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Rhodium(III)-catalyzed C–H functionalization of C-alkenyl azoles with sulfoxonium ylides for the synthesis of bridgehead *N*-fused [5,6]-bicyclic heterocycles

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ABSTRACT

The synthesis of bridgehead *N*-fused [5,6]-bicyclic heterocycles via rhodium(III)-catalyzed C–H functionalization of C-alkenyl azoles with sulfoxonium ylides is disclosed. Reactions proceeded in good to high yields for a range of aryl, heteroaryl and alkyl sulfoxonium ylides. In addition, 2-alkenyl imidazoles with different substitution patterns as well as C-alkenyl triazoles were effective inputs. The reaction could also be performed under straightforward bench top conditions.

1. Introduction

The [5,6]-bicyclic nitrogen heterocycle class is exemplified by the purine motif and is heavily represented in U.S. FDA approved drugs.[1] In recent years the sub-class of [5,6]-bicyclic heterocycles with a ring junction nitrogen have increasingly been investigated and have resulted in a number of approved drugs[2] as well as candidates in clinical trials.[3] Transition-metal-catalyzed C–H functionalization can provide an efficient approach for the convergent synthesis of nitrogen heterocycles from readily available starting materials.[4] Nevertheless, only a few approaches have been reported for the preparation of fused bicyclic heterocycles with ring-junction nitrogens. The most extensive related research has focused on C–H functionalization of C-aryl azoles for the synthesis of tricyclic and higher order aza-fused heterocycles.[5–13] Dong and co-workers reported the first examples of C–H functionalization for the preparation of ring-junction nitrogen [5,6]-bicyclic heterocycles by annulation of *N*-alkenyl imidazoles with internal alkynes.[14] More recently, we reported the C–H functionalization of C-alkenyl azoles with various electrophiles, including internal alkynes and diazoketones, for the synthesis of bridgehead *N*-fused bicyclic heterocycles (Scheme 1A).[15] While a variety of different products were obtained with high regioselectivity, in all cases, the methods required placement of carbon substituents at both the R^3 and R^4 positions.

Sulfoxonium ylides have been introduced as convenient carbene precursors[16] that are a safer alternative to analogous diazo compounds.[17] Recently these reagents have been shown to be particularly effective for the Rh(III)-catalyzed acylmethylation of arenes with the carbonyl functionality in the product available for further elaboration.[18,19] Herein, we report Rh(III)-catalyzed coupling of C-alkenyl azoles with sulfoxonium ylides with in situ cyclodehydration to give differently substituted bridgehead N-fused [5,6]-bicyclic heterocycles with complete regioselectivity (Scheme 1B).

2. Results and discussion

Preformed catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ in toluene at 120 °C provided effective conditions for annulation of C-alkenyl imidazole **1a** with sulfoxonium ylide **2a** (entry 1, Table 1). Lowering the temperature to 100 °C resulted in a slightly lower yield (entry 2). The optimal conditions were similarly effective for the electron rich sulfoxonium ylide **2b** (entry 3). When the stoichiometry of sulfoxonium ylide **2b** was reduced from 2.0 to 1.5 equiv, only a slight

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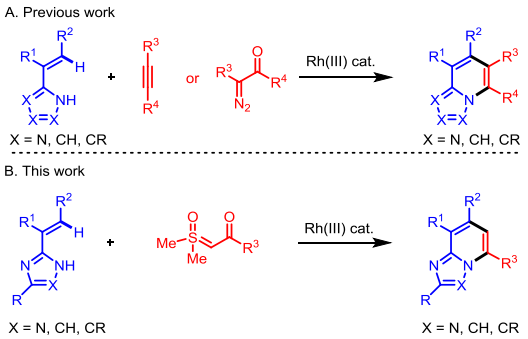
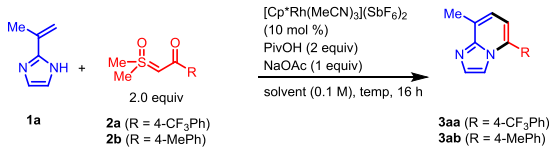


Scheme 1. Rh(III)-catalyzed synthesis of fused [5,6]-bicyclic heterocycles from C-alkenyl azoles.

Table 1
C–H functionalization of **1a** and **2**.[a]



Entry	Ylide	Solvent	Temp (°C)	Variation	Yield %[b]
1	**2a**	toluene	120	none	73 (71)[c]
2	**2a**	toluene	100	none	61
3	**2b**	toluene	120	none	68 (69)[c]
4	**2b**	toluene	120	**2** (1.5 equiv)	67
5	**2b**	toluene	120	no NaOAc	29
6	**2b**	toluene	120	no PivOH	33
7	**2b**	toluene	120	No Rh	0
8	**2b**	toluene	120	$[Cp^*RhCl_2]_2$[d]	65
9	**2b**	toluene	120	$[Cp^*RhCl_2]_2$[e]	45
10	**2b**	toluene	120	0.2 M	45
11	**2b**	dioxane	120	none	45
12	**2b**	DCE	120	none	53
13	**2b**	MeCN	120	none	50
14	**2b**	xylenes	120	bench-top	65

[a] Conditions: **1a** (0.10 mmol), **2** (0.20 mmol), 0.1 M, 16 h.
[b] Yield determined by ^{1}H NMR relative to 1,3,5-trimethoxybenzene as external standard.
[c] Isolated yield of a 0.30 mmol scale (see Fig. 1).
[d] $[Cp^*RhCl_2]_2$ (5 mol %) and $AgSbF_6$ (20 mol %).
[e] $[Cp^*RhCl_2]_2$ (5 mol %) only.

reduction in yield was observed (entry 4). The importance of both PivOH and NaOAc were documented by the lower yields that were obtained in the absence of these additives (entries 5 and 6, respectively). As expected, the Rh(III) catalyst was essential to the reaction (entry 7). While the cationic Rh(III) catalyst could be prepared in situ without any effect on the reaction yield (entry 8), when the chlorides were not abstracted from $[Cp^*RhCl_2]_2$, a lower yield was observed (entry 9). Doubling the concentration also resulted in a lower yield (entry 10). The reaction was dependent on solvent with dioxane, DCE and acetonitrile all resulting in lower yields (entries 11–13). The optimal reaction temperature of 120 °C required that a pressurized reaction vessel be used when toluene was used as the reaction solvent. Therefore, xylenes, with a boiling point higher than 120 °C was evaluated, with bench-top set up, and provided a comparable reaction yield (entry 14).

With optimized reaction conditions in hand, the scope for the sulfoxonium ylide input was next explored. A variety of aryl ylides with different electronic properties coupled equally well under the standard conditions to afford products **3aa**–**ad** in good yields

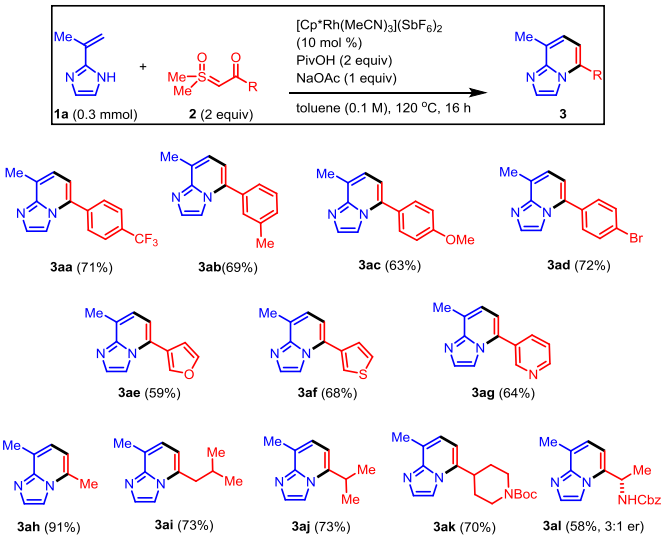


Fig. 1. Sulfoxonium ylide scope in Rh(III)-catalyzed C–H functionalization of C-alkenyl imidazoles.

(63–72%). Both electron rich and deficient heteroaryl ylides were also effective coupling partners as exemplified for products **3ae**–**ag**. A number of alkyl ylides, including methyl (**2h**), β-branched (**2i**), and α-branched (**2j**–**l**) were also effective inputs and provided good to excellent yields of the products **3ah**–**al**. Under the reaction conditions, chiral product **3al** is obtained in reasonable yield though with significant epimerization (3:1 er).[21] Notably, the tertiary *N*-Boc piperidine- and secondary *N*-Cbz-containing adducts, **3ak** and **3al**, respectively, establish that *N*-protected amine functionality can readily be introduced to provide versatile handles for further elaboration.

We next turned our attention to different C-alkenyl azoles (Fig. 2). Imidazoles **1b**–**e** bearing a range of substituents at different sites on the alkene and/or imidazole ring all effectively coupled with both aryl and alkyl ylides (**3ba**–**ek**). Only the unsubstituted C-vinyl imidazole **1f** was found to be ineffective (**3fk**). The C-alkenyl

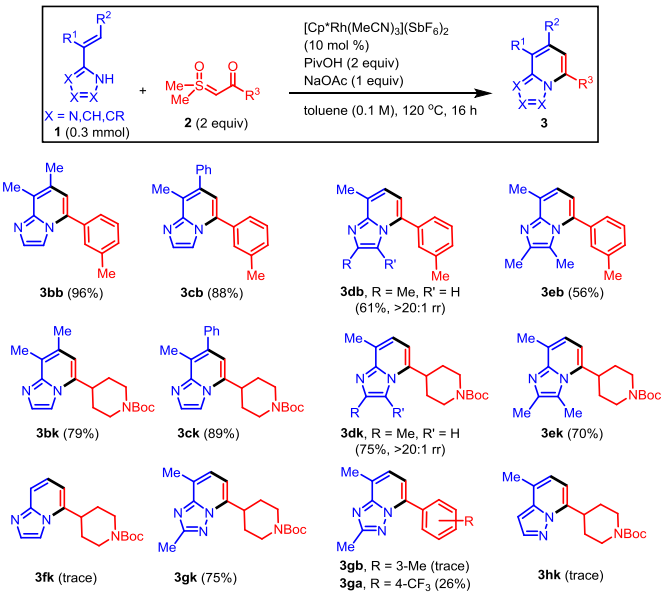


Fig. 2. C-alkenyl azole scope in Rh(III)-catalyzed C–H functionalization with sulfoxonium ylides.

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