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Rhodium-catalyzed olefination of aryl tetrazoles *via* direct C–H bond activation†

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Rh(III)-catalyzed direct olefination reaction *via* aromatic C–H bond activation is described using tetrazole as the directing group. This reaction provides a straightforward way for the synthesis of *ortho*-alkenyl aryl tetrazoles. Various functional groups tolerate the reaction conditions and afford the corresponding products in moderate to excellent yields.

Over the past few decades, catalytic C–H functionalization has emerged as a powerful and atom-economic strategy for the elaboration of useful organic molecules.[1] Particularly, the utilization of transition metal catalysts together with directing groups provides an efficient way to facilitate the C–H bond cleavage and the C–C bond formation.[2] For the alkenylation of the C–H bond, namely the Fujiwara–Moritani reaction,[3] a large number of examples have been reported in recent years using diverse directing groups such as imino,[4] hydroxyl,[5] imidazolyl,[6] carbonyl,[7] oxazolyl,[8] amido,[9] pyridyl,[10] oxime ether,[11] carboxyl,[12] carbamate,[13] pyrazole,[14] guanidine,[15] *N*-nitroso, *etc*.[16]

Meanwhile, tetrazoles have received considerable attention owing to their wide applications in synthetic organic chemistry,[17] medicinal and pharmaceutical fields,[18] as well as materials science.[19] For example, biphenyl tetrazoles are well known intermediates for the synthesis of sartan family drugs such as losartan and valsartan. Shuman reported the direct *ortho*-lithiation of a phenyltetrazole followed by an electrophilic reaction to afford the 2-aryl substituted carbapenems (Fig. 1, A).[20] Yasuda described the synthesis of this angiotensin II antagonist *via* palladium-catalyzed coupling of an enol triflate with aryl boronic acids.[21] However, the prefunctionalization of the substrates as well as long steps limited their applications, especially in the large-scale synthetic process.

To the best of our knowledge, the tetrazole moiety chelating-assisted C–H functionalization of aromatics has not been fully explored.[22] Seki reported the arylation of aryl tetrazoles in the $RuCl_3/PPh_3$ system and this procedure was successfully applied to a practical synthesis of angiotensin II receptor blockers.[22a–c] Similarly, Ackermann developed a Ru(II)-catalyzed C–H arylation of 5-benzyl substituted aryl tetrazoles, which provided a step-economical access to valsartan.[22d] Based on these, we believed that the tetrazole moiety is not only important in lots of organic intermediates but also an useful directing group for further functionalization, which could afford compounds with potential bioactivities. Herein, we wish to report rhodium-catalyzed direct *ortho* C–H olefination reactions between aryl tetrazoles and alkenes (Scheme 1).

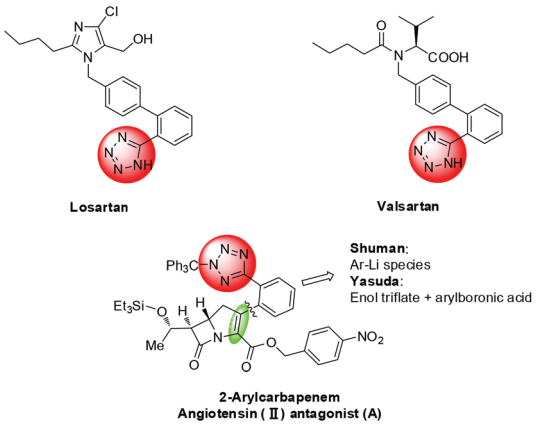
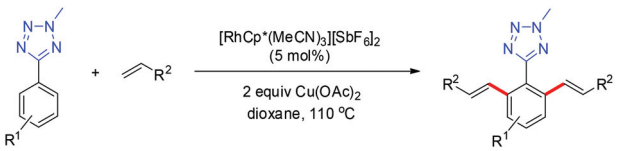


Fig. 1 Bioactivated compounds with the tetrazole moiety.

The reaction conditions were first explored by employing 2-methyl substituted aryl tetrazole (**1a**, 1.0 equiv.) and methyl acrylate (**2a**, 2.0 equiv.) as the substrates. The reaction did not



Scheme 1 Rhodium-catalyzed direct C–H olefination of aryl tetrazoles.

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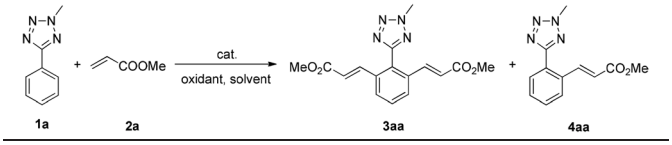
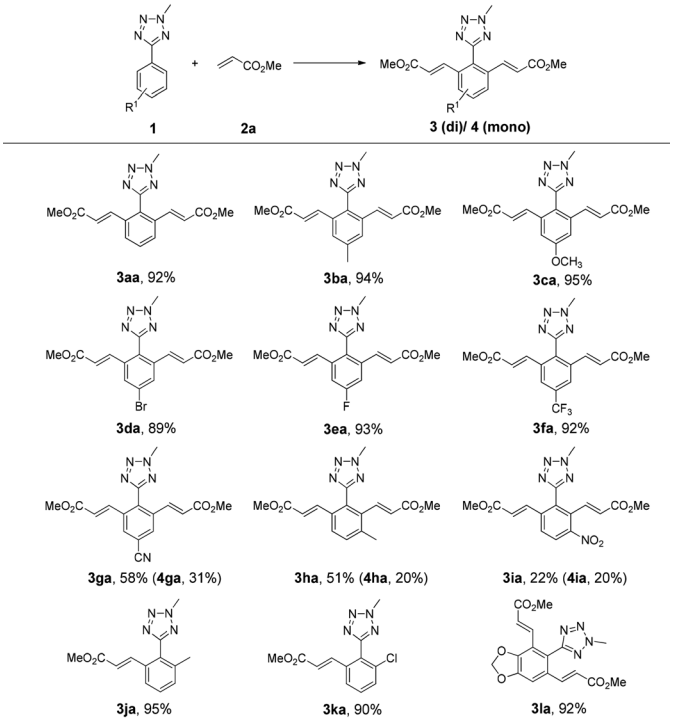
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Yield[b] (%) 3aa	4aa
1	$RhCl_3$	$Cu(OAc)_2$	DCE	0	0
2	$Rh(OOCCF_3)_2$	$Cu(OAc)_2$	DCE	0	0
3	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$	DCE	46	31
4	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	DCE	15	18
5[c]	$[RhCp^*Cl_2]_2/AgSbF_6$	$Cu(OAc)_2$	DCE	84	7
6	None	$Cu(OAc)_2$	DCE	0	0
7	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	DCE	90	Trace
8	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	DMF	Trace	16
9	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	Benzene	52	34
10	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	Dioxane	92	Trace
11	$RhCp^*L_3(SbF_6)_2$	—	Dioxane	13	27
12	$RhCp^*L_3(SbF_6)_2$	Ag_2CO_3	Dioxane	68	15
13	$RhCp^*L_3(SbF_6)_2$	B.Q.	Dioxane	55	19
14	$RhCp^*L_3(SbF_6)_2$	$PhI(OAc)_2$	Dioxane	51	22
15[d]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	Dioxane	85	Trace
16[e]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	Dioxane	62	23
17[f]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	Dioxane	92	Trace
18[g]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	Dioxane	88	Trace
19[h]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	Dioxane	72	16
20[i]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	Dioxane	44	30

[a] Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (5 mol%), oxidant (2 equiv.), solvent (1.5 mL), 110 °C, air, 12 h. For entries 6–18, L = CH_3CN. [b] Isolated yield. [c] $AgSbF_6$ (4 equiv.) was added. [d] $Cu(OAc)_2$ (1.5 equiv.). [e] 2.5 mol% catalyst was used. [f] Under O_2. [g] Under N_2. [h] 100 °C. [i] 1 equivalent of **2a** was used.

Table 2 Reaction scope for substituted tetrazoles[a]



[a] Reaction conditions: **1** (0.1 mmol), methyl acrylate **2a** (0.2 mmol), $[RhCp^*(MeCN)_3][SbF_6]_2$ (5 mol%), $Cu(OAc)_2$ (2 equiv.), dioxane (1.5 mL), 110 °C, air, 12 h.

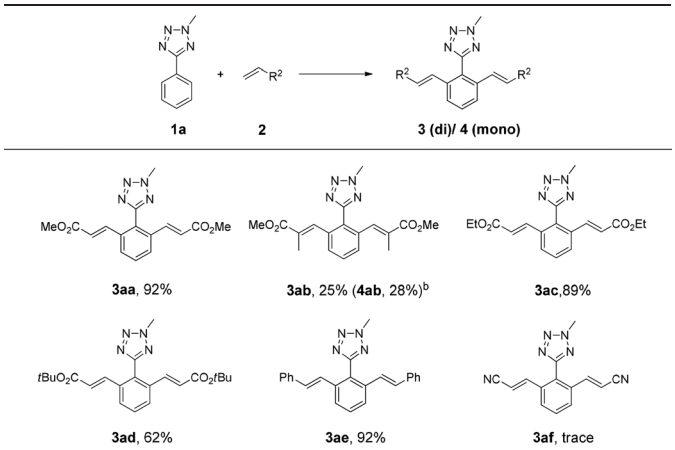
proceed in the absence of a catalyst. Other catalysts such as $RhCl_3$, $Rh(CF_3COO)_2$ and $[RhCp^*Cl_2]_2$ were also ineffective for this transformation. Treatment of **1a** and **2a** using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and $Cu(OAc)_2$ as the oxidant in dichloroethane gave the products **3aa** and **4aa** in 46% and 31% yield, respectively (Table 1, entry 3). Good yields were obtained (**3aa**, 84%; **4aa**, 7%) when the reaction was carried out using $[RhCp^*Cl_2]_2$ as the catalyst and $AgSbF_6$ as the additive (Table 1, entry 5). To our delight, switching the catalyst to $[RhCp^*(MeCN)_3][SbF_6]_2$ afforded the diolefinated product **3aa** in 90% yield and only a trace amount of **4aa** was detected (Table 1, entry 7).

With the promising preliminary result in hand, different solvents including DMF, dioxane and benzene were then evaluated (Table 1, entries 7–10). The reaction was sluggish in DMF, providing **4aa** as the major product in 16% yield. A total of 86% yield was observed using benzene as the solvent, albeit the di/mono selectivity was not satisfactory. Changing the solvent to dioxane gave the highest yield (92%) and selectivity (Table 1, entry 10). The substitution of $Cu(OAc)_2$ with other oxidants was investigated using dioxane as the solvent, although all modifications resulted in either a reduced yield or selectivity (Table 1, entries 11–14). Decreasing the amount of the catalyst as well as oxidant also led to a lower yield and selectivity (Table 1, entries 15 and 16). The reactions under either O_2 or N_2 gave similar results to that under air, while a lower reaction temperature slightly decreased the yields (Table 1, entries 17–19). Finally, decreasing the amount of **2a** to 1 equivalent led to a lower conversion, together with a mixture of mono- and di-olefinated products (Table 1, entry 20). Thus, the optimized reaction conditions were ultimately identified as 5 mol% of $[RhCp^*(MeCN)_3][SbF_6]_2$ and 2 equiv. of $Cu(OAc)_2$ in dioxane at 110 °C.

Various substituted tetrazoles were then subjected to the standard conditions to determine the scope and limitations of the present method as summarized in Table 2.

Generally, all the cases were *ortho*-selective and gave the desired products in moderate to excellent yields. For the *para*-substituted tetrazoles, a series of functional groups such as methyl, methoxy, bromo, fluoro, trifluoromethyl and cyano tolerate the reaction conditions, affording the corresponding products in high yields (**3aa**–**3ga**, 89–95%). Notably, nearly all the reactions gave di-olefinated products except the cyano-substituted tetrazoles which delivered a mono-olefinated product **4ga** in 31% yield. The steric hindrance had a little influence on the reaction. Interestingly, the *meta*-substituted tetrazoles gave di-olefinated products **3ha** and **3ia** in 51% and 20% yield, respectively. The corresponding mono-olefinated products **4ha** and **4ia**, however, were only obtained in 20% yields (the structures for **4ha** and **4ia** are provided in ESI†). The *ortho*-substituted tetrazoles worked well to provide the mono-olefinated product in excellent yields (**3ja**, 95%; **3ka**, 90%). Moreover,

Table 3 Olefination of **1a** with alkene derivatives[a]



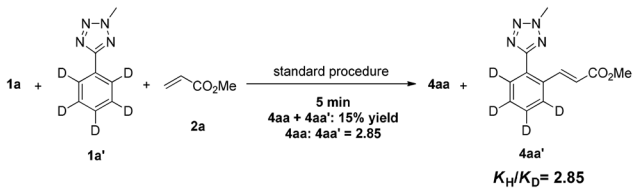
[a] Reaction conditions: **1a** (0.1 mmol), alkene **2** (0.2 mmol), $[RhCp^*(MeCN)_3][SbF_6]_2$ (5 mol%), $Cu(OAc)_2$ (2 equiv.), dioxane (1.5 mL), 110 °C, air, 12 h. [b] Methyl methacrylate amount was 0.3 mmol.

reactions of tetrazoles **3l** also proceeded smoothly to give the products **3la** in 92% yield.

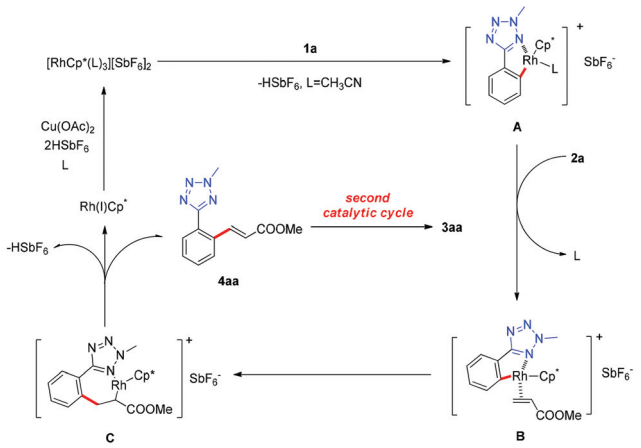
Next, we examined the substrate scope of alkene derivatives. As shown in Table 3, a series of olefins including methyl acrylate, methyl methacrylate, ethyl acrylate, *tert*-butyl acrylate and styrene readily participated in this transformation, providing the corresponding products in moderate to excellent yields (53–92%). All these reactions gave di-olefinated tetrazoles except methyl methacrylate, which afforded a mixture of di- and mono-olefinated tetrazoles in 25% and 28% yield, respectively. For acrylonitrile and other aliphatic alkenes, however, only a trace amount of the product was observed.

To gain more detailed information about the mechanism of the present reaction, the following experiment was conducted. A mixture of **1a** and **1a′** in a 1 : 1 ratio was used to determine the intermolecular kinetic isotope effect and significant kinetic isotope effect (k_H/k_D = 2.85) for the mono-olefinated product **4aa**/**4aa′** was observed (Scheme 2). This result revealed that the C–H bond cleavage was the rate-determining step.

On the basis of above results and literature information,[23–25] a plausible mechanism is proposed in Scheme 3. The first step involves the coordination of the tetrazole nitrogen of **1a** to the rhodium complex, which is followed by insertion of the metal into the *ortho* C–H bond. Then, coordination of **2a** to intermediate **A** gives the intermediate **B**, which is transformed into seven-membered rhodacycle **C** by migratory insertion of olefin.



Scheme 2 Kinetic isotope effect study.



Scheme 3 Proposed reaction mechanism.

Subsequently, β-hydride elimination and reductive elimination take place to release the monoolefinated product **4aa** and Rh(I)Cp*, and reoxidation of Rh(I) to Rh(III) by $Cu(OAc)_2$ to complete the first catalytic cycle. Since nitrogen atoms at 2 and 5 positions of tetrazole can form a rhodium complex with the catalyst, the di-olefinated product **3aa** is then obtained *via* a second same catalytic cycle.

Conclusions

In summary, we have developed an efficient Rh(III)-catalyzed C–H olefination reaction between aryl tetrazoles and alkenes. This procedure afforded the olefinated aryl tetrazoles in moderate to excellent yields. Various functional groups such as methyl, methoxy, bromo, fluoro, trifluoromethyl and cyano survived the reaction conditions. Importantly, this reaction provided a straightforward way for the synthesis of olefinated tetrazole derivatives which may be having some potential bioactivities.

Acknowledgements

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