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Palladium-Catalyzed Oxidative Direct C3- and C7-Alkenylations of Indazoles: Application to the Synthesis of Gamendazole

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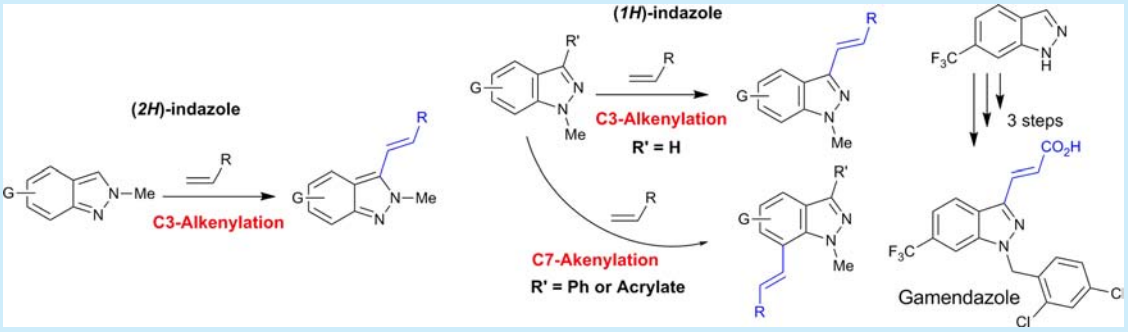
Supporting Information



ABSTRACT: The first palladium-catalyzed oxidative alkenylation of (1*H*)- and (2*H*)-indazole derivatives with various olefins is described. The use of $Pd(OAc)_2$ as the catalyst and Ag_2CO_3 as the oxidant promoted the selective C3-monoalkenylation of (1*H*)-indazoles and (2*H*)-indazoles, affording the desired products in good yields. An original oxidative C7-alkenylation of 3-substituted (1*H*)-indazoles was also developed. The oxidative alkenylation of (1*H*)-indazole was successfully applied to the total synthesis of the drug candidate gamendazole in a step- and atom-economical fashion.

The indazole system is a ubiquitous motif found in various biologically active molecules.[1] Moreover, various drugs and drug candidates containing indazole have been developed such as pazopanib (Votrient),[2] benzydamine,[3] bendazac,[4] granisetron (Kytril),[5] tetrydamine (or tetridamine),[6] and gamendazole.[7] The development of new synthetic methods for the preparation of original functionalized indazoles is therefore a very attractive task. The oxidative Heck-type reaction, also called the Fujiwara−Moritani reaction, has received considerable attention during the past decade.[8,9] Although several heterocyclic systems have been alkenylated using this C−H/C-H alkenylation reaction,[10] to our knowledge, (1*H*)- and (2*H*)-indazoles including functionalized derivatives have never been used as substrates for the Fujiwara reaction. Moreover, oxidative alkenylation of the six-membered ring of 6−5-bicyclic systems containing no heteroatom on the six-membered ring and at least one heteroatom on the five-membered ring is unprecedented. Only two examples of C7-alkenylation of indole using directing groups have been reported so far.[11] Recently, we and others reported the direct arylation of both (1*H*)-indazole[12] and (2*H*)-indazole[13] systems. Pursuing our research program on the development of new procedures for the C−H activation of indazoles, we here report on a palladium-catalyzed oxidative C3-alkenylation of (2*H*)- and (1*H*)-indazoles as well as C7-alkenylation of (1*H*)-indazole. We also describe a concise three-step synthesis of gamendazole using direct C3-alkenylation of (1*H*)-indazole.

We first carried out the alkenylation of 2-methyl (2*H*)-indazole **1** with ethyl acrylate in the presence of $Pd(OAc)_2$ as the catalyst and either $Cu(OAc)_2$, CuO, or Ag_2O_3 as the oxidant. The reactions conducted in xylene without additives afforded the C-3 alkenylated product **2** in moderate yields (44 to 70%, Table 1, entries 1−3). When AcOH, Ac_2O, or $AcOH/Ac_2O$ was the additive to the reaction conditions, significant improvements in the reaction yields were noticed (Table 1, entries 4−6). Replacing the xylene solvent by dioxane in the presence or absence of additives resulted in lower yields (Table 1, entries 7−9). When Ag_2CO_3 was used as the oxidant in the presence of $AcOH/Ac_2O$, a very good isolated yield of compound **2** was obtained (Table 1, entry 10). Importantly, when only 5 mol % of $Pd(OAc)_2$ instead of 10 mol % was used, no significant decrease in the reaction yield was observed (Table 1, entry 11). All of the other attempts to improve the reaction yield by replacing the solvent (Table 1, entry 12), the oxidant (Table 1, entries 17 and

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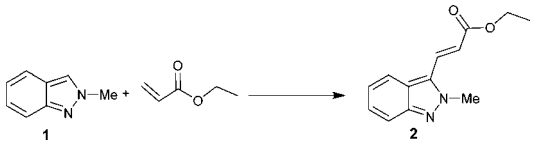
Table 1. Optimization of C3-Alkenylation of (2*H*)-Indazole 1



entry	catalyst	oxidant	additive	solvent	time (h)	yield (%)
1	$Pd(OAc)_2$ (10%)	$Cu(OAc)_2$		xylene	24	70
2	$Pd(OAc)_2$ (10%)	CuO		xylene	18	44 (31)[a]
3	$Pd(OAc)_2$ (10%)	Ag_2CO_3		xylene	18	54 (23)[a]
4	$Pd(OAc)_2$ (10%)	$Cu(OAc)_2$	AcOH	xylene	18	78
5	$Pd(OAc)_2$ (10%)	$Cu(OAc)_2$	Ac_2O	xylene	18	73
6	$Pd(OAc)_2$ (10%)	$Cu(OAc)_2$	AcOH/Ac_2O	xylene	18	79
7	$Pd(OAc)_2$ (10%)	$Cu(OAc)_2$		dioxane	24	64
8	$Pd(OAc)_2$ (10%)	$Cu(OAc)_2$	AcOH	dioxane	18	75
9	$Pd(OAc)_2$ (10%)	$Cu(OAc)_2$	AcOH/Ac_2O	dioxane	18	51 (24)[a]
10	$Pd(OAc)_2$ (10%)	Ag_2CO_3	AcOH/Ac_2O	dioxane	18	88
11	$Pd(OAc)_2$ (5%)	Ag_2CO_3	AcOH/Ac_2O	dioxane	18	87
12	$Pd(OAc)_2$ (5%)	Ag_2CO_3	AcOH/Ac_2O	xylene	18	79
13	$Pd(OAc)_2$ (5%)	Ag_2CO_3	PivOH/Ac_2O	doxane	18	67
14	$Pd(OAc)_2$ (5%)	Ag_2CO_3	AcOH	dioxane	18	75
15	$Pd(OAc)_2$ (5%)	Ag_2CO_3	PhCOOH	dioxane	18	59
16	$Pd(OAc)_2$ (5%)	Ag_2CO_3	Ac_2O	dioxane	18	50 (17)[a]
17	$Pd(OAc)_2$ (5%)	AgOAc	AcOH/Ac_2O	dioxane	18	69
18	$Pd(OAc)_2$ (5%)	$AgNO_3$	AcOH/Ac_2O	dioxane	18	65
19	$Pd(OAc)_2$ (5%)	Ag_2CO_3	BQ/AcOH	dioxane	18	77
20	$Pd(OAc)_2$ (5%)	Ag_2CO_3	PhCOOH/AcOH	dioxane	18	61
21	Pd/C 5%	Ag_2CO_3	AcOH/Ac_2O	dioxane	18	56 (24)[a]
22	$Pd(PPh_3)_4$ 5%	Ag_2CO_3	AcOH/Ac_2O	dioxane	18	39 (36)[a]

[a]Amount of starting material **1** recovered.

18), the additive (Table 1, entries 19 and 20), or the catalyst (Table 1, entries 21 and 22) failed (Table 1, entries 13−23).

Under the best reaction conditions identified as follows, [5 mol % of $Pd(OAc)_2$, 2.5 equiv of Ag_2CO_3, 1 equiv of AcOH/Ac_2O in dioxane at 120 °C under argon], the scope and limitation of Pd-catalyzed direct alkenylation of (2*H*)-indazoles were examined. Various substituted indazoles **1** and **3a−h** were used as starting substrates in the presence of either acrylates, acrylamide, acrylonitrile, or vinylarenes as coupling partners. The treatment of indazole **1** in the presence of acrylates led to the expected products **4a−f** in very good isolated yields (77% to 93%) (Table 2). When *N*-*tert*-butylacrylamide was used as olefin, the corresponding alkenylated product **4g** was obtained in 75% yield. Moderate yields were observed when either styrene or 1-ethenyl-4-methoxybenzene was used. In these cases, the desired products **4h** and **4i** were isolated in 57% and 65% yield, respectively (Table 2). The use of acrylonitrile as coupling partner produced the alkenylated product **4j** in a moderate yield (Table 2). We then used substituted (2*H*)-indazoles as starting materials. The treatment of **3a−h** with ethyl acrylate under the optimized reaction conditions led to the expected products **4k−r** in yields ranging between 68% and 90% (Table 2).

Continuing our investigation of C−H/C−H activation of indazoles, under reaction conditions similar to those developed above, the regioselective C3-alkenylation of (1*H*)-indazole **5** was successfully achieved, producing the expected product **6** in 67% yield (Table 3, entry 1). Further modifications of the reaction parameters (e.g., oxidant and/or additive) did not lead to any significant improvement in the reaction yield (Table 3, entries 2−4).

Table 2. Scope and Limitation of the Oxidative Alkenylation of (2*H*)-Indazoles

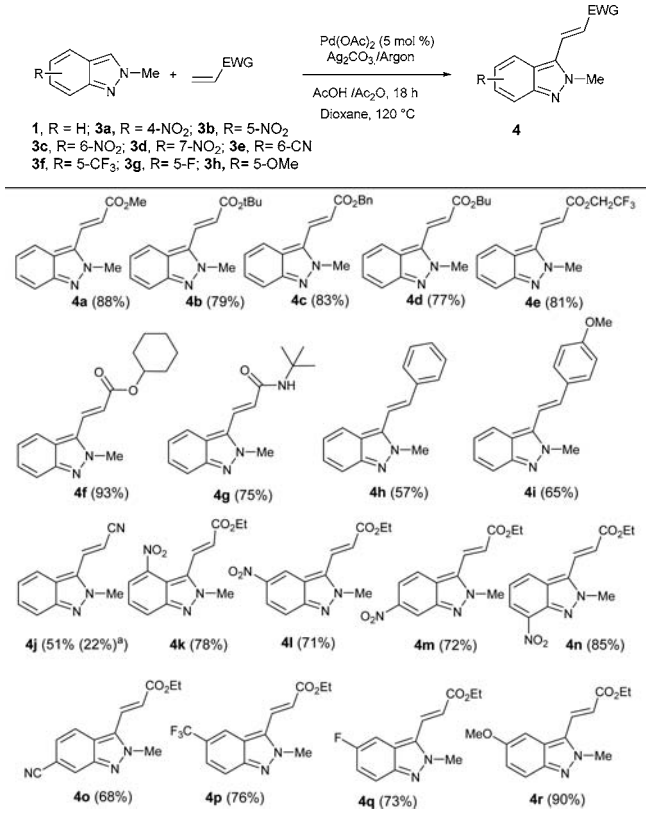


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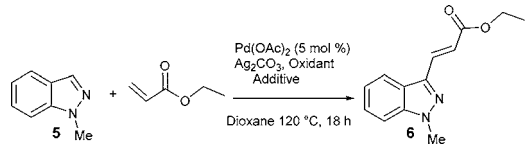
Table 3. Optimization of C3-Alkenylation of (1*H*)-Indazole 5

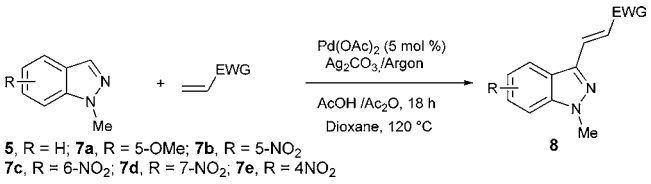


entry	oxidant	additive	yield (%)
1	Ag_2CO_3	AcOH/Ac_2O	67
2	$Cu(OAc)_2$	AcOH	0 (89)[a]
3	Ag_2CO_3	PhCOOH/AcOH	27 (41)[a]
4	Ag_2CO_3	BQ/AcOH	45 (23)[a]

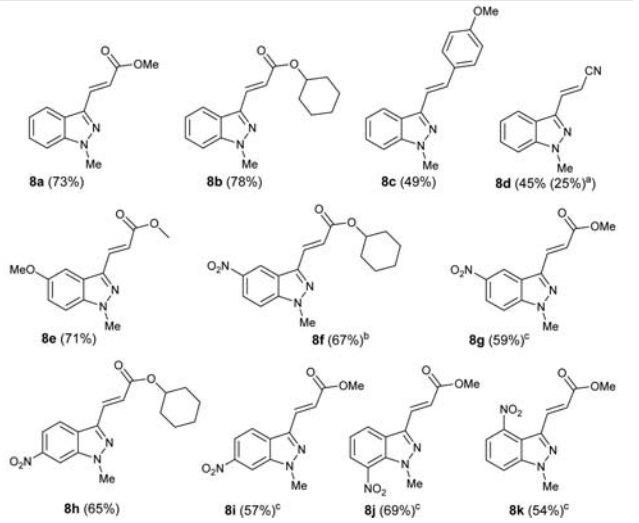
[a]Amount of starting material **5** recovered.

With the optimized reaction conditions in hand, we next explored the scope of the oxidative Heck-type reaction of (1*H*)-indazoles. In the case of nonsubstituted 1-methylindazole **5** treated by methyl acrylate, cyclohexyl acrylate, acrylonitrile, or 1-ethenyl-4-methoxybenzene, the desired C3-alkenylated products **8a–d** were obtained in moderate to good yields (45 to 78%, Table 4). Indazole containing a methoxy group at the 6-position

Table 4. Results of C3-Oxidative Alkenylation of (1*H*)-Indazoles 5 and 7a–e



5, R = H; **7a**, R = 5-OMe; **7b**, R = 5-NO_2
7c, R = 6-NO_2; **7d**, R = 7-NO_2; **7e**, R = 4NO_2



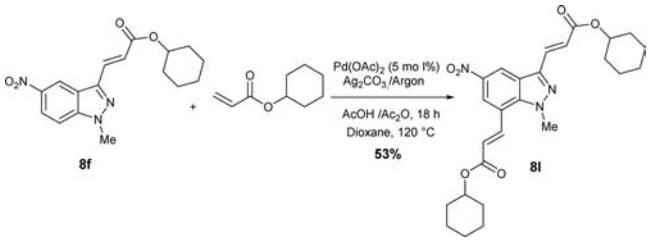
[a]Amount of starting material **5** recovered. [b]In this case, 17% of dialkenylated indazole **8l** was also isolated. [c]In this case, the reaction times were prolonged to 48 h.

(starting material **7a**) also underwent the alkenylation reaction with methyl acrylate to afford the expected product **8e** in 71% yield.

As we previously reported on the direct arylation of substituted indazoles containing electron-withdrawing groups on the six-membered ring,[14] a competition between C3- and C7-alkenylation occurred when 1-methyl 5-nitroindazole **7b** was treated by cyclohexyl acrylate, which led to two products, the C3-alkenylated product **8f** and the C3-/C7-dialkenylated product **8l** (Table 4). This phenomenon was not observed when 1-methyl 5-nitroindazole **7b** was treated by methyl acrylate. In this case, only the C3-alkenylated product **8g** was obtained. In addition, when 1-methyl-6-nitroindazole **7c** was treated with cyclohexyl acrylate we isolated only the C-alkenylated product **8h**. The treatment of either 1-methyl 6-nitroindazole **7c** or 1-methyl 7-nitroindazole **7d** by methyl acrylate led to the expected products **8i** and **8j** in 57 and 69% yield, respectively. Surprisingly, while the direct arylation of 4-nitroindazole **7e** gave only the C7-arylated product (see our previous work),[14] conversely, oxidative alkenylation gave exclusively the C3-alkenylated product **8k** in 54% yield.

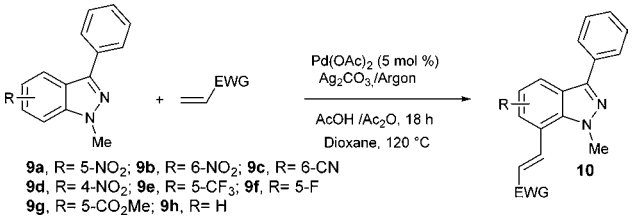
Very interestingly, when **8f** was treated with 3 equiv of cyclohexyl acrylate, the dialkenylated product **8l** was obtained in 53% yield (Scheme 1). Encouraged by this result, we decided to explore the C7-alkenylation of (1*H*)-indazoles.

Scheme 1. C7-Alkenylation of 3-Substituted (1*H*)-Indazole 8f

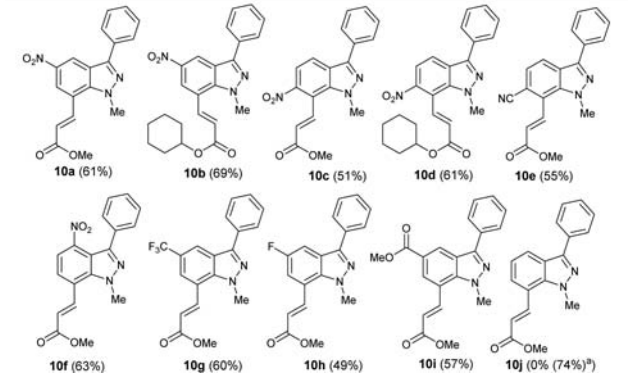


To explore the scope and limitation of this new C7-alkenylation reaction of (1*H*)-indazoles, 3-phenylated indazoles **9a–h** were prepared[14] and used as starting materials in the presence of either methyl acrylate or cyclohexyl acrylate as alkenylating agents. The reaction proceeded successfully, leading to the desired C7-alkenylated products **10a–h** in moderate to good yields (Table 5). The reactions required long reaction times (48 h), however, to achieve total conversion. As expected, no reaction was observed when 3-phenylindazole containing no

Table 5. Scope and Limitation of C7-Oxidative Alkenylation of 3-Phenyl-(1*H*)-indazoles 9a–h



9a, R= 5-NO_2; **9b**, R= 6-NO_2; **9c**, R= 6-CN
9d, R= 4-NO_2; **9e**, R= 5-CF_3; **9f**, R= 5-F
9g, R= 5-CO_2Me; **9h**, R= H



[a]Amount of starting material **9h** recovered.

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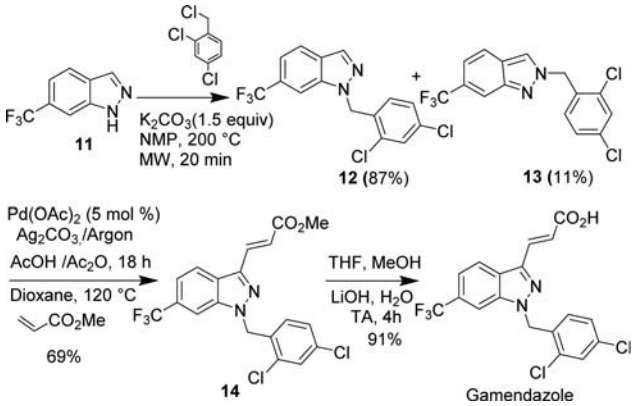
substituent on the six-membered ring **9h** was treated by acrylates; only the starting material was recovered in 74% yield.

Finally, we decided to apply our method to the synthesis of gamendazole, a drug candidate for male contraception, by using only three steps instead of the nine steps reported in the literature (Scheme 2).[7] The treatment of the commercially

Scheme 2. Synthesis of Gamendazole by C3-Oxidative Alkenylation of Indazole 11



available indazole **11** by 2,4-dichloro-1-(chloromethyl)benzene led to intermediate **12** in 87% yield; we also observed the formation of a byproduct **13** in 11% yield. Regioselective C3-alkenylation of **12** with ethyl acrylate under the optimized reaction conditions gave compound **14** in 69% yield. Finally, the treatment of **14** by LiOH·H_2O in a mixture of THF and MeOH led to gamendazole in 91% yield.

In conclusion, we have developed the first regioselective C3-oxidative alkenylation of both (1*H*)- and (2*H*)-indazoles. We have also applied the reaction conditions to the oxidative C7-alkenylation of 3-substituted (1*H*)-indazoles, which is also the first example of regioselective oxidative alkenylation of the six-membered rings in 6,5-heterocyclic systems without directing groups. Moreover, we highlighted the utility of our method by its application to the synthesis of the drug candidate gamendazole in only three steps.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02136.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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