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Rhenium- and Manganese-Catalyzed Selective Alkenylation of Indoles

Chengming Wang,[a] Magnus Rueping*[a,b]

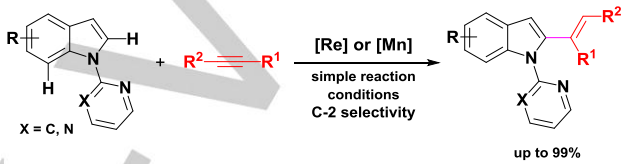
Abstract: An efficient rhenium-catalyzed regioselective C-H bond alkenylation of indoles is reported. The protocol operates well for internal as well as terminal alkynes, affording products in good to excellent yields. Furthermore, a manganese catalyzed, acid free, regioselective C2-alkenylation of indoles with internal alkynes is described. The directing groups can be easily removed after the reaction and the resulting products can be used as valuable building blocks for the synthesis of diverse heterocyclic compounds.

Introduction

Since the pioneering work of Murai and coworkers,[1] transition metal-catalyzed direct C-H bond functionalization,[2] which avoids the use of preactivated substrates such as haloarenes and stoichiometric amounts of organometallic reagents, has emerged as a powerful and versatile synthetic methodology in organic chemistry. Among the vast array of C-H bond transformations developed to date, alkenylation through C-H addition represents an important atom-economical reaction.[3,4] Precious late transition metals, such as Pd, Rh and Ru, are mainly used to attain these challenging transformations. In contrast, middle transition metals, such as rhenium,[5,6] or naturally abundant and inexpensive manganese,[7-9] have scarcely been explored towards this conversion.

Indoles and derivatives have attracted great attention due to their important biological and pharmaceutical activities and synthetic applications.[10,11] Thus, numerous methods have been developed for the regioselective synthesis of C2 and C3 functionalized indoles.[12] Compared to the well established indole C2-arylation, direct regioselective C2-alkenylation is less explored.[12c,d] In general, alkenes are used as reaction partners for the alkenylation of indoles.[13] When alkynes are employed, an external Brønsted acid is usually needed for protonolysis to afford the alkenylation products. Nevertheless, alkenylation through direct indolyl C-H bond addition to alkynes represents one of the most straightforward, highly efficient and atom-economical strategies. While several groups have independently reported on the alkenylation of indoles with internal alkynes, regioselective alkenylation of indoles using unactivated terminal alkynes has rarely been reported.[14,15]

Herein, we report a Re- and Mn-catalyzed regioselective and highly efficient C-H activation C2-alkenylation of indoles with internal as well as unactivated terminal alkynes. In the case of unactivated terminal alkynes, the anti-Markovnikov addition products are mainly obtained.



- Ligand and acid free
- Internal and terminal alkynes
- Highly regio- and stereoselectives
- Removable directing groups
- Useful functionalized heterocyclic products

Scheme 1. Rhenium and manganese catalyzed C-H activation of indoles.

Results and Discussion

Initially we selected *N*-(2-pyrimidinyl)indole (**1a**) and internal 1,2-diphenylacetylene (**2a**) as model substrates for our transformation with $ReBr(CO)_5$ as catalyst. Without additives, no product formation was detected (Table 1, entries 1 and 2). Next, different additives and solvents were tested, however no noticeable improvements were observed (Table 1, entries 3-6). To our delight, the desired product **3a** was obtained in 55% yield by raising the temperature to 130 °C (Table 1, entry 7). With Na_2CO_3 as additive, the product **3a** was obtained in 99% yield (entry 8).

With $MnBr(CO)_5$ as catalyst, we tested the influence of different solvents and THF proved to be the best reaction medium, providing the desired product **3a** in 68% yield (Table 1, entries 11-14). Evaluation of different additives revealed that additives are crucial for this transformation (Table 1, entries 15-20). While K_2CO_3 gave the product with a slightly lower yield, PPh_3 completely inhibited the reaction. On the other hand, applying Et_3N and NaOAc as additives, provided the product **3a** in 84 and 98% yield, respectively. Further extensive screening of various Mn-based catalysts revealed $MnBr(CO)_5$ as the best choice for our reaction (for details see Table S1 in Supporting Information). With the optimized reaction conditions in hand, we next examined the substrate scope for this transformations. Both electron-donating and electron-deficient substituted indoles worked well under Re- as well as Mn-catalysis to afford the corresponding products **3a-i** with good to excellent yields. It is interesting that 5-methyl carboxylate substituted indole gave only the related C2-alkenylated product **3g** with good yield, rather than the 4- or 6-alkenylated indole product, which means

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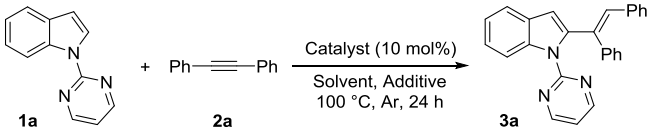
that, in our case, pyrimidyl is a better directing group compared to carboxylate. To our surprise, the 3-Me indole substrate **1j** is also tolerated in this transformation, affording the desired product **3j** with up to 81% and 99% yield, respectively, despite its steric hindrance. It is worth noticing that *N*-pyridinyl indole (**1k**) is also a good reaction partner for this transformation.

Table 1. Evaluation of the reaction conditions.[a]

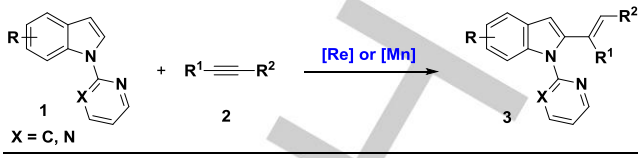


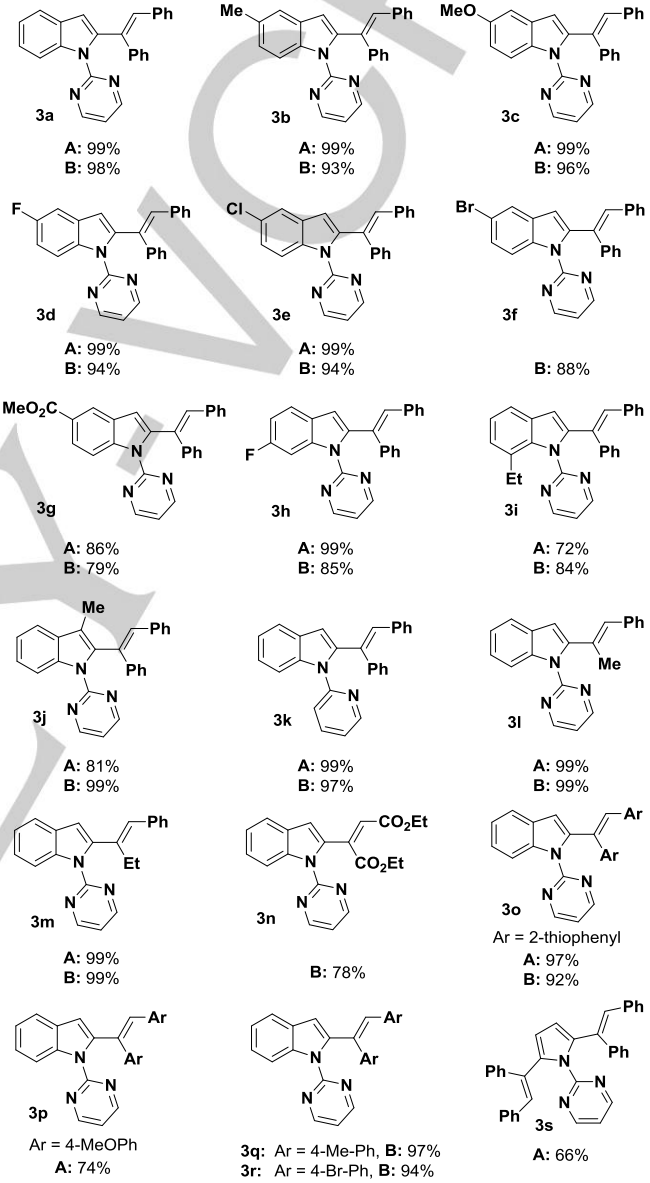
Entry[a]	Catalyst	Solvent	Additive	Yield (%)[b]
1	$ReBr(CO)_5$	THF	-	-
2	$ReBr(CO)_5$	Toluene	-	-
3	$ReBr(CO)_5$	THF	NaOAc	Trace
4	$ReBr(CO)_5$	MeCN	NaOAc	-
5[c]	$ReBr(CO)_5$	DMF	Na_2CO_3	-
6[c]	$ReBr(CO)_5$	Dioxane	Na_2CO_3	<5
7[d]	$ReBr(CO)_5$	Toluene	-	55
8[d,e]	$ReBr(CO)_5$	Toluene	Na_2CO_3	99
9[d,e]	$ReBr(CO)_5$	Toluene	CsOAc	<5
10[d-f]	$ReBr(CO)_5$	Toluene	Na_2CO_3	68
11	$MnBr(CO)_5$	MeCN	-	5
12	$MnBr(CO)_5$	THF	-	68
13	$MnBr(CO)_5$	DMF	-	Trace
14	$MnBr(CO)_5$	t-AmOH	-	14
15	$MnBr(CO)_5$	THF	PivOH	<5
16	$MnBr(CO)_5$	THF	K_2CO_3	57
17	$MnBr(CO)_5$	THF	PPh_3	-
18	$MnBr(CO)_5$	THF	Et_3N	84
19[g]	$MnBr(CO)_5$	THF	AgOAc	<5
20	$MnBr(CO)_5$	THF	NaOAc	98

[a] Reaction conditions for entries 1-10: **1a** (0.2 mmol, 1.0 equiv.), **2a** (1.5 equiv.), [Re] (10 mol%), additive (0.5 equiv.), solvent (2.0 mL), 100 °C, 24 h. Reaction conditions for entries 11-20: **1a** (0.15 mmol, 1.0 equiv.), **2a** (1.5 equiv.), [Mn] (10 mol%), additive (0.5 equiv.), solvent (1.0 mL), 100 °C, 70 h. [b] Yield after purification. [c] 0.3 equiv. additive. [d] 130 °C. [e] 2.0 equiv. additive. [f] 5 mol% [Re] was used. [g] 10 mol% AgOAc was used.

Various internal alkynes are also tolerated in this reaction, as illustrated by the obtained products **3l-s**, which greatly broadens the application of this reaction. For unsymmetrical alkynes **2** with R^1 = Me, Et and R^2 = Ph the reaction seems to be highly efficient and regioselective, as only one isomer was isolated (**3l,m**).

Table 2. Re- and Mn-catalyzed C-H alkenylation with internal alkynes.[a]

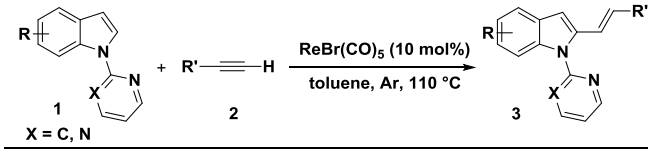


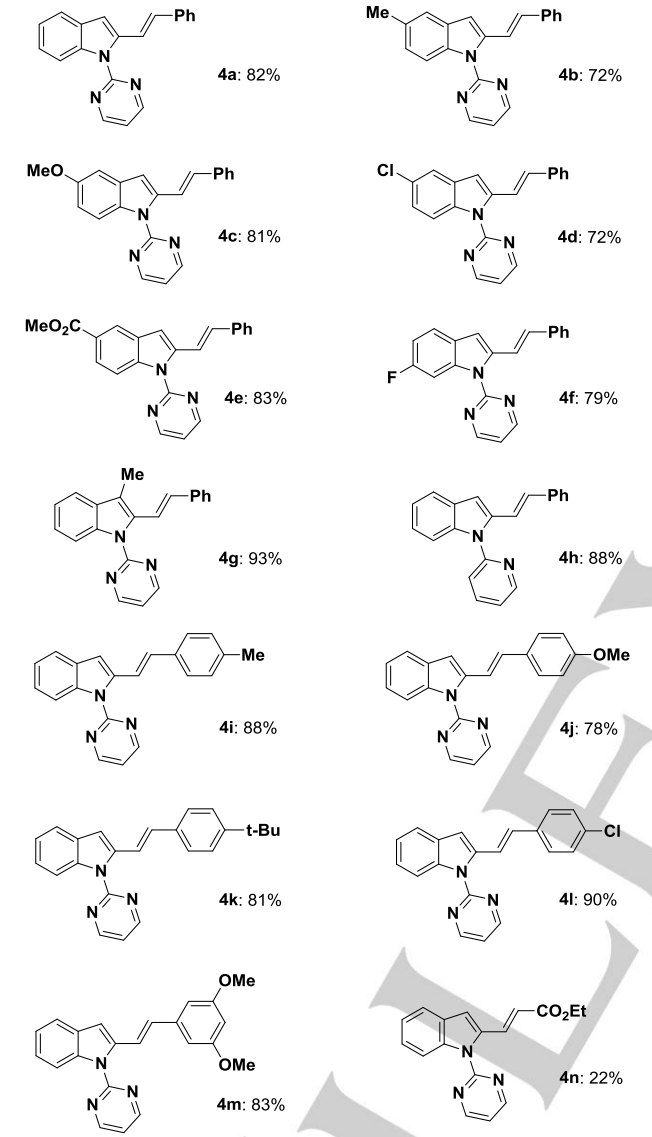


[a] Reaction conditions. **A**: **1** (0.2 mmol, 1.0 equiv.), **2** (1.5 equiv.), $ReBr(CO)_5$ (10 mol%), Na_2CO_3 (2.0 equiv.), toluene, 130 °C, Ar, 24 h. **B**: **1** (0.3 mmol, 1.0 equiv.), **2** (1.5 equiv.), [Mn] (10 mol%), NaOAc (0.5 equiv.), THF (1.5 mL), 100 °C, Ar, 70 h.

Interestingly, a pyrrole substrate reacted well in this reaction to produce the di-alkenylation product **3s** by using three equivalents of alkyne.

Table 3. Re-catalyzed C-H alkenylation with terminal alkynes.[a]

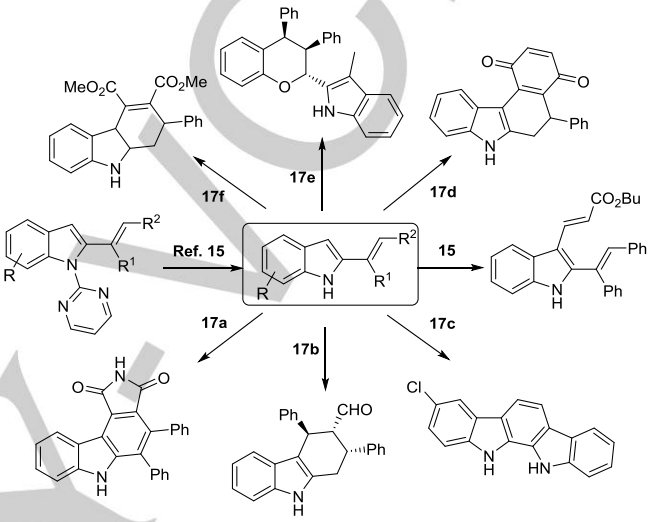




[a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (1.5 equiv.), $ReBr(CO)_5$ (10 mol%), Na_2CO_3 (2.0 equiv.), toluene, 110 °C, Ar.

Next, we focused our attention towards extending our protocol to terminal alkynes. Notably, by slightly modifying the standard conditions, terminal alkynes are also good reaction partners for this transformation. As illustrated in Table 3, use of various substituted electron rich as well as deficient indoles provided the desired products (Table 3, **4a-g**). As expected, *N*-pyridinyl indole is also effective for this transformation, affording the product **4h** in 88% yield. Different terminal aryl alkynes[16] are well tolerated in this reaction and the products **4i-m** were obtained in high yields. Finally, ethyl acrylate produced also the desired product **4n**, albeit with a low yield.

In addition, this method allows quick access to a number of functional heterocycles (Scheme 3). Firstly, the *N*-pyrimidinyl directing group can be easily removed to afford the *N*-H free indoles,[4i] which can be converted into several useful heterocycles via reported methods.[17]



Scheme 2. Diversity of the products.

Conclusions

In conclusion, we have reported a practical, highly efficient, and regioselective Re- and Mn-catalyzed C-H bond alkenylation of indoles through C-H bond activation and functionalization. The protocol is applicable to a wide range of indole derivatives and internal as well as terminal alkynes, affording products in good to excellent yields. Further exploration of the synthetic utility and the detailed reaction mechanism are currently in progress in our laboratories and will be reported in due course.

Experimental Section

General Procedure for Re(I)-Catalyzed C-H Bond Alkenylation with internal alkynes. *N*-2-pyrimidinyl indole **1** (0.20 mmol, 1.0 equiv.), $ReBr(CO)_5$ (10 mol%), Na_2CO_3 (0.40 mmol, 2.0 equiv.) and internal alkyne **2** (0.30 mmol, 1.5 equiv.) were weighed in a Schlenk tube. The reaction vessel was capped and subjected to three vacuum-purge/argon-flush cycles. Toluene (2.0 mL) was then added through the side-arm via syringe. The reaction was stirred under argon at 130 °C for 26 h. Upon complete consumption of the indole material, the reaction was cooled to room temperature. Volatile solvent and reagents were removed by rotary evaporation and the residue was purified by flash chromatography on silica gel using n-Hexane/EtOAc (20:1 to 8:1) to afford the desired product **3**.

General Procedure for Re(I)-Catalyzed C-H Bond Alkenylation with terminal alkynes. *N*-2-pyrimidinyl indole **1** (0.20 mmol, 1.0 equiv.) and $ReBr(CO)_5$ (10% equiv.), were weighed in a Schlenk tube. The reaction vessel was capped and subjected to three vacuum-purge/argon-flush cycles. Then terminal alkyne **2** (0.30 mmol, 1.5 equiv.) in toluene (1.0 mL) was then added through the side-arm via syringe. The reaction was stirred under argon at 110 °C for 48 h. Upon complete consumption of the indole material, the reaction was cooled to room temperature. Volatile solvent and reagents were removed by rotary evaporation and the residue was purified by flash chromatography on silica gel using n-Hexane/EtOAc (20:1 to 8:1) to afford the desired product **4**.

General Procedure for Mn(I)-Catalyzed C-H Alkenylation. *N*-2-pyrimidinyl indole **1** (0.30 mmol, 1.0 equiv.), $MnBr(CO)_5$ (10 mol%), NaOAc (0.15 mmol, 0.5 equiv.) and alkyne **2** (0.45 mmol, 1.5 equiv.) were weighed in a Schlenk tube. The reaction vessel was capped and subjected to three vacuum-purge/argon-flush cycles. THF (1.5 mL) was then added through the side-arm via syringe. The reaction was stirred under argon at 100 °C for 70 h. Upon complete consumption of the indole material, the reaction was cooled to room temperature. Volatile solvent and reagents were removed by rotary evaporation and the residue was purified by flash chromatography on silica gel using n-Hexane/EtOAc (20:1 to 8:1) to afford the desired product **3**.

Acknowledgements ((optional))

Acknowledgements Text.

Keywords: Rhenium • Manganese • C-H activation • alkenylation • indole

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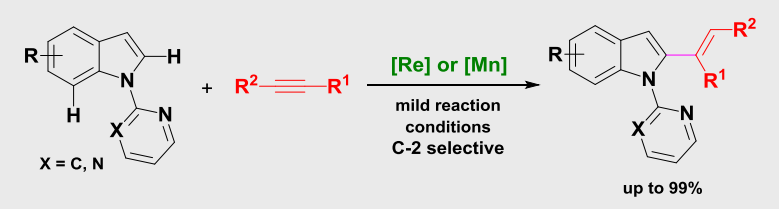

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