of simple oxindoles *via* the $C(sp^3)\text{-H}$ functionalization of a methyl group attached to a benzene ring.

Given that the oxindole ring is a fundamental heterocyclic skeleton that can be found in a wide range of biologically active natural products and medicines,^{69,70)} the development of a concise and versatile method for the construction of oxindoles and spirooxindoles is highly desirable. We envisioned that the oxidative addition of carbamoyl chloride **9** to $Pd(0)$ would give intermediate **10**, which would be followed by the $C(sp^3)\text{-H}$ activation of the methyl group to give palladacycle **11** (Chart 4). Finally, intermediate **11** would undergo a reductive elimination step to give oxindole **12**. Given that the starting carbamoyl chloride **9** could be readily prepared from a simple *ortho*-methyl aniline by introduction of a substituent (R) and a carbamoyl chloride moiety, this $C(sp^3)\text{-H}$ activation method for the construction of oxindoles would provide a concise method for the construction of various oxindoles. At the time, there were no other examples of $C\text{-H}$ functionalization reactions involving carbamoyl chlorides. Furthermore, if successful, this idea could be extended to the synthesis of various other heterocycles based on the methyl, methylene, or methine $C(sp^3)\text{-H}$ activation, followed by an intramolecular $C\text{-C}$ bond forming reaction.

2.1. Development of a New Method for the Synthesis of Oxindoles Based on a Pd -Catalyzed Benzylic $C(sp^3)\text{-H}$ Functionalization Reaction³³⁾ To assess the feasibility of our initial idea, we synthesized carbamoyl chloride **9a** bearing two *ortho* methyl groups by the formylation of 2,6-dimethylaniline (**13**), followed by the reduction of the resulting formamide and the formation of a carbamoyl chloride moiety (Chart 5).

Based on earlier reports, carbamoyl chloride **9a** was treated with $Pd(OAc)_2$ (3 mol%), $PCy_3 \cdot HBF_4$ (6 mol%), and Cs_2CO_3 (1.1 equiv.) in mesitylene at $135\text{ }^\circ\text{C}$ under argon.⁶³⁾ Fortunately, the desired oxindole **16a** was obtained in 10% yield along with a large amount of *N*-2,6-trimethylaniline (**15**) (Table 1, entry 1). As reported by Fagnou and colleagues,⁶³⁾ the addition of $PivOH$ led to an improvement in the yield, with aniline **15** being obtained in a slightly higher yield of 20% (Table 1, entry 2). To avoid the elimination of CO , the reaction was performed under a CO atmosphere both with and without $PivOH$. Both reactions proceeded smoothly to give **16a** in 67

Chart 4. Pd(0)-Catalyzed C(sp^3)-H Carbamoylation for the Synthesis of Oxindoles Chart 5. Synthesis of Carbamoyl Chloride **9a** for Pd(0)-Catalyzed C(sp^3)-H CarbamoylationTable 1. Investigation of Pd(0)-Catalyzed C(sp^3)-H Carbamoylation of **9a**

<div><div> </div><div><div><p>$\text{Pd}(\text{OAc})_2$ (3 mol%) ligand (6 mol%) Cs_2CO_3 (1.1 equiv) additive (30 mol%)</p><p>mesitylene, temp atmosphere</p></div><div> </div><div> </div></div></div>							
entry	ligand	additive	temp.	atmosphere	16a	yield 15	9a
1*	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	none	135 °C	Ar	10%	60%	-
2*	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	PivOH	135 °C	Ar	40%	20%	-
3	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	none	135 °C	CO	35%	1%	-
4	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	PivOH	135 °C	CO	67%	9%	-
5	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	PivOH	120 °C	CO	74%	trace	-
6	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	PivOH	100 °C	CO	55%	2%	-
7	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	AdCOOH	120 °C	CO	65%	1%	-
8	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	$^t\text{BuCONH}_2$	120 °C	CO	28%	11%	20%
9	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	$(\text{MeCO})_2\text{NH}$	120 °C	CO	52%	3%	13%
10	$\text{Cy}_3\text{P}\cdot\text{HBF}_4$	PivNHOH	120 °C	CO	84%	10%	-
11	dppf	PivNHOH	120 °C	CO	50%	29%	-
12	$(2\text{-furyl})_3\text{P}$	PivNHOH	120 °C	CO	46%	6%	39%
13	Cyclohexyl Johnphos	PivNHOH	120 °C	CO	ca. 3%	40%	27%
14	$\text{Ad}_2\text{P}^n\text{Bu}$	PivNHOH	120 °C	CO	88%	6%	-

- not detected

* 5 mol% of Pd(OAc)₂ and 10 mol% of ligand was used.

and 35% yields, respectively (Table 1, entries 3 and 4). These results indicate that the presence of CO was important to the success of this reaction, and that its inclusion was compatible with the addition of PivOH. Based on these results, we screened a variety of different reaction temperatures, ligands, and additives against this reaction (Table 1, entries 5–14). The optimum temperature for this reaction was determined 120 °C, although the reaction also proceeded at 100 °C, albeit in a lower yield (Table 1, entries 5 and 6). It was also found that *N*-hydroxypivalamide (PivNHOH) is a good additive, leading to improvements in the yield up to 84% (Table 1, entries 7–10). In terms of the ligands, Ad₂PⁿBu,^{71,72)} which is a bulky trialkyl phosphine, gave the best results (Table 1, entries 11–14). The optimum conditions were therefore determined as follows: Pd(OAc)₂ (3 mol%), Ad₂PⁿBu (6 mol%), Cs₂CO₃ (1.1 equiv.), and PivNHOH (0.3 equiv.) under CO in mesitylene at 120 °C (Table 1, entry 14).

The optimum reaction conditions were subsequently applied to the synthesis of various oxindoles (**16b–f**, **h–p**) from the corresponding carbamoyl chlorides (**9b–f**, **h–p**) bearing a

wide range of different substituents on their aromatic ring and nitrogen atom (Table 2). These investigations revealed the following features of this reaction.

- The inclusion of a substituent at the other *ortho* (C6) position of **9** was not critical to the success of this reaction (**16b**, **e**, **f**).
- The C(sp^3)-H functionalization reaction only occurred at the benzylic position of the methyl group (e.g., **16c** vs. **g**).
- Various electron-donating and electron-withdrawing groups, including alkyl, methoxy, chloro, fluoro, ester, and trifluoromethyl groups were tolerated under these conditions (**16b–f**, **h–n**).
- The C(sp^3)-H functionalization reaction proceeded smoothly in the presence of a potentially competitive C(sp^2)-H bond (e.g., **16p**).
- The formation of the four-membered amide ring did not proceed *via* a C(sp^2)-H activation.

Having established the optimal reaction conditions, we proceeded to investigate: (i) the extension of this method to the

Table 2. Synthesis of Oxindole **16** Based on a Pd(0)-Catalyzed C(sp³)-H Carbamoylation Reaction Chart 6. Attempted Pd(0)-Catalyzed Methine C(sp³)-H Carbamoylation for the Synthesis of Spirooxindoles Containing Three- to Five-Membered Carbocycles

synthesis of spirooxindoles; and (ii) improving the selectivity of this reaction.

2.2. Synthesis of Spirooxindoles Based on a Pd-Catalyzed Benzylic C(sp³)-H Functionalization³⁵⁾ When we began our work towards the development of a Pd-catalyzed benzylic C(sp³)-H functionalization for the synthesis of spirooxindoles, there was very little precedent in the literature for the activation of methine C(sp³)-H bonds.^{73,74)} Furthermore, previous research indicated that there could be potential regioselectivity issues.⁷⁴⁾ For example, the intramolecular cyclization of an aryl bromide containing a cyclopropyl group gave a 3:1 mixture of dihydrobenzofuran and chromane products *via* the C(sp³)-H functionalization of the cyclopropyl methine and methylene groups, respectively.⁷⁴⁾

We initially applied our newly developed conditions to carbamoyl chlorides bearing cycloalkyl groups instead of

a methyl group.^{33,35)} In the case of carbamoyl chloride **17a** bearing a cyclopropyl group the desired spirooxindole **18a** was selectively obtained in 60% yield (Chart 6). In contrast, carbamoyl chlorides **19** and **21** containing cyclobutyl and cyclopentyl groups failed to afford the desired spirooxindole products **20** and **22** under the same conditions, and gave the corresponding anilines. Given that methine C(sp³)-H activation was rare at the time^{73,74)} and a spirooxindole fused with a cyclopropane moiety could be readily converted to various other fused systems,⁵⁷⁾ we proceeded to investigate the cyclization of carbamoyl chlorides with cyclopropyl groups.

Extensive investigations of the catalyst, phosphine ligand, and base revealed that the conditions developed for oxindole synthesis³³⁾ were applicable to the spirooxindole synthesis. With this in mind, we proceeded to examine the scope and limitations of this reaction (Table 3). As well as being suitable for the synthesis of oxindoles, we confirmed that the optimized conditions could be applied to synthesis of various spirooxindoles fused with cyclopropanes. It is noteworthy that the methine C(sp³)-H bond of the cyclopropyl group was selectively functionalized in the presence of the methylene C(sp³)-H of the ethyl group and the methine C(sp³)-H bond of the isopropyl group. Although the substituent at the other *ortho* position was found non-essential, it had a positive effect on the cyclization (*e.g.*, **18g** vs. **h**). The methine C(sp³)-H functionalization proceeded without any erosion in the stereochemistry (*e.g.*, **18i** vs. **j**). In short summary, we established a new method for the synthesis of spirooxindoles based on the Pd(0)-catalyzed methine C(sp³)-H functionalization of a cyclopropyl group.³⁵⁾

2.3. Regioselectivity of the Pd-Catalyzed Benzylic C-H Functionalization (*i.e.*, C(sp³)-H vs. C(sp²)-H, and Methyl vs. Methylene vs. Methine)^{33,35)} Prior to conducting our own research towards the synthesis of oxindoles, it was well known that C(sp²)-H activation proceeds selectively in the presence of competitive C(sp³)-H bonds. For example, Glorius and colleagues⁷⁵⁾ reported an intramolecular competi-

Table 3. Synthesis of Spirooxindoles **18** Based on Pd(0)-Catalyzed Methine C(sp³)-H Carbamoylation (a) Glorius and colleagues⁷⁵; (b) Fagnou and colleagues.⁷⁶Chart 7. Reports Pertaining to the Selectivity Issues Encountered between C(sp²)-H and C(sp³)-H Bonds Chart 8. Selectivity between C(sp³)-H and C(sp²)-H Bonds in the Pd(0)-Catalyzed Carbamoylation

tion experiment between $C(sp^2)$ -H and $C(sp^3)$ -H bonds in an amination reaction. The activation of the $C(sp^3)$ -H bond was only observed under their reaction conditions. Fagnou and colleagues⁷⁶⁾ also reported an exclusive selectivity for the activation of 2-bromo-*N*-methyl-*N*-phenylbenzamide (**26**), which only reacted at the arene $C(sp^2)$ -H bond. It was therefore clear that we would have to address the selectivity of the $C(sp^3)$ -H activation step to allow for the application of this C-H activation chemistry to complex molecules (Chart 7).

Based on the selective $C(sp^3)$ -H activation that we observed for the synthesis of oxindole **16p**, we proceeded to investigate whether the selectivity could be controlled by changing the electron density of the aromatic ring. In the case of substrate **9s** bearing a methoxy group, the competitive $C(sp^2)$ -H activation was almost completely suppressed, whereas the reactions of substrates **9q** and **9r** bearing methyl and trifluoromethyl groups gave the desired oxindoles **16q** and **16r** by $C(sp^3)$ -H activation, along with small amounts of the corresponding isooxindoles **29q** and **29r** (11–15%), which were derived from $C(sp^2)$ -H activation (Chart 8). When the previously reported reaction conditions of another group (*i.e.*, $\text{Pd}(\text{OAc})_2$ (3 mol%), $\text{Cy}_3\text{P}\cdot\text{HBF}_4$ (6 mol%), and Cs_2CO_3 (1.1 equiv.) in mesitylene at 135°C)⁶³⁾ were applied to **9p**, no selectivity was observed, resulting in the formation of **16p** (24%), **29p** (23%), and the corresponding aniline (36%). The reaction of carbamoyl chloride **9t** with a naphthalene moiety gave only oxindole **16t** under the developed conditions. These results therefore indicate that $C(sp^3)$ -H activation was favored over $C(sp^2)$ -H activation under our conditions. To the best of our knowledge, this work represents the first reported example of a Pd-catalyzed chemoselective $C(sp^3)$ -H activation.³³⁾

Next, we investigated the regioselectivity of this reaction for two functionalizable C-H bonds using carbamoyl chlorides containing cyclopropyl, alkyl, phenyl, and allyl groups. Compounds **17k–m** were treated under the optimized conditions as shown in Chart 9. These reactions revealed that the functionalization process occurred preferentially in the order Heck

reaction > cyclopropyl methine $C(sp^3)$ -H activation > methyl $C(sp^3)$ -H activation > arene $C(sp^2)$ -H activation under the optimized conditions.³⁵⁾

The proposed mechanism is shown in Chart 10. According to this mechanism, the reaction would begin with the oxidative addition of the carbamoyl chloride to Pd(0) to give intermediate **34**.⁷⁷⁾ Under the optimum conditions, the elimination of CO from **34** would be suppressed by performing the reaction under a CO atmosphere. A ligand exchange process would lead to the formation of intermediate **36**, which would undergo $C(sp^3)$ -H activation through a concerted metalation-deprotonation^{78,79)} to give palladacycle **37**. A subsequent reductive elimination would give oxindole **16** and spirooxindole **18** along with the regeneration of Pd(0). The effect of PivNHOH currently remains unclear, but we assume that it assists in the

Chart 9. Selectivity between the Methyl and Methylene $C(sp^3)$ -H Bonds and the Arene $C(sp^2)$ -H Bonds in the Pd(0)-Catalyzed Carbamoylation

Chart 10. Proposed Mechanism for the Pd(0)-Catalyzed $C(sp^3)$ -H Carbamoylation

Chart 11. Strategy for the Synthesis of 2-Arylindoles Based on Pd(0)-Catalyzed C(sp^3)-H Activation and Isocyanide Insertion

activation of the benzylic C(sp^3)-H in **36**, as well as stabilizing intermediate **35**.⁸⁰⁾

3. Synthesis of Heterocycles Based on Benzylic C-H Functionalization

3.1. Synthesis of 2-Arylindoles from Isonitriles³⁴⁾ Having established a synthetic method for the construction of oxindoles from carbamoyl chloride,^{33,35)} we investigated the extension of this method to the synthesis of several other heterocycles. We initially focused on a cascade reaction involving a combination of benzylic C(sp^3)-H functionalization with Pd-catalyzed isocyanide insertion^{81–86)} for the synthesis of indole derivatives, which are an important class of nitrogen-containing heterocycles in the pharmaceutical sciences. Several other groups had previously reported concise methods for the synthesis of carbo- and heterocyclic systems through isocyanide insertion and C(sp^2)-H activation steps.^{87–89)} While there have been several reports describing the formation of indoles *via* the Ru-catalyzed C(sp^3)-H activation of 2,6-disubstituted isocyanides,^{90,91)} there have been no reports pertaining to the synthesis of heterocycles through Pd-catalyzed isocyanide insertion and C(sp^3)-H functionalization steps. We envisioned that the reaction of *o*-methylphenyl isocyanide **38** with aryl halide **39** in the presence of a palladium catalyst would give 2-arylindole **40** through a cascade process consisting of the oxidative addition of Pd(0) to the aryl halide, isocyanide insertion, benzylic C(sp^3)-H functionalization, and reductive elimination (Chart 11). Notably, this strategy would be divergent and applicable to simple starting materials; however, the coordination of the isocyanide substrate to palladium would hamper the Pd(0)-catalyzed cascade process, especially the C(sp^3)-H functionalization step.

To realize this strategy, we investigated a variety of different reaction conditions using 2,6-dimethylphenyl isocyanide **38a** ($R^1=H$, $R^2=Me$) and iodobenzene **39a** ($R^3=H$) as model substrates. The results revealed that Pd(OAc)₂ (5 mol%), Ad₂P^{*n*}Bu (10 mol%) and Cs₂CO₃ (1.2 equiv.) in toluene at 100°C gave the best results for the desired product **40a**. The key to the success of this reaction was determined the slow addition of isocyanide **38a** to the reaction mixture, because the presence of an excess of this reagent would deactivate the catalyst *via* the formation of palladium clusters.⁹²⁾ Notably, no

additives were required for this reaction, although a bulky carboxylic acid was found essential for the synthesis of oxindoles *via* benzylic C(sp^3)-H functionalization.

With the optimal conditions in hand, we evaluated the scope of this reaction using various aryl halides **39** bearing a range of electron-withdrawing and electron-donating groups (Table 4, **40b–g**). Bromobenzene was also successfully converted to indole **40a** in 73% yield, whereas chlorobenzene did not react under the optimized conditions (not shown in Table 4). Heteroaromatic rings such as thiophenes and pyrroles were also successfully introduced at the 2-position of the indole ring, as exemplified by compounds **40h** and **i**. Isocyanides bearing nitro and methoxy groups also reacted smoothly to give the corresponding 2-substituted indoles **40j** and **k**, respectively. The replacement of one of the *ortho* methyl groups on the isocyanide substrate with a chloro or ethyl group was also well tolerated, with the C–H bond of the remaining methyl group reacting selectively to give the desired corresponding indoles **40l** and **m** as single products. The use of an isocyanide substrate bearing only one *ortho* substituent (*i.e.*, 2,4-dimethylphenyl isocyanide) failed to afford any of the desired product **40n**, most likely because of the poor stability of the less hindered isocyanide^{93,94)} and the flexible conformation of the reaction intermediate.

This reaction was subsequently extended to the synthesis of several benzocarbazole **43** and indolocarbazole **46** systems³⁴⁾ (Chart 12). It was envisioned that *o*-alkynylphenyl isocyanide **41** would react with iodo-2,6-dimethylbenzene (**42a**) in the presence of a Pd catalyst to give a tetracyclic carbazole *via*: i) oxidative addition of the iodobenzene substrate to Pd(0); ii) sequential insertion steps involving the isocyanide and alkyne moieties; iii) benzylic C(sp^3)-H functionalization; and iv) reductive elimination. An initial attempt under the optimal conditions (*i.e.*, Pd(OAc)₂, Ad₂P^{*n*}Bu, and Cs₂CO₃ in toluene at 100°C) resulted in a low conversion. This decrease was attributed to the reaction proceeding *via* a seven-membered palladacycle, which would be much less favorable than a five- or six-membered palladacycle. In this case, the addition of PivOH led to a considerable increase in the yield of the tetracyclic carbazole **43a** (66% yield). Notably, the electronic state of the alkyne had no discernible impact on the yields of carbazoles **43b**, **c** ($R=NO_2C_6H_4$, $MeOC_6H_4$). Furthermore, this strategy

Table 4. Synthesis of 2-Arylindoles Based on Pd(0)-Catalyzed C(sp³)-H Activation and Isocyanide Insertion Reactions Chart 12. Synthesis of Benzocarbazoles and Indolocarbazoles via a Domino Process Involving Pd(0)-Catalyzed C(sp³)-H Activation and Isocyanide Insertion Reactions

can be readily applied to the synthesis of several indolo[2,3-*a*]carbazole derivatives, which have interesting biological effects.⁹⁵ The treatment of 1-Boc-2-bromo-3-methyl-1*H*-indole **45** with PivOH under the optimal conditions gave the desired carbazole **46** in 36% yield. These results represent the first example of a Pd(0)-catalyzed domino reaction containing a C(sp³)-H functionalization step.

3.2. Synthesis of Indoloquinazolinone³⁸ We also developed a new benzylic C(sp³)-H functionalization method for the synthesis of indoloquinazolinones, which represent an important structural class found in several biologically active alkaloids, including tryptanthrin,^{96,97} phaitanthirins,⁹⁸ and ophiuroidine^{38,99} (Fig. 2). The tetracyclic skeleton of an indoloquinazolinone, which consists of a quinazolinone ring fused to an indole, is generally prepared by the coupling of an isatin to an isatoic anhydride under basic conditions.⁹⁷ However, considerable opportunities still exist to improve the scope and limitations of these methods, especially for the direct synthesis of indoloquinazolinones bearing a methylene moiety at their C6 position.^{100–102}

The reaction conditions were investigated using chloroquin-

azolinone **47a** as a model substrate, which was prepared from 2,6-dimethylaniline in four steps, including the formation of the isocyanate, its subsequent condensation with anthranilic acid, and the chlorination of the 2-position with POCl₃. We initially applied the optimum conditions for the oxindole synthesis³³ without CO (*i.e.*, Pd(OAc)₂ (5 mol%), Ad₂PⁿBu (10 mol%), Cs₂CO₃ (2 equiv.), and PivNHOH (30 mol%) in mesitylene at 140°C; Table 5, entry 1). Fortunately, the reaction gave indoloquinazolinone **48a** in 22% yield. To improve the yield, we evaluated a wide range of different Pd sources, bases, ligands, and solvents. The results revealed that the use of Pd(PPh₃)₄ (5 mol%), Na₂CO₃ (2 equiv.), and PivNHOH (30 mol%) in PhCl at 120°C gave the best results for the synthesis of indoloquinazolinone **48a**. It is noteworthy that the addition of an additive was critical to the success of this reaction, with PivNHOH giving a much higher yield than PivOH (Table 5, entries 4–6).

We subsequently investigated the scope and limitations of this reaction (Table 6). Substrates bearing an alkyl, methoxy, or chloro group at the second *ortho* position of their benzene ring (*i.e.*, the C6 position) reacted smoothly to give the cor-

Fig. 2. Indoloquinazolinone Alkaloids

Table 5. Optimization of the Reaction Conditions for Synthesis of Indoloquinazolinones

entry	Pd cat.	ligand	base	additive	solvent	temp.	yield
1*	Pd(OAc) ₂	Ad ₂ P ⁿ Bu	Cs ₂ CO ₃	PivNHOH	mesitylene	140 °C	22%
2	Pd(OAc) ₂	Ad ₂ P ⁿ Bu	Na ₂ CO ₃	PivNHOH	mesitylene	140 °C	56%
3	Pd ₂ (dba) ₃	PCy ₃ ·HBF ₄	Na ₂ CO ₃	PivNHOH	mesitylene	140 °C	68%
4	Pd(PPh ₃) ₄	-	Na ₂ CO ₃	PivNHOH	mesitylene	140 °C	68%
5	Pd(PPh ₃) ₄	-	Na ₂ CO ₃	none	mesitylene	140 °C	0%
6	Pd(PPh ₃) ₄	-	Na ₂ CO ₃	PivOH	mesitylene	140 °C	34%
7	Pd(PPh ₃) ₄	-	Na ₂ CO ₃	PivNHOH	toluene	100 °C	46%
8	Pd(PPh ₃) ₄	-	Na ₂ CO ₃	PivNHOH	DMA	120 °C	0%
9	Pd(PPh ₃) ₄	-	Na ₂ CO ₃	PivNHOH	PhCl	120 °C	76%

*Our optimum conditions (without CO atmosphere) for oxindole synthesis.
DMA = dimethylacetamide

responding indoloquinazolinones **48** (Table 6, entries 1–4) in good to excellent yields. However, substrates bearing no substituent at the C6 position gave much lower yields of the desired products, along with significant amounts of unreacted starting material (Table 6, entries 5–8). In contrast, substrates bearing a fluoro, chloro, methoxy, phenyl, vinyl, or ester group on the phenyl ring of their 2-chloroquinazolin-4(3H)-one moiety were tolerated under the optimal conditions, and gave the desired indoloquinazolinones **48** in moderate to excellent yields (Table 6, entries 9, 10, 12–17). However, the introduction of a bromo group at the C5' position of the substrate resulted in the complete failure of the reaction (Table 6, entry 11). As described previously,¹⁰³⁾ most indoloquinazolinones are unstable and readily oxidized to the corresponding indoloquinazolinones on exposure to the atmosphere.

We subsequently investigated the possibility of conducting the benzylic C(sp³)–H functionalization and oxidation steps in one-pot for the synthesis of indoloquinazolinones (Table 7). Chloroquinazolinone **47a** was initially subjected to the reaction conditions described above (Table 5, entry 9), and the resulting mixture was then agitated under an atmosphere of oxygen at room temperature for several hours to give indoloquinazolinone **50a** in 57% yield (Table 7, entry 1). Several indoloquinazolinones bearing fluoro, chloro, and alkyl groups were successfully synthesized using this procedure, albeit in low yields compared with the corresponding indoloquinazolinone **48** (Table 7, entries 2–5).

In summary, we established an effective procedure for the construction of heterocycles based on a 2-arylindole skeleton

with multi-bond formation *via* Pd-catalyzed isocyanide insertion and benzylic C(sp³)–H functionalization reactions.³⁶⁾ We also developed a new method for the synthesis of indoloquinazolinones and indoloquinazolinones based on benzylic C(sp³)–H functionalization.³⁸⁾ In both cases, the presence of an additional *ortho* substituent was important to the success of the reaction. These results indicate that there is an important steric factor at play resulting from the second *ortho* substituent, which positively affects the distance between the C(sp³)–H bond and the Pd center during the C(sp³)–H activation step.

4. Synthetic Application to Natural Products

4.1. Total Synthesis of Pyrrolophenanthridine Alkaloids³⁷⁾ Pyrrolophenanthridine alkaloids, which can be biogenetically produced by the dehydration and aromatization of lycorine, belong to the Amaryllidaceae alkaloids¹⁰⁴⁾ (Fig. 3). Assoanine (**51**),¹⁰⁵⁾ pratosine (**52**),¹⁰⁶⁾ hippadine (**53**),¹⁰⁷⁾ and dihydroanhydrolycorin (**54**)¹⁰⁸⁾ have been isolated from plants belonging to the Amaryllidaceae family. These alkaloids exhibit various biological activities, including acetylcholinesterase inhibitory activity, anticancer activity, and antitrypanosomal activity.¹⁰⁴⁾ Consequently, they have received considerable attention from chemists and biological scientists alike. Among the many total syntheses of these alkaloids,^{109,110)} much attention has been focused on construction of the biaryl moiety.¹¹¹⁾ There have, however, been no reports in the literature concerning the total synthesis of these alkaloids using a C(sp³)–H functionalization. With this in mind, we investigated

Table 6. Scope and Limitations of the Optimal Conditions for the Synthesis of Indoloquinazolinones

entry	R	R'	48	49	47
1	6-Et	H	quant.	0%	0%
2	6-MeO	H	70%	0%	0%
3	6-Me, 4-NMe ₂	H	90%	0%	0%
4	6-Cl	H	68%	0%	0%
5*	H	H	58%	<40%	0%
6	3-Me	H	32%	0%	58%
7	4-Me	H	14%	<44%	51%
8	4-MeO	H	16%	<23%	68%
9	6-Me	5'-F	quant.	0%	0%
10	6-Me	5'-Cl	93%	0%	0%
11	6-Me	5'-Br	0%	0%	78%
12**	6-Me	3'-Me	63%	0%	19%
13**	6-CO ₂ Me	3'-Me	44%	0%	54%
14	6-Me	5'-Ph	74%	0%	0%
15	6-Me	5'-CH=CH ₂	52%	0%	0%
16	6-Me	4'-MeO, 5'-MeO	99%	0%	0%
17	6-Me	4'-CO ₂ Me	80%	0%	0%
18	6-Me	5'-OH	0%	0%	0%
19	6-Me	4'-CO ₂ H	0%	0%	0%

* The reaction performed at 140 °C.

** Pd(PPh₃)₄ (10 mol%), Na₂CO₃ (3 equiv) were used.

Table 7. One-Pot Synthesis of Indoloquinazolinones

entry	R ¹	R ²	R ³	yield
1	Me	H	H	57%
2	Et	H	H	80%
3	Me	F	H	50%
4	Me	Cl	H	55%
5	Me	OMe	OMe	24%

Fig. 3. Pyrrolophenanthridine Alkaloids

the application of our newly developed method for the construction of oxindoles to the total synthesis of Amaryllidaceae alkaloids to evaluate its scope and generality.³³⁾

Retrosynthetically, it was envisioned that tetracyclic compound **55** could be used as a common intermediate for the synthesis of pyrrolophenanthridine alkaloids. The oxindole and phenanthridine rings could be constructed by C(sp³)-H and C(sp²)-H functionalization reactions involving the methyl and phenyl groups, respectively (Chart 13). In other words, compound **55** could be accessed from iodotoluene (**59**) and benzyaniline **60** through stepwise C(sp³)-H and C(sp²)-H

functionalization reactions to give the lactam ring and the dihydrophenanthrine skeleton (path a). In contrast, compound **55** could be synthesized from compound **56** or **57** according to a one-pot process involving C(sp³)-H and C(sp²)-H functionalization reactions (path b). Initial attempts indicated that the latter of these two aims would be difficult to achieve because

Chart 13. Retrosynthesis of Pyrrolophenanthridine Alkaloids Using $C(sp^3)$ -H and $C(sp^2)$ -H Functionalization Chart 14. Total Synthesis of Pyrrolophenanthridine Alkaloids Based on Pd(0)-Catalyzed $C(sp^2)$ -H and $C(sp^3)$ -H Functionalization

of undesired side reactions³⁷); therefore the stepwise strategy was employed for the total synthesis.

The synthesis started with the coupling of compound **60a**, which was prepared from 6-bromoveratraldehyde,¹¹² to 2-iodotoluene **59** using a Catellani reaction¹¹³ via sequential $C(sp^2)$ -H functionalization and oxidation reactions to give phenanthridine **61a** in 66% yield. The subsequent reduction of compound **61a** with NaBH_3CN , followed by the introduction of a carbamoyl moiety with triphosgene, gave the cyclization precursor **58a** in 79% yield over two steps. We then applied our newly developed conditions to **58a** to allow for the formation of an oxindole through $C(sp^3)$ -H functionalization. The treatment of **58a** with $\text{Pd}(\text{OAc})_2$ (5 mol%), $\text{Ad}_2\text{P}^n\text{Bu}$ (10 mol%),

Cs_2CO_3 (1.1 equiv.), and PivNHOH (0.3 equiv.) in mesitylene (0.2 M) under an atmosphere of CO at 100 °C gave the desired tetracyclic product **55a** (30%) together with a significant amount of phenanthridine **61a** (60%), which was presumably derived from the elimination of CO and aerobic oxidation. Unfortunately, we were unable to suppress this side-reaction despite screening an extensive range of different Pd sources, ligands, bases, and additives. Compound **61a** was subsequently separated from the product by column chromatography over silica gel and recycled by conversion back to **58a**. Because the carbamoyl moiety was fixed by the rigid tricyclic skeleton, the C-H bond of the methyl group was positioned further away from the Pd center compared with the simple carbamoyl chlo-

Fig. 4. Benzohopanes and Related Natural Products

Chart 15. Retrosynthesis of Benzohopane

ride **9a** derived from 2,6-dimethylaniline. The positioning of the carbamoyl group in this way made the elimination of CO much more competitive. The resultant tetracyclic compound **55a** was converted to dehydroassoanine **62a** in 57% yield by the reduction of the lactam moiety with diisobutylaluminum hydride (DIBAL-H). The reduction of this common intermediate with NaBH_3CN ¹¹⁴ afforded assoanine (**51**). In contrast, the oxidation of **62a** with BaMnO_4 gave pratosine (**52**).¹¹⁵ The established synthetic route was also applied to the synthesis of hippadine (**53**) and dehydroanhydrolycorine (**54**) using amine **60b** as a starting material, which was derived from commercially available 6-bromopiperonal in two steps. In a similar manner, the tetracyclic compound **55b**, which was obtained from carbamoyl chloride **58b** by an oxindole formation, was converted to dehydroanhydrolycorine (**54**) using DIBAL-H. Hippadine (**53**) was also synthesized by the oxidation of dehydroanhydrolycorine (**54**). Spectroscopic data for the synthetic materials **51–54**, including their high-resolution mass spectra, were consistent with those previously reported for these compounds. The total synthesis of several pyrrolophenanthridine alkaloids was achieved using 7 and 8 step sequences.³⁷ This new route is short and concise because it does not require the use of protecting groups, and could therefore be used to provide facile access to various analogs from simple starting materials (Chart 14).

4.2. Synthetic Studies of Benzohopanes⁴²⁾ Benzohopanes (**63**) have been isolated from rock extractions and petroleum samples collected from Guatemala by Hussler's group^{116,117} (Fig. 4). Although these natural products have not been detected in living organisms, they can be generated by the aromatization of C35 hopanoids (*ex.* bacteriohopanetetraol (**64**)) *via* an interesting mechanism. Structurally, these compounds consist of a tetracyclic skeleton with a *cis*-fused

bicyclo[4.3.0]nonane core. Before our report, there had been no synthetic studies about these compounds in the literature.

Retrosynthetically, it was envisioned that benzohopane (**63**) could be synthesized by the coupling of tricyclic compound **68** to farnesyl halide **67**, followed by sequential cationic or radical polyene-cyclization¹¹⁸ and deoxygenation reactions (Chart 15). Tetrahydro-2*H*-fluorene **69** was identified as a key intermediate for the stereoselective construction of the right-hand *cis*-fused hexahydrofluorene core **68**. Although tetrahydro-2*H*-fluorenes are considered useful intermediates for the construction of complex systems, there were no general synthetic methods for preparation of these compounds in the literature when we initiated this work.^{119,120} Considering our experience of $\text{C}(\text{sp}^3)\text{--H}$ functionalization reactions, we envisaged that these structures could be synthesized from enol triflate **70**. With this in mind, we developed a new method for the synthesis of tetrahydro-2*H*-fluorene based on a $\text{Pd}(0)$ -catalyzed benzylic $\text{C}(\text{sp}^3)\text{--H}$ functionalization reaction for the synthesis of the right-hand fragment of benzohopane.⁴²⁾

The synthesis of tetrahydro-2*H*-fluorene **69** would begin with the oxidative addition of enol triflate **70** to $\text{Pd}(0)$ (Chart 16). Because there are two methyl groups at its ortho positions ($\text{R}=\text{Me}$), $\text{C}(\text{sp}^3)\text{--H}$ activation would only occur to give a six-membered palladacycle **71**. Finally, reductive elimination would give tetrahydro-2*H*-fluorene (**69**). Although enol triflates are useful synthetic intermediates, there have been very few examples of their use in $\text{Pd}(0)$ -catalyzed $\text{C}(\text{sp}^3)\text{--H}$ activation reactions¹²¹ compared with $\text{C}(\text{sp}^2)\text{--H}$ activation processes.^{122,123)}

Enol triflate **70**, which was prepared from cyclohexanone through sequential Pd -catalyzed α -arylation¹²⁴ and triflation reactions, was treated with $\text{Pd}(\text{PPh}_3)_4$ (10 mol%), Cs_2CO_3 (1.1 equiv.), and PivOH (30 mol%) in *N,N*-dimethylformamide

Chart 16. Formation of Tetrahydro-2H-fluorene via Pd(0)-Catalyzed Benzylic C(sp^3)-H Functionalization Chart 17. Synthesis of the Right-Hand Fragment of Benzohopane **68**

(DMF) at 140°C, resulting in the formation of tetrahydro-2H-fluorene **69** (Table 8, entry 1). We then screened a variety of different Pd sources, ligands, reaction temperatures, and additives, as shown in Table 8, and the optimal conditions were determined as follows: Pd(OCOCF₃)₂ (10 mol%), PPh₃ (20 mol%), Cs₂CO₃ (1.2 equiv.), and PivOH (30 mol%) in DMF at 80–100°C. For this transformation, PPh₃ was found better than bulky trialkyl phosphine ligands, including Cy₃P, Ad₂PⁿBu, and ^tBu₃P, which were otherwise effective for our oxindole synthesis^{33,35} through C(sp^3)-H activation (Table 8, entries 4–10). Additionally, this reaction proceeded at temperatures in the range 80–100°C, which are lower than those required of our oxindole synthesis. This result can be explained in terms of the greater accessibility of the Pd center to the benzylic C(sp^3)-H bond because of the flexible sp^3 carbon linkage. The presence of a carboxylic acid additive (*i.e.*, 1-AdCOOH) was found essential to the success of this reaction, which proceeded through a concerted metalation deprotonation (CMD) pathway, as previously reported.^{78,79}

We subsequently investigated the scope and limitations of the optimal conditions. Various tetrahydro-2H-fluorenes were synthesized from the corresponding enol triflate substrates, and the substituent at the opposite *ortho* position was found essential for avoiding the undesired formation of benzocyclobutene **73** (Chart 16). Notably, all these products were unstable and readily decomposed at room temperature after a few days.

With tetrahydro-2H-fluorene **69** in hand, we proceeded to synthesize the right-hand fragment of benzohopane **68** (Chart

17). Freshly prepared **69** was converted to the *cis*-fused tricyclic ketone **74** through sequential hydroboration and tetrapropylammonium perruthenate (TPAP) oxidation reactions.¹²⁵ The site-selective bis-methylation was difficult; therefore an ester group was introduced to ketone **74** using Mander's procedure.¹²⁶ The stepwise methylation reaction was followed by the hydrolysis of the ester group under basic conditions to give methyl ketone **76** as a 3.3:1 mixture, along with a small amount of the corresponding *trans*-fused isomers. After triflation with Comins' reagent,¹²⁷ Pd-catalyzed carbonylation of **77** gave the α,β -unsaturated ester **78**, which was converted to the right-hand fragment of benzohopane **68** using a DIBAL-H reduction and Dess–Martin oxidation. The *cis*-fused stereochemistry of the product was confirmed by nuclear Overhauser effect (NOE) experiments involving **79**. This synthetic route was found robust for the construction of the *cis*-fused tricyclic skeleton of benzohopane. Our newly developed Pd(0)-catalyzed benzylic C(sp^3)-H activation method for the synthesis of tetrahydro-2H-fluorene was extended to the concise synthesis of the substructure of benzohopane.⁴²

Summary

We initially developed a new synthetic method for the construction of oxindoles and spirooxindoles *via* a Pd(0)-catalyzed benzylic C(sp^3)-H functionalization reaction. This method was subsequently extended to the synthesis of various other heterocycles, including 2-arylindoles, benzocarbazole, indolo-carbazole, indoloquinazolinone, and indoloquinazolinone.

Table 8. Optimization of the Reaction Conditions for Synthesis of Tetrahydro-2H-fluorenes

entry	Pd source	ligand	base	additive	temp. (°C)	yield
1	Pd(PPh ₃) ₄	---	Cs ₂ CO ₃	PivOH	140	69%
2	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	PivOH	140	64%
3	Pd ₂ (dba) ₃	PPh ₃	Cs ₂ CO ₃	PivOH	140	60%
4	Pd(TFA) ₂	PPh ₃	Cs ₂ CO ₃	PivOH	140	83%
5	Pd(TFA) ₂	P(tol) ₃	Cs ₂ CO ₃	PivOH	140	32%
6	Pd(TFA) ₂	P(C ₆ H ₅ OMe) ₃	Cs ₂ CO ₃	PivOH	140	34%
7	Pd(TFA) ₂	P(C ₆ H ₅ F) ₃	Cs ₂ CO ₃	PivOH	140	64%
8	Pd(TFA) ₂	Cy ₃ P	Cs ₂ CO ₃	PivOH	140	35%
9	Pd(TFA) ₂	Ad ₂ P ⁿ Bu	Cs ₂ CO ₃	PivOH	140	29%
10	Pd(TFA) ₂	P ^t Bu ₃	Cs ₂ CO ₃	PivOH	140	29%
11	Pd(TFA) ₂	PPh ₃	Cs ₂ CO ₃	PivOH	100	93%
12	Pd(TFA) ₂	PPh ₃	Na ₂ CO ₃	PivOH	100	10%
13	Pd(TFA) ₂	PPh ₃	KOAc	PivOH	100	78%
14	Pd(TFA) ₂	PPh ₃	Et ₃ N	PivOH	100	4%
15	Pd(TFA) ₂	PPh ₃	K ₂ CO ₃	PivOH	100	42%
16	Pd(TFA) ₂	PPh ₃	Cs ₂ CO ₃	none	100	0%*
17	Pd(TFA) ₂	PPh ₃	Cs ₂ CO ₃	1-AdCOOH	100	98%
18	Pd(TFA) ₂	PPh ₃	Cs ₂ CO ₃	1-AdCOOH	80	quant.

*No reaction.

It is noteworthy that our synthetic method for the preparation of oxindoles was successfully applied to the total synthesis of several pyrrolophenanthridine alkaloids. In this case, a concise synthetic route was achieved without protecting groups using a Pd-catalyzed C(sp³)-H functionalization reaction. Additionally, a new method was developed for the construction of tetrahydro-2H-fluorenes based on a Pd-catalyzed benzylic C(sp³)-H functionalization strategy. These structures are useful building blocks for the introduction of other functional groups and the construction of increasingly complex structures. This method was also successfully applied to synthesis of the right-hand fragment of benzohopane. In terms of our future work, we hope to apply C(sp³)-H functionalization chemistry to the total synthesis of complex natural products by developing more concise and direct methods.

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interest.

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