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Synthesis of tetrahydroindolones and tetrahydrocarbazolones *via* palladium catalyzed C–H activation

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Abstract: The treatment of bromo homoallyl pyrrolyl/indolyl ketone derivatives with $Pd(OAc)_2$ in the presence of PPh_3 and Cs_2CO_3 in DMF resulted in the formation of tetrahydroindolones and tetrahydrocarbazolones in moderate to good isolated yields.

Keywords: palladium; C–H alkenylation; tetrahydroindolone; tetrahydrocarbazolone

Introduction

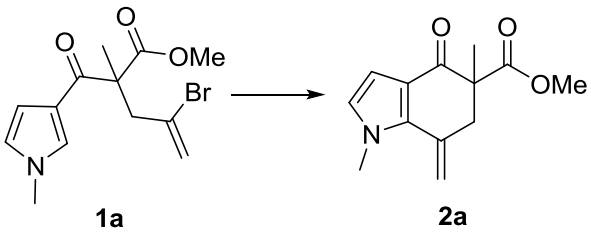
The indole and carbazole moieties are important structural motifs found in many natural products and bioactive molecules.[1] Therefore, the development of efficient strategies toward these molecules has become a central theme in organic synthesis.[1d,e,2] Among them, the transition metal-catalyzed intramolecular C–H activation of indoles has emerged as an attractive method to access the scaffolds of carbazoles and analogues.[3-5] However, literature reports concerning the intramolecular C–H functionalization of pyrroles for the assembly of indoles and related analogues are rare.[3g,5a,c,6] As part of our continued interest in transition metal catalyzed C–H activation[7,8] and application in natural product synthesis,[9] we have developed valuable approaches toward indeno[2,1-*b*]pyrrol-8-ones *via* the palladium catalyzed intramolecular C–H arylation of pyrroles.[8] Herein, we report our recent findings for the synthesis of tetrahydroindolones and tetrahydrocarbazolones *via* palladium catalyzed C–H alkenylation.

Results and Discussion

Our investigation started with compound **1a**. The desired tetrahydroindolone **2a** was obtained in 41% isolated yield after exposing **1a** to $Pd(OAc)_2$ and K_2CO_3 in DMF[7c] at 100 °C for 15 h (Table 1, entry 1). Further palladium catalyst screening indicated that $Pd(OAc)_2$ was the best choice (Entries 2–8). Next, different bases were explored. No reaction occurred in the presence of the organic base DIPEA (Entry 9) or the strong inorganic base ^{t}BuOK (Entry 12). While K_3PO_4 gave less satisfactory results (Entry 11), Cs_2CO_3 led to the formation of **2a** in much higher yield than K_2CO_3 (Entry 10 vs 1). With $Pd(OAc)_2$ as catalyst and Cs_2CO_3 as base, other solvents (NMP, DMSO, 1,4-dioxane) were explored. However, none of these provided better yields than DMF (Entries 13–15 vs 10). The reaction could not be driven to completion when the catalyst loading was reduced to 5 mol% (Entry 17 vs 10), while other side reactions began to take place in the presence of 20 mol% catalyst loading (Entry 16 vs 10). Reduced yields were obtained in both cases. Further study indicated that the yield could be

improved to 76% in the presence of added PPh_3 (Entry 18 vs 10). However, no reaction occurred without the base (Entry 21). Finally, the reaction temperatures were briefly screened, and 100 °C gave the highest yield (Entries 19, 20 vs 18).

Table 1. Reaction conditions optimization for the synthesis of tetrahydroindolone **2a**.



1a **2a**

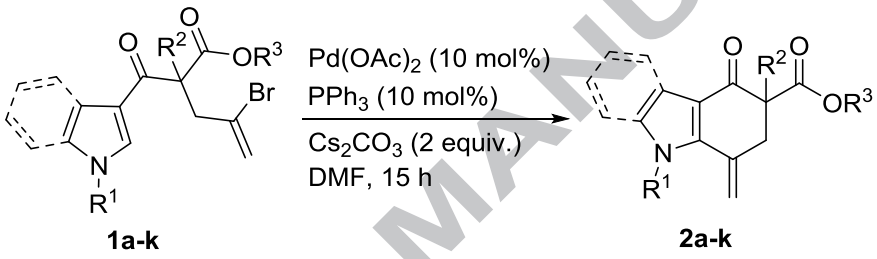
Entry	Catalyst	Ligand [a]	Base [b]	Solvent	Temp (°C)	Yield (%) [c]
1	$Pd(OAc)_2$ [d]	-	K_2CO_3	DMF	100	41
2	$PdCl_2$ [d]	-	K_2CO_3	DMF	100	18
3	$PdCl_2(PPh_3)_2$ [d]	-	K_2CO_3	DMF	100	13
4	$PdCl_2(CH_3CN)_2$ [d]	-	K_2CO_3	DMF	100	24
5	$PdCl_2$(dppf)[d]	-	K_2CO_3	DMF	100	0
6	Pd/C [d]	-	K_2CO_3	DMF	100	0
7	$Pd(dba)_3$ [d]	-	K_2CO_3	DMF	100	16
8	$Pd(PPh_3)_4$ [d]	-	K_2CO_3	DMF	100	30
9	$Pd(OAc)_2$ [d]	-	DIPEA	DMF	100	0
10	$Pd(OAc)_2$ [d]	-	Cs_2CO_3	DMF	100	70
11	$Pd(OAc)_2$ [d]	-	K_3PO_4	DMF	100	24
12	$Pd(OAc)_2$ [d]	-	^{t}BuOK	DMF	100	0
13	$Pd(OAc)_2$ [d]	-	Cs_2CO_3	NMP	100	40
14	$Pd(OAc)_2$ [d]	-	Cs_2CO_3	DMSO	100	24
15	$Pd(OAc)_2$ [d]	-	Cs_2CO_3	1,4-dioxane	100	56
16	$Pd(OAc)_2$ [e]	-	Cs_2CO_3	DMF	100	49
17	$Pd(OAc)_2$ [f]	-	Cs_2CO_3	DMF	100	64
18	**$Pd(OAc)_2$ [d]**	**PPh_3**	**Cs_2CO_3**	**DMF**	**100**	**76**
19	$Pd(OAc)_2$ [d]	PPh_3	Cs_2CO_3	DMF	90	71
20	$Pd(OAc)_2$ [d]	PPh_3	Cs_2CO_3	DMF	110	65
21	$Pd(OAc)_2$ [d]	PPh_3	-	DMF	100	0

[a] 10 mol%; [b] 2 equiv.; [c] Isolated yield; [d] 10 mol%; [e] 20 mol%; [f] 5 mol%.

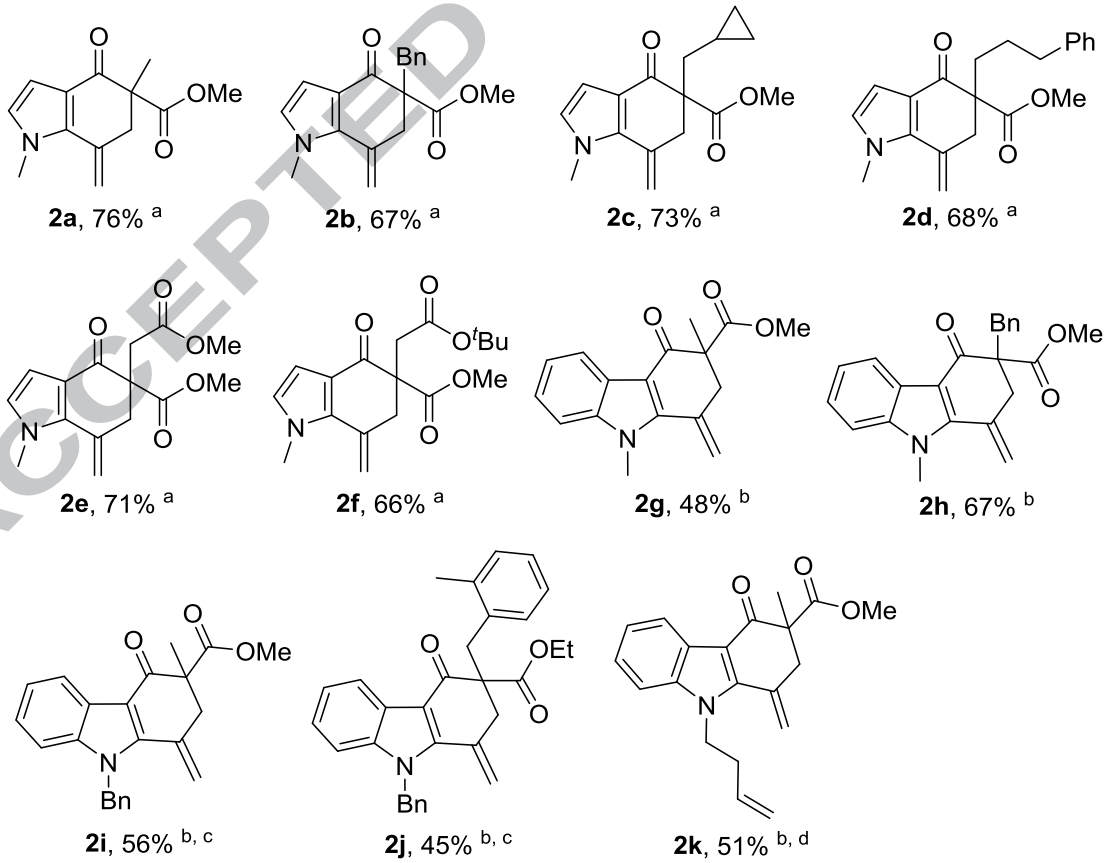
With the optimal conditions in hand, the substrate scope was explored (Table 2). A variety of 2-(2-bromoallyl)-3-(*N*-methylpyrrolyl)-3-oxo-1-carboxylates **1a**–**f** could be effectively converted into the corresponding tetrahydroindolones **2a**–**f** in good isolated yields. Under the reaction conditions, the *N*-methylindolyl derivatives **1g**,**h** could also be successfully converted into tetrahydrocarbazolones **2g**,**h**, although slightly higher reaction temperatures were required to drive the reaction to completion.

Next, the palladium catalyzed intramolecular C–H alkenylation of the benzyl group protected substrates **1i**,**j** was investigated, which provided tetrahydrocarbazolones **2i**,**j** in moderate isolated yields. Similarly, the reaction of *N*-butenylindole derivative **1k** proceeded to give tetrahydrocarbazolone **2k** in 51% isolated yield, ring-closing metathesis of which provided tetrahydropyrido[3,2,1-*jk*]carbazolone **3** in an unoptimized 67% isolated yield (Scheme 1). Finally, we explored the palladium catalyzed C–H alkenylation reaction of **1l**. Without an extra 2-substituent, this type of 2-(2-bromoallyl)-1,3-dicarbonyl compound can easily give rise to the formation of furans.[7a,10] Gratifyingly, under our reaction conditions, indole-5-carboxylate **4** could be isolated in 35% yield (Scheme 2). We believe that compound **4** was formed through the desired palladium catalyzed pyrrolyl C–H alkenylation and subsequent double-bond isomerization.

Table 2. Substrate scope for the synthesis of tetrahydroindolones and tetrahydrocarbazolones *via* palladium catalyzed C–H alkenylation.



1a-k **2a-k**

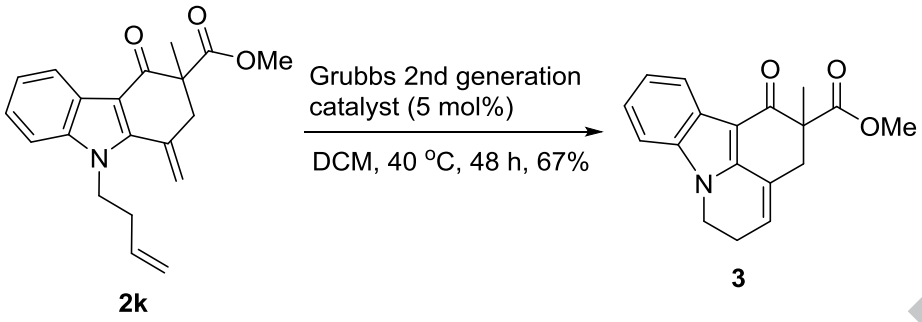


2a, 76% [a] **2b**, 67% [a] **2c**, 73% [a] **2d**, 68% [a]

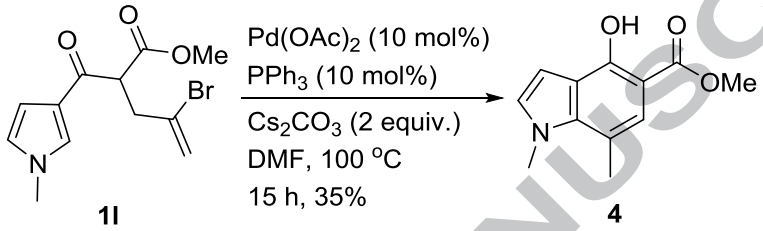
2e, 71% [a] **2f**, 66% [a] **2g**, 48% [b] **2h**, 67% [b]

2i, 56% [b, c] **2j**, 45% [b, c] **2k**, 51% [b, d]

[a] 100 °C; [b] 110 °C; [c] 21 h; [d] 24 h.



Scheme 1. Synthesis of tetrahydropyrido[3,2,1-*jk*]carbazolone **3** *via* ring-closing metathesis of **2k**.



Scheme 2. Synthesis of indole-5-carboxylate **4** *via* palladium catalyzed C–H alkenylation of **1l**.

Conclusion

In summary, we have developed an efficient strategy toward the synthesis of tetrahydroindolones and tetrahydrocarbazolones *via* palladium catalyzed intramolecular C–H alkenylation of the corresponding pyrrolyl and indolyl derivatives. This strategy is well adapted to the synthesis of indole and carbazole natural products, which is currently underway in our laboratory.

Acknowledgment

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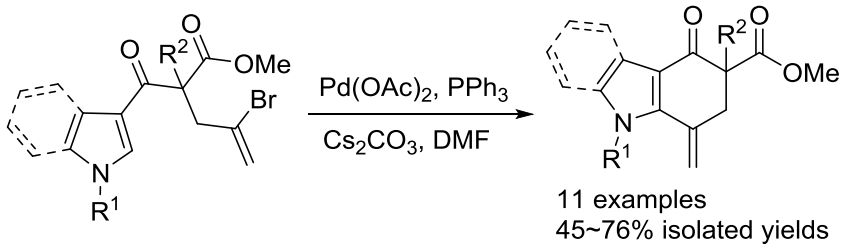

11 examples
45~76% isolated yields

- Palladium catalyzed synthesis of tetrahydroindolones has been developed;
- Palladium catalyzed synthesis of tetrahydrocarbazolones has been developed;
- Tetrahydropyrido[3,2,1-*jk*]carbazolone has been synthesized.