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Synthesis of Pyrroles through Rhodium(III)-Catalyzed Reactions of Allylamines and Alkenes

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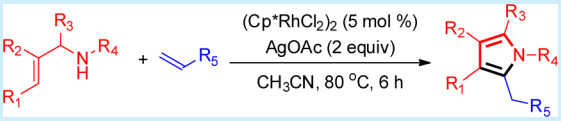
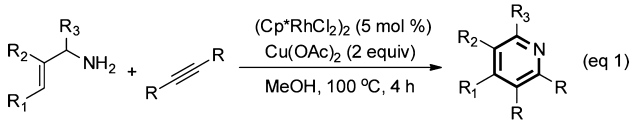
Supporting Information

ABSTRACT: Pyrrole derivatives are generated in reactions of allylamines with alkenes that are promoted by a Rh(III) catalyst in the presence of AgOAc. This process, which involves chelation assisted C−H bond activation and *N*-annulation, is applied to a three step synthesis of Zomepirac.

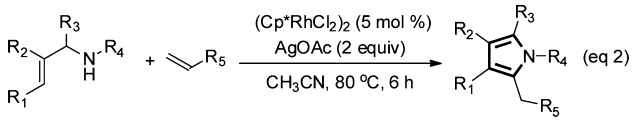


Much attention has been given recently to transition metal catalyzed reactions that are applicable to the synthesis of heterocyclic compounds such as isoquinolines, pyridines, isocumarins, isoquinolones, and isoindoles.[1] Among these heterocycles, pyrrole derivatives are notable because of their wide use in constructing various natural products and bioactive molecules.[2] In this regard, several transition-metal catalyzed processes, which produce pyrroles that employ enamines,[3] enamides,[4] and oximes,[5] have been developed.[6]

Recently, we described a method for the facile synthesis of pyridines from allylamines and internal alkynes that utilizes Rh(III) and Cu(II), eq 1.[7] This process can be employed to



This work



prepare multiply-substituted pyridines from simple allylamine derivatives. During the course of these studies, we observed that electron-withdrawing group substituted alkenes participate in modified Rh(III) and Ag(I) promoted reactions with allylamines to form highly substituted pyrroles, eq 2. Below, we describe the results of an effort that has led to the development of the new method for facile synthesis of pyrrole derivatives and its application to the preparation of the bioactive compound, Zomepirac.[8]

N-Phenethyl-*N*-2-phenyl-1-prop-2-enyl amine (**1a**) was chosen as a model allylamine substrate to explore the new process and to uncover optimized reaction conditions (Table 1). Reaction of **1a** with ethyl acrylate (**2a**) was carried out in the presence of $[Cp^*RhCl_2]_2$ (**3a**, 5 mol %) and AgOAc (**4a**, 2 equiv) at 80 °C for 6 h. This process produces pyrrole **5a** in 86% yield (entry 1). Notably, the reaction does not take place in the absence of **4a** (entry 6) and an optimized yield is obtained when 2 equiv of **4a** are used (entries 1−5).

Among other oxidants, $Cu(OAc)_2$ (**4b**, 77%) and $CuSO_4$ (**4c**, 40%) display lower activity than does AgOAc, and $CuCl_2$ (**4d**), $K_2S_2O_8$ (**4e**), OXONE (**4f**), and benzoquinone (**4g**) do not have any activity (entries 7−12). In addition, the results show that Rh(I) complex **3c** does not promote the reaction and that the use of the cationic Rh(III) complex **3b** does not lead to an improved yield of the pyrrole forming reaction (entries 13−14). Finally, of the various solvents tested, CH_3CN was found to be the best one for this process (entries 1, 15−19).

The allylamine and alkene scope of the pyrrole forming process was explored. As can be seen by viewing the results displayed in Table 2, reaction of **1a** with alkenes **2a**−**2e** under optimized reaction conditions produces the corresponding pyrroles **5a**−**5e** in good to moderate yields (entries 1−5). Steric bulkiness of the alkoxy group in acrylic esters, as in *n*-butyl acrylate (**2b**)[9] and *tert*-butyl acrylate (**2c**), does not affect the efficiency of the process (entries 2−3). Reactions of nitrogen containing alkenes such as acrylonitrile (**2d**) and *N*,*N*-dimethyl acrylamide (**2e**) form the respective pyrroles **5d** and **5e** in 34 and 59% yield, which are lower than reactions of acrylic esters (entries 4−5). Additionally, nonelectron withdrawing group substituted alkenes such as styrene, 1-hexene, 1-(vinyloxy)-butane, and (allyloxy)benzene do not participate in this pyrrole forming process. The reaction is also very sensitive for steric hindrance of substituent on alkene. Methyl-substituted acrylates at alpha or beta position did not give any product.[10]

To obtain insight of the reactivity of *N*-phenethylallylamines **1** containing different allyl substituents, reactions with **1b**, **1c**, **1d**, and **1e** were explored (entries 6−9). Reaction of **1b** with **2a** was found to take place to give pyrrole **5f** in 15% yield, while that of **1c** with **2a** occurs in 75% yield to form **5g**. However, reactions of 3-methyl-substituted *N*-phenethylallylamine **1d** and *N*-phenethylallylamine (**1e**) with **2a** do not take place. The results suggest that the position of the substituent in the allylamine is an important factor governing the efficiency of the process.

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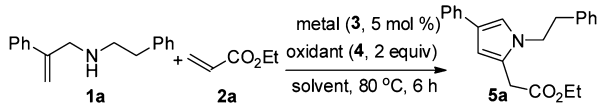
Table 1. Optimization of the Rh(III) Catalyzed Pyrrole Synthesis Method[a]



entry	metal	oxidant	solvent	yield (%)[b]
1	$[Cp^*RhCl_2]_2$ (**3a**)	AgOAc (**4a**, 2.0 equiv)	CH_3CN	86
2	**3a**	**4a** (2.5 equiv)	CH_3CN	46
3	**3a**	**4a** (1.5 equiv)	CH_3CN	59
4	**3a**	**4a** (1.0 equiv)	CH_3CN	42
5	**3a**	**4a** (0.5 equiv)	CH_3CN	14
6	**3a**		CH_3CN	0
7	**3a**	$Cu(OAc)_2$ (**4b**)	CH_3CN	77
8	**3a**	$CuSO_4$ (**4c**)	CH_3CN	40
9	**3a**	$CuCl_2$ (**4d**)	CH_3CN	0
10	**3a**	$K_2S_2O_8$ (**4e**)	CH_3CN	0
11	**3a**	OXONE (**4f**)	CH_3CN	0
12	**3a**	BQ(**4g**)	CH_3CN	0
13	$[Cp^*Rh(MeCN)_3SbFe]_2$ (**3b**)	**4a**	CH_3CN	68
14	$(Ph_3P)_3RhCl$ (**3c**)	**4a**	CH_3CN	0
15	**3a**	**4a**	*t*-BuOH	36
16	**3a**	**4a**	DMF	53
17	**3a**	**4a**	AcOH	42
18	**3a**	**4a**	$ClCH_2CH_2Cl$	63
19	**3a**	**4a**	*o*-xylene	18

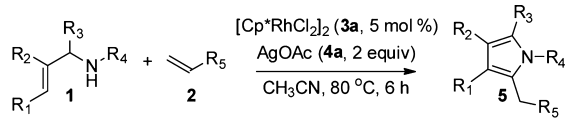
[a]Unless otherwise noted, reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), **3** (5 mol %), and **4** (0.4 mmol) in 0.1 mL of solvent at 80 °C. [b]All yields are isolated yields.

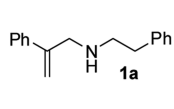
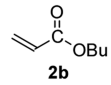
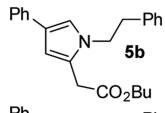
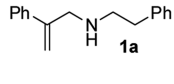
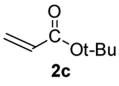
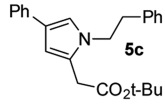
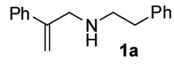
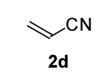
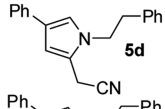
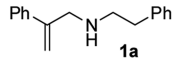
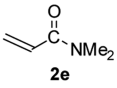
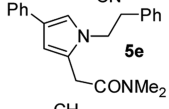
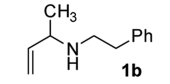
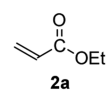
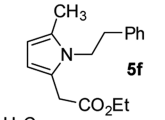
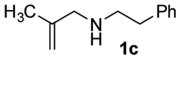
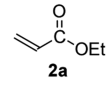
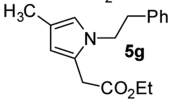
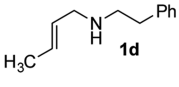
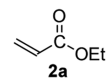
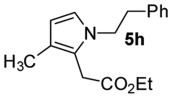
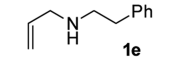
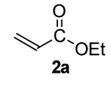
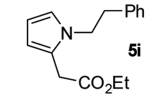
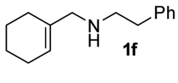
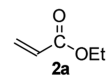
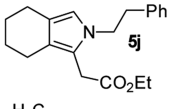
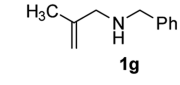
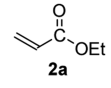
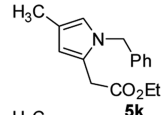
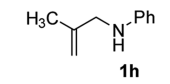
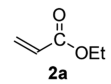
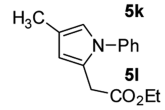
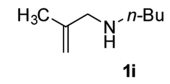
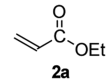
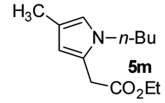
Specifically, it appears that allylamines containing a 2-substituent react with highest efficiencies. Interestingly, reaction of the 2,3-disubstituted analogue **1f** leads to formation of corresponding pyrrole **5j** in 29% yield (entry 10). Finally, the *N*-phenylallylamine **1h** participates in a lower yielding reaction with **2a** than does its *N*-*n*-butyl analogue (entries 12−13).

Based on the above result, it is possible to propose the mechanism depicted in Scheme 1 for the reaction of **1a** with **2a**. In this pathway, chelation assisted cleavages of allylic C−H bond and N−H bond in allylamine takes place initially to form five-membered rhodacycle **6a**. Carbometalation of **6a** with ethyl acrylate (**2a**) gives seven-membered rhodacyclic complex **7a**, which undergoes β-H elimination to generate **8a**. Intramolecular Michael type reaction of **8a** leads to formation of complex **9a**, which upon β-H elimination followed by olefin isomerization of the resulting **10a** affords pyrrole **5a**[11] along with Rh(III)-H_2. Reduction of **2a** with Rh(III)-H_2 gives the Rh(I) species,[9] which is oxidized by AgOAc (**4a**) to regenerate the active Rh(III) catalyst.

Next, reactions of primary allylamine with various alkenes were examined. The results (Table 3) show that reaction of 2-methylallylamine (**1j**) with ethyl acrylate (**2a**) in the presence of **3a** and **4a** at 80 °C for 6 h generates ethyl 3-(2-(2-ethoxy-2-oxoethyl)-4-methyl-1*H*-pyrrol-1-yl)propanoate (**5n**) in 77% yield (entry 1). Moreover, reactions of **1j** with *n*-butyl **2b** and *t*-butyl acrylate (**2c**) give the corresponding pyrroles **5o** and **5p** in 66% and 63% respective yields. However, reaction of **1j** with acrylonitrile (**2d**) results in only low yielding (8%) formation of the pyrrole **5q** (entry 4).

Table 2. Secondary Allylamine and Alkene Substrate Scope of Pyrrole Synthesis Method[a]



entry	amine	olefin	product	yield (%)[b]
1	**1a**	**2a**	**5a**	86
2	 **1a**	 **2b**	 **5b**	67
3	 **1a**	 **2c**	 **5c**	77
4	 **1a**	 **2d**	 **5d**	34
5	 **1a**	 **2e**	 **5e**	59
6	 **1b**	 **2a**	 **5f**	15
7	 **1c**	 **2a**	 **5g**	75
8[c]	 **1d**	 **2a**	 **5h**	0
9[d]	 **1e**	 **2a**	 **5i**	0
10	 **1f**	 **2a**	 **5j**	29
11	 **1g**	 **2a**	 **5k**	66
12	 **1h**	 **2a**	 **5l**	12
13	 **1i**	 **2a**	 **5m**	54

[a]Unless otherwise noted, reactions were carried out with **1** (0.2 mmol), **2** (0.4 mmol), **3a** (5 mol %), and **4a** (0.4 mmol) in 0.1 mL of CH_3CN at 80 °C. [b]All yields are isolated yields. [c]91% of the 1,4-addition product is formed. [d]65% of the 1,4-addition product is formed.

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Scheme 1. Proposed Mechanism of the Pyrrole Forming Reaction

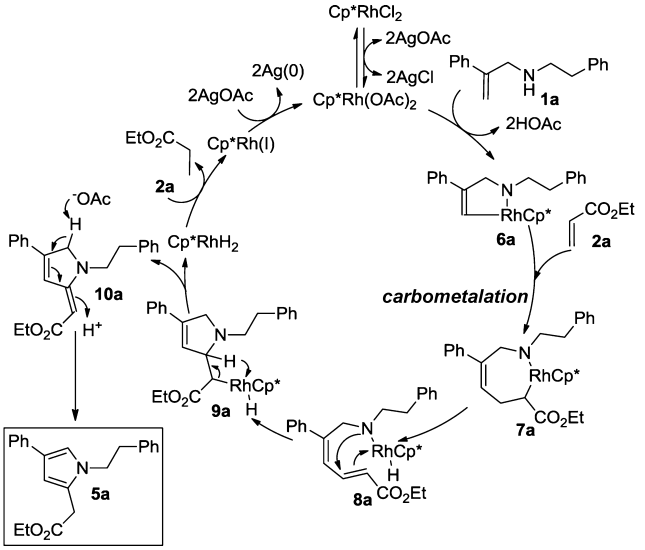
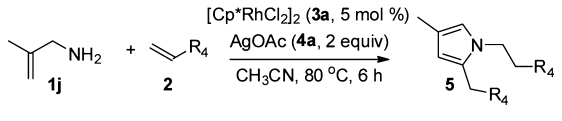


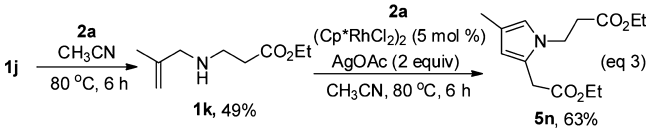
Table 3. Primary Allylamine Scope of the Pyrrole Forming Reaction[a]



entry	olefin	product	yield (%)[b]
1	2a	5n	77
2	2b	5o	66
3	2c	5p	63
4	2d	5q	8

[a]Unless otherwise noted, reactions were carried out with **1j** (0.2 mmol), **2** (0.4 mmol), **3a** (5 mol %), and **4a** (0.4 mmol) in 0.1 mL of CH_3CN at 80 °C. [b]All yields are isolated yields.

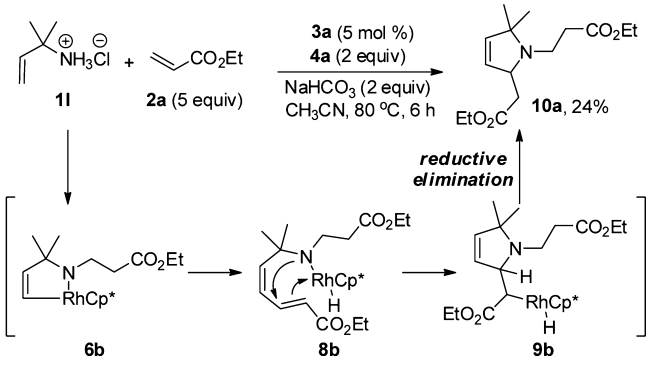
In reactions of the primary allylamine **1j**, *N*-alkylated pyrroles are produced exclusively. To gain information about the origin of these products, two separate reactions were performed, eq 3.



Reaction of 2-methylallylamine (**1j**) with ethyl acrylate (**2a**) in the absence of **3a** and **4a** at 80 °C for 6 h was found to produce ethyl 3-((2-methylallyl)amino)propanoate (**1k**) in 49% yield. Furthermore, reaction of secondary allylamine **1k** with **2a** in the presence of **3a** and **4a** produces pyrrole **5n** in 63% yield.

The HCl salt of α,α-dimethylallylamine **1l**[12] was utilized in the reaction to gain further mechanistic insight. Specifically, **1l** was found to react with **2a** using the standard catalytic system in the presence of $NaHCO_3$ to give 3-pyrroline **10a** in 24% yield (Scheme 2). Pyrroline **10a** is formed in this process by reductive

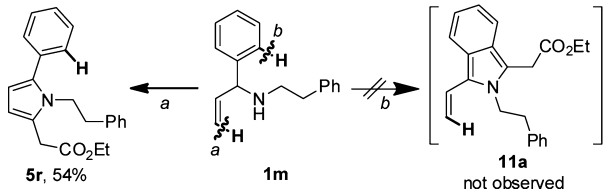
Scheme 2. Reaction of α,α-Dimethylallyl Ammonium Chloride



elimination of intermediate Rh complex **9b**.[13] Note that the presence of gem-dimethyl substitution in **9b** prevents olefin isomerization. This result confirms that the reaction in Scheme 1 takes place through intermediate **9a**.

The reaction of 1-phenylallylamine **1m**, which has both benzylamine and allylamine groups (Scheme 3), was explored.[14]

Scheme 3. Comparison of Reactivity of Allylic and Benzylic C−H Bonds[a]



[a]Reaction is carried out with **1m** (0.2 mmol), **2a** (0.4 mmol), **3a** (5 mol %), and **4a** (0.4 mmol) in 0.1 mL of CH_3CN at 80 °C.

We observed that reaction of **1m** with **2a** in the presence of **3a** and **4a** leads to exclusive formation of ethyl 2-(1-phenethyl-5-phenyl-1*H*-pyrrol-2-yl)acetate (**5r**) in 54% yield without any formation of isoindole **11a**. This result shows that the sp^2-vinyl C−H bond is more reactive than sp^2-aromatic C−H bond in this process.

The applicability of Rh(III) catalyzed pyrrole forming method was demonstrated by its use in the total synthesis of the Zomepirac (**5u**), which has been shown to have antipyretic activity (Scheme 4). In the first step of the three-step route, reaction of *N*-2-dimethylprop-2-en-1-aminium chloride (**1n**) with **2a** in the presence of **3a**, **4a**, and $NaHCO_3$ at 80 °C for 12 h produces pyrrole **5s** in 51% yield. Reaction of **5s** with 4-chlorobenzoyl chloride in the presence of DBN (15 mol %) in toluene at 115 °C for 4 h then generates ethyl 2-(5-(4-chlorobenzoyl)-1,4-dimethyl-1*H*-pyrrol-2-yl)acetate (**5t**) in 30% isolated yield.[15] Finally, hydrolysis of **5t** gives Zomepirac (**5u**) in 66% yield.

In the effort described above, we developed a new procedure for the synthesis of multiply-substituted pyrroles from allylamines and alkenes. The process, promoted by a combination of

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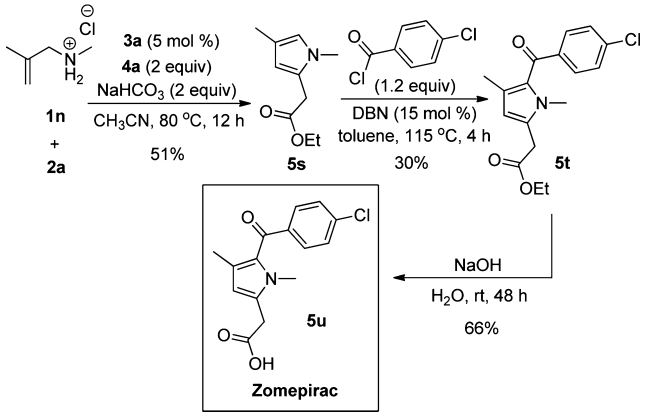
Scheme 4. Total Synthesis of Zomepirac



Rh(III) and Ag(I), takes place through Rh(III) promoted vinyl C−H bond activation of the allylamine substrate followed by carbometalation of the alkene. Reactive substrates are limited to secondary amine with allyl groups and alkenes possessing electron-withdrawing groups. Finally, the utility of this method was demonstrated by its application to the three-step total synthesis of bioactive Zomepirac.

■ ASSOCIATED CONTENT

Supporting Information

Compound characterization data, ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01811.

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Notes

The authors declare no competing financial interest.

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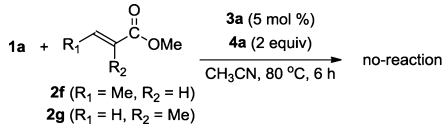
(9) Due to volatility of ethyl propionate, the reaction was carried out with butyl acrylate (Table 2, entry 2), and 45% G.C. yield of butyl propionate was obtained.

(10) The reaction of **1a** with methyl but-2-enoate (**2f**) or methyl methacrylate (**2g**) in the standard reaction condition did not take place.



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(12) The primary amine is readily generated *in situ* from the HCl salt **1l** by addition of $NaHCO_3$.

(13) Stable aromatic pyrrole can be generated from intermediate complex **9a** in Scheme 1 through β-hydride elimination, while gem-dimethyl substitution in complex **9b** prevents formation of pyrrole by olefin isomerization. As a result, direct reductive elimination in complex **9b** occurs.

(14) Recently, it was reported that the reaction of α,α-dimethyl benzylamine with butyl acrylate in the presence of Rh(III)/Cu(II) system results in formation of butyl 2-(3,3-dimethylisoindolin-1-yl) acetate. In this system, only aryl C−H bonds can be activated by Rh(III). For an example of this work, see: Suzuki, C.; Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Adv. Synth. Catal.* **2014**, *356*, 1521.

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