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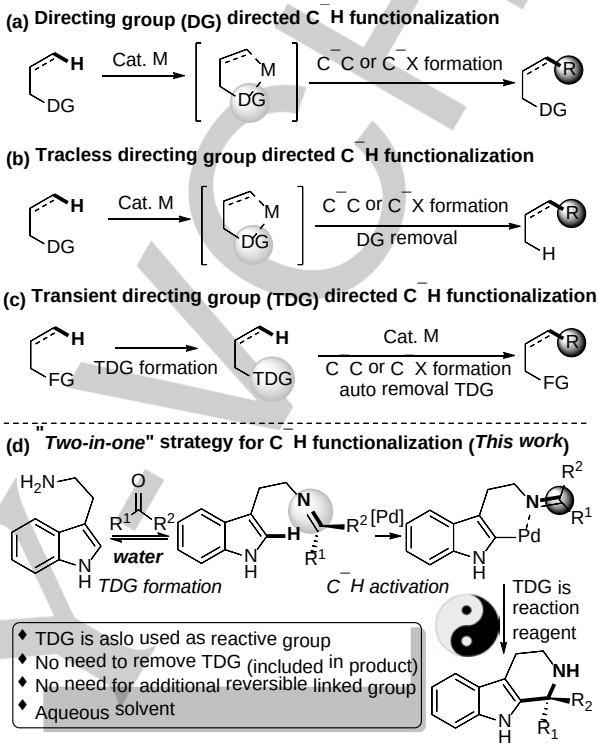
COMMUNICATION

"Two-in-One" Strategy for Palladium-Catalyzed C–H Functionalization in Water

Huiying Zeng,[a,*] Zemin Wang[a] and Chao-Jun Li[a,b,*]

Abstract: Transition metal-catalyzed C–H functionalizations have been developed as powerful methods for C–C bond formations. Directing group, removable directing group, traceless directing group and transient directing group (TDG) were successively used to improve the efficiency. For further development of greener and more sustainable methods, it is highly desirable to develop C–H functionalization in which the TDG also plays the role of reagent reacting with the activated C–H position to avoid separating the extra reversibly linked directing group, especially in aqueous solvent. Towards this endeavor, herein, palladium-catalyzed C–H functionalization of tryptamine derivatives in water for synthesizing tetrahydro-β-carbolines is reported. Various tryptamine derivatives and ketones reacted successfully to generate tetrahydro-β-carbolines, including quaternary carbon at C-1 position. Deuterium labeling experiments were also carried out to understand the mechanism. The C-2 position of pyridine was also successfully functionalized by this strategy.

Transition-metal catalyzed C—H functionalization has become a powerful tool to form C—C bonds and C—X bonds over the past decade,[1] which has enabled more efficient chemical synthesis by avoiding the traditional requirement of preinstalled functional handles such as halide, triflate, boron or zinc reagents etc. As only minute difference in reactivity exists between various C—H bonds, regioselective activation of these C—H bonds constitutes a great challenge. To solve such a problem, directing group can help to direct the catalyst to activate proximal C—H bonds via cyclometallated intermediates. However, the directing group needs to be pre-installed in the substrate and, upon finishing its mission, it is usually hard to remove from the product (Scheme 1a). Therefore, removable or traceless directing group has been developed to overcome the above challenges.[2] These directing groups can be removed with further manipulation or in the same reaction vessel (Scheme 1b). However, stoichiometric removable or traceless directing groups are generally required. More recently, to overcome these shortcomings, transient directing groups were developed by adding catalytic amount of reversibly linked directing group (Scheme 1c).[3] For greener and more atom-economical transformations, as well as considering the difficulty to separate the reversibly linked directing group from product, the development of a "two-in-one" strategy for



Scheme 1. Representative strategies of C–H bond functionalization.

C—H functionalization in which the transient directing group is also used as a reagent to react with the activated C—H bond is highly attractive.

On the other hand, tetrahydro-β-carboline skeleton bearing a quaternary carbon at C-1 position is an important framework in natural products and pharmaceutical agents (Figure 1). Examples include Komavine (**1**) (and Acetylkomavine)[4], Spiroindolone (**2**)[5], Tabertinggine (**3**)[6], Peharmaline A (**4**)[7], Subincanadine B (**5**)[8] and antimalarial drug NITD609 (**6**)[9]. Herein, based on the "two-in-one" strategy, *we report a palladium-catalyzed C—H bond activation at the C-2 position of*

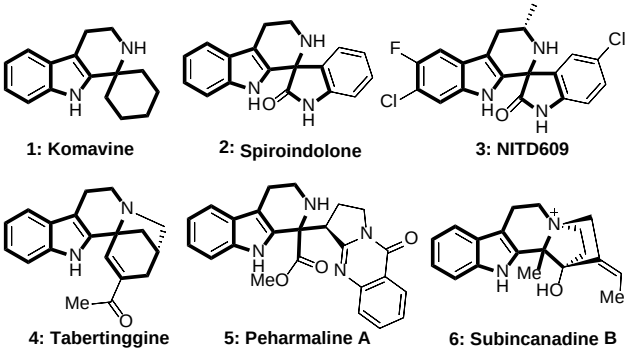


Figure 1. Representative natural products and bioactive molecules with a tetrahydro-β-carboline skeleton bearing a quaternary carbon at C-1 position.

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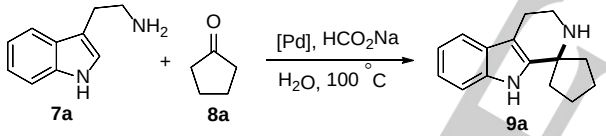
indole and pyridine in water followed by cyclization with a transient directing group (imine group) to form the C─C bond, in which the transient directing group is subsequently integrated into the product (Scheme 1d). Various tetrahydro-β-carbolines bearing quaternary carbon at C-1 position, including natural products Komavine (**1**) and Spiroindolone (**2**), are generated by this method.

Our initial efforts were focused on the optimization of reaction conditions for the C─H bond functionalization of tryptamine (**7a**) with cyclopentanone (**8a**). When these reagents were explored using 5 equiv of sodium formate with Pd/C as a catalyst in water at 100 ºC under an argon atmosphere for 24 h, moderate yield (50%) of spiro-product **9a** was obtained (Table 1, entry 1). Encouraged by this result, different palladium catalysts were tested (Table 1, entries 2-6), and the best yield (80%) was obtaind when $Pd(OH)_2$/C was used as the catalyst (Table 1, entry 6). Without the active carbon support, the yield (39%) was lowered significantly (Table 1, entry 5). Reducing the amount of sodium formate to 3 equiv, **9a** was obtained with a similar yield (Table 1, entry 7). Further reducing the amount of sodium formate to 2 equiv reduced the yield (Table 1, entry 8). Shortening the reaction time to 6 h had no significant effect on the yield (Table 1, entries 9-10). The best yield (93%) was obtained when increasing the amount of ketone to 3 equiv (Table 1, entry 11). Lowering the amount of catalyst to 5 mol% decreased the yield (87%) slightly (Table 1, entry 12). Both elevating and lowering the reaction temperature reduced the yield (Table 1, entries 13-14). Other metal formates instead of sodium formate were tested, and the yield was not increased (Table 1, entries 15-16). Considering that the $Pd(OH)_2$ could also play the role of Lewis acid to catalyze the classical Pictet-Spengler reaction[10], control experiments were performed: in absence of either HCO_2Na or $Pd(OH)_2$, **9a** was not detected even after prolonging the reaction time to 72 h (Table 1, entries 17-18). This result illustrated that the reaction did not proceed via the Pictet-Spengler process. For details of studies on the reaction solvent and others, please see Supporting Information.

With the optimized reaction conditions in hand, we next proceeded to explore different ketones to react with tryptamine at 100 ºC under an argon atmosphere using 10 mol% of $Pd(OH)_2$/C as the catalyst and 3.0 equiv of sodium formate in water (1 mL) for 6 h (Table 2). While cyclopentaone gave the spiro-product **9a** in excellent yield (90%), further increasing the

Table 1. Evaluation of various conditions[a]

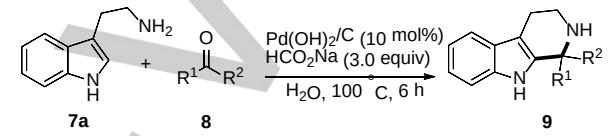


7a **8a** **9a**

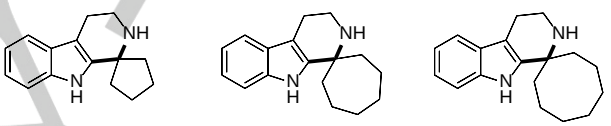
Entry	Catalyst	Ketone [mmol]	HCO_2Na [mmol]	Time [h]	9a[b] [%]
1	Pd/C	0.4	1.0	24	50
2	$Pd(PPh_3)_4$	0.4	1.0	24	trace
3	$PdCl_2$	0.4	1.0	24	55
4	$Pd(OAc)_2$	0.4	1.0	24	37
5	$Pd(OH)_2$	0.4	1.0	24	39
6	$Pd(OH)_2$/C	0.4	1.0	24	80
7	$Pd(OH)_2$/C	0.4	0.6	24	80
8	$Pd(OH)_2$/C	0.4	0.4	24	44
9	$Pd(OH)_2$/C	0.4	0.6	12	79
10	$Pd(OH)_2$/C	0.4	0.6	6	78
11	$Pd(OH)_2$/C	0.6	0.6	6	93(90)
12[c]	$Pd(OH)_2$/C	0.6	0.6	6	87
13[d]	$Pd(OH)_2$/C	0.6	0.6	6	85
14[e]	$Pd(OH)_2$/C	0.6	0.6	6	39
15[f]	$Pd(OH)_2$/C	0.6	0.6	6	84
16[g]	$Pd(OH)_2$/C	0.6	0.6	6	80
17	$Pd(OH)_2$/C	0.6	-	72	0
18	-	0.6	0.6	72	0

[a] General conditions: Tryptamine **7a** (0.2 mmol), [Pd] (10 mol%), H_2O (1 mL) at 100 ºC under an argon atmosphere. [b] Yields were determined by ^1H NMR with nitromethane as internal standard; isolated yields in brackets. [c] 5 mol% $Pd(OH)_2$/C. [d] 80 ºC. [e] 120 ºC. [f] $HCO_2Li \cdot H_2O$ was used instead of HCO_2Na. [g] HCO_2K was used instead of HCO_2Na.

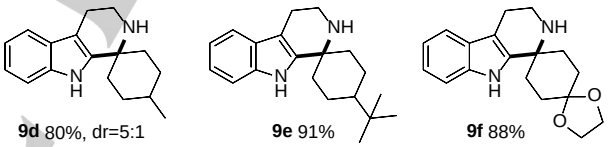
Table 2. C–H bond functionalization of tryptamine with various ketones[a]



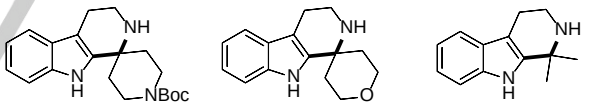
7a **8** **9**



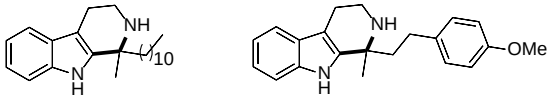
9a 90% **9b** 74%[b] **9c** 46%[c,d]



9d 80%, dr=5:1 **9e** 91% **9f** 88%

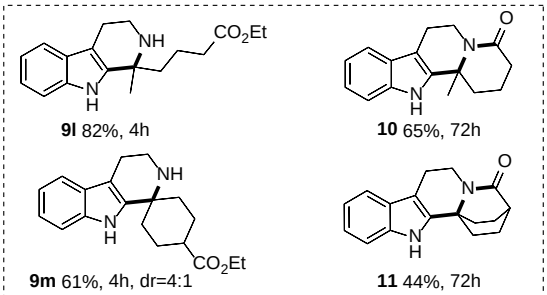


9g 80% **9h** 67%[b] **9i** 90%



9j 85%[d] **9k** 90%

gram scale: 84%, 30h



9l 82%, 4h **10** 65%, 72h

9m 61%, 4h, dr=4:1 **11** 44%, 72h

[a] Reaction conditions: **7a** (0.2 mmol), **8** (0.6 mmol), $Pd(OH)_2$/C (10 mol%), and HCO_2Na (0.6 mmol) in water (1 mL) under an argon atmosphere at 100 ºC for 6 h; yields of isolated products. [b] 15 mol% $Pd(OH)_2$/C. [c] 20 mol% $Pd(OH)_2$/C. [d] 24 h.

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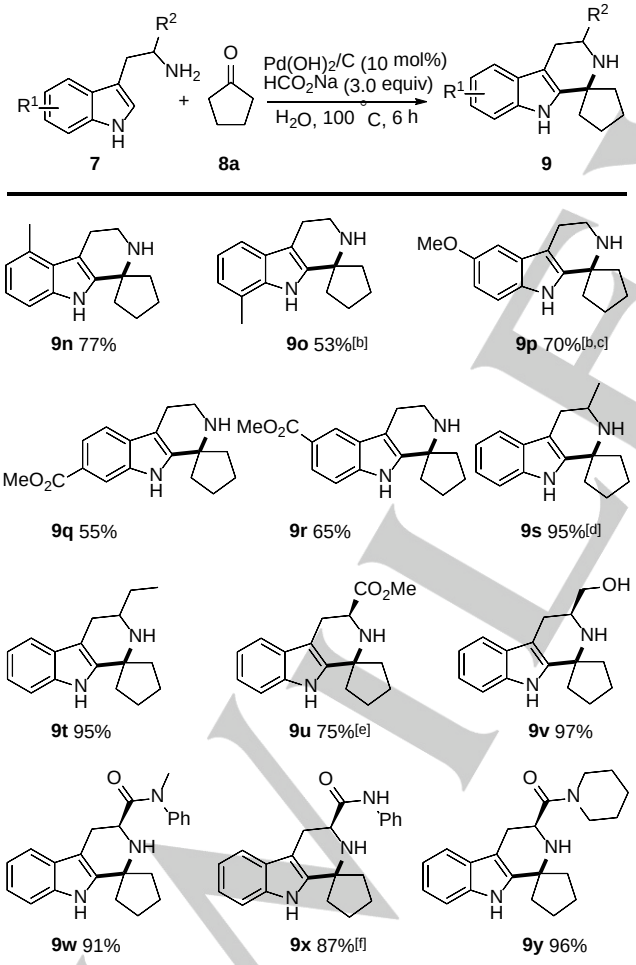
ring size of cycloketone lowered the yields of corresponding products **9b-c** consecutively possibly due to the increased steric hindrance. When 4-methylcyclohexanone was used as a substrate, the cyclization product **9d** was obtained in high yield with a moderate diastereomeric ratio (Table 2, **9d**). With cyclohexanone bearing a bulky *tert*-butyl substituent on the C-4 position, a single diastereoisomer was isolated in excellent yield (Table 2, **9e**). Ketal was also tolerated in this system (Table 2, **9f**). Heterocyclic ketones reacted smoothly with tryptamine in good to high yields (Table 2, **9g-h**). Linear ketone was also explored and cyclization products **9i-k** were formed with excellent results. To test the scaling-up ability of the reaction, compound **9k** was synthesized on gram scale in 84% yield when prolonging the reaction to 30 h. Bifunctional *δ*-ketoester substrates were also investigated, and good to high yields of C–H functionalization products **9l** and **9m** were obtained in 4 h. Prolonging the reaction time to 72 h gave further intramolecular fused-ring amidation products **10** and bridged-ring amide **11**, respectively (Table 2, **10** and **11**).

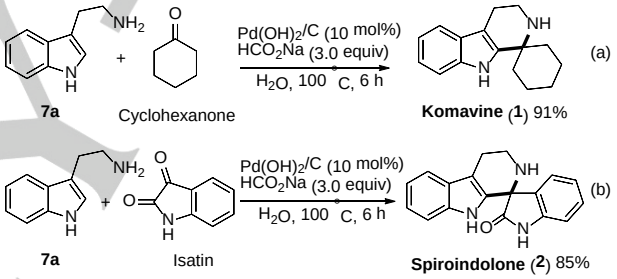
Table 3. C–H bond functionalisation of tryptamine derivatives with cyclopentanone[a]



[a] Reaction conditions: **7** (0.2 mmol), **8a** (0.6 mmol), $Pd(OH)_2/C$ (10 mol%), and HCO_2Na (0.6 mmol) in water (1 mL) under an argon atmosphere at 100 ºC for 6 h; yields of isolated products were given. [b] 15 mol% $Pd(OH)_2/C$. [c] 10 h. [d] 4 h. [e] HCO_2Na (20 equiv) and methyl tryptophanate hydrochloride was used. [f] 20 mol% $Pd(OH)_2/C$.

We subsequently investigated the generality of the system with a wide range of substituted tryptamines (Table 3). Tryptamines bearing electron-donating group at different positions of the phenyl ring reacted smoothly to give the corresponding cyclization products (Table 3, **9n-p**). Good yields were also obtained with substrates bearing the corresponding electron-withdrawing substituents (Table 3, **9q-r**) and having alkyl substitutions at the C-1 position of the chain (Table 3, **9s-t**). When methyl tryptophanate hydrochloride was used as substrate, the spiro-product **9u** was obtained without ester-amide exchange (Table 3, **9u**). Remarkably, tryptophanol reacted smoothly to give the corresponding product **9v** in excellent yield without hemiaminal ether product. Moreover, various tryptophanamide derivatives also reacted with excellent yields in this system (Table 3, **9w-y**).

To illustrate synthetic applications of this C-H functionalization strategy, natural products Komavine (**1**) and Spiroindolone (**2**) were synthesized under standard reaction conditions in excellent yields (91% and 85%, respectively) in water by reacting tryptamine with cyclohexanone and Isatin, respectively (Scheme 2a and 2b).



Scheme 2. Synthesizing natural products via the C–H functionalization strategy.

To further understand the mechanism of this catalytic reaction, deuterium labeling experiments were carried out. As shown in Scheme 3, tryptamine (**7a**) and 3 equiv of cyclopentanone (**8a**) were explored under standard reaction conditions using deuterium oxide instead of water as solvent. Even though the reaction was run for a very short time (1 min), imine **12** was obtained in 87% yield with *ca.* 45% deuteration at the C-2 position of indole ring, together with 2% yield of cyclization product **9a** (Scheme 3a). Considering amine can also coordinate with palladium catalyst, control experiment for the deuterium reaction without cyclopentanone (**8a**) was also performed (Scheme 3b), and the C-2 position of indole ring was only deuterated in 24%. The results indicated that the imine group is a more effective ligand than amine group, to coordinate with palladium catalyst to accelerate the deuteration at C-2 position of the indole ring. To further corroborate this rationale, 3-methylindole (**13**) without coordination site in the chain was also tested, and only 5% C-2 deuteration was observed (Scheme 3c). These results illustrated that the intermediate imine functioned as a transient directing group and accelerated the C–H bond activation of C-2 position on indole ring.

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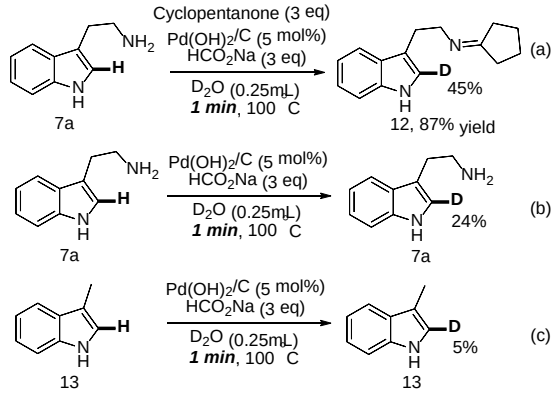


Scheme 3. Deuterium labelling experiments

Based on these results, a tentative mechanism is proposed in Figure 2: the $HPd^{II}H$ species is generated from palladium and sodium formate in water.[11] The TDG imine **A** is formed by condensation of tryptamine and cyclopentanone. Highly selective C–H activation of the C-2 position[12] is obtained due to the electron-lone pair coordination of imine to form a cyclopalladated intermediate **B**[13] with the loss of hydrogen gas. Then, the electron-lone pair coordination of imine with palladium is transformed into the π bond coordination (intermediate **C**) at an elevated temperature, which is followed by cyclization with the polar unsaturated bond[14] of imine to form intermediate **D**. Finally, the spiro-product **9a** is obtained by ligand exchange of intermediate **D** with sodium formate and regenerates the $HPd^{II}H$ species.

To explore the application of the "two-in-one" strategy for C–H functionalization to other system as well as to further exclude the classical Pictet-Spengler reaction pathway, electron-deficient aromatic systems, which would not be effective under the standard Pictet-Spengler conditions, were investigated. To our delight, reaction of 1-(6-(4-methoxyphenyl)pyridin-3-yl)propan-2-amine (**14**) with cyclopentanone (**2a**) at 100 ºC under an argon atmosphere using 20 mol% of $Pd(OH)_2/C$ as the

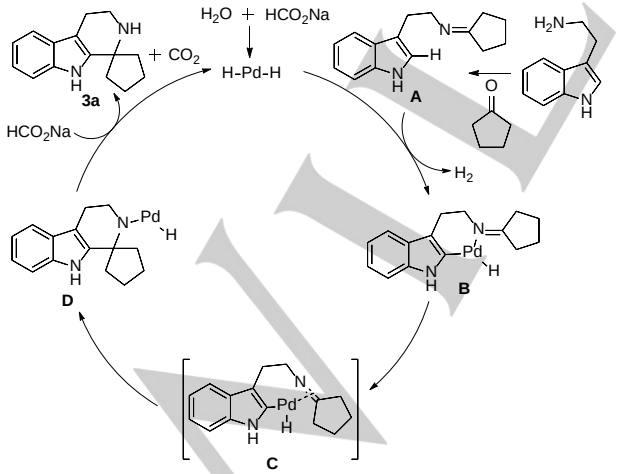
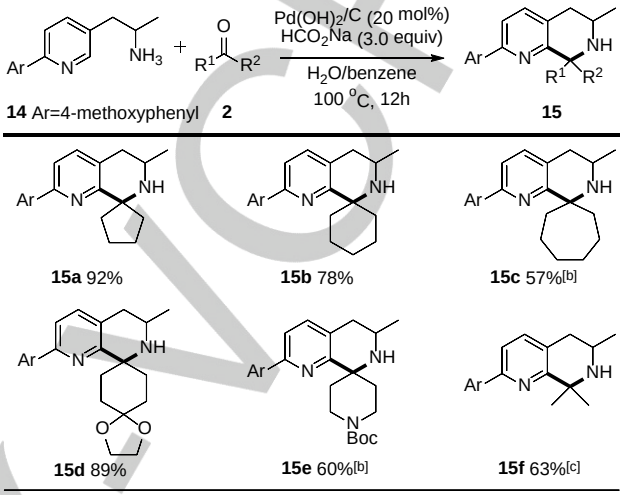


Figure 2. Proposed reaction pathway of C–H functionalisation of tryptamine.

catalyst and 3.0 equiv of sodium formate in water (1 mL) (with 0.2 mL benzene) for 12 h gave the C–H functionalization product **15a** in excellent yield (92%) (Table 4). Other cycloketones also reacted successfully with compound **14** to give the corresponding annulation products **15b-c**. Ketal group and hetero-ring were tolerated in this catalytic system, affording annulation products **15d-e**. Compound **15f** was generated smoothly by reacting with acetone.

Table 4. C–H bond functionalization of 1-(6-(4-Methoxyphenyl)pyridin-3-yl)propan-2-amine with ketones[a]



[a] Reaction conditions: **14** (0.2 mmol), **2** (0.6 mmol), $Pd(OH)_2/C$ (20 mol%), and HCO_2Na (0.6 mmol) in water (1 mL) and benzene (0.2 mL) under an argon atmosphere at 100 ºC for 12 h; yields of isolated products were given. [b] 25 mol% $Pd(OH)_2/C$. [c] Acetone (1.0 mmol) was used.

In conclusion, we have developed a "two-in-one" strategy for C–H functionalisation of tryptamine derivatives in water. The TDG played dual roles of directing group and reagent. Various tetrahydro-β-carboline skeleton products (including natural products Komavine (**1**) and Spiroindolone (**2**)) were synthesized by this strategy. Furthermore, this strategy can be expanded to electron-deficient aromatic systems which would not be effective under the standard Pictet-Spengler conditions. We envisage that this "two-in-one" strategy will be applicable to the development of other useful TDG directed C–H functionalization followed by cyclization processes to construct important structural motifs rapidly.

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Keywords: C–H functionalisation • aqueous solvent • tetrahydro-β-carbolines • palladium-catalyzed • tryptamine

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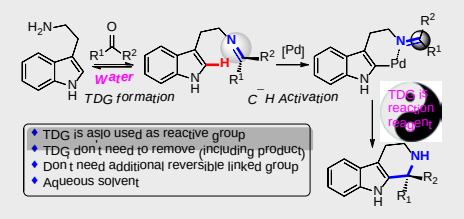

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