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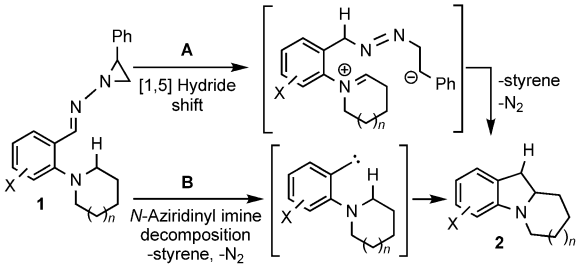
N-Fused Indolines through Non-Carbonyl-Stabilized Rhodium Carbenoid C–H Insertion of *N*-Aziridinyl Imines

Stuart J. Mahoney and Eric Fillion*[a]

Metal-catalyzed methods of functionalizing C–H bonds have seen incredible advancements in recent times, allowing for new retrosynthetic disconnections to otherwise unreactive bonds and executing transformations with high chemo-, regio-, and stereocontrol.[1] A more established area of functionalizing C(sp^3)–H bonds has been rhodium-catalyzed C–H insertions from carbonyl-stabilized diazo substrates, which has reached a level at which even intermolecular C–H insertions with high enantioselectivity have been achieved.[2] Key to the success of the intermolecular methodology was shifting the focus from studying ligand alterations to substrate design, specifically in moving to donor–acceptor carbenoids.[2a–b] Despite the progression, analogous C–H insertions of carbenoids without an acceptor (primarily carbonyl functionalities) have remained elusive due to the inherent difficulties with controlling selectivity of the reactive species. Alternatively, a rapidly developing redox-neutral method of functionalizing C(sp^3)–H bonds has been catalyzed variants of the *tert*-amino effect,[3] which now includes unactivated alkyne and allene acceptors,[4] tertiary aliphatic hydride donors,[5] domino reactions,[6] and enantioselective protocols.[7] Seeking to develop a methodology to give direct access to the privileged *N*-fused indoline scaffold[8] through C(sp^3)–H bond functionalization, we turned our attention to *N*-aziridinyl imines **1** (Eschenmoser hydrazones),[9] which potentially offered two distinct reactivity modes to achieve the desired transformation (Scheme 1), namely, hydride acceptor and decomposition to a benzylic carbene.[10] By virtue of the proposed [1,5] hydride shift/cyclization mechanism (Scheme 1, path A), the benzylic carbon would act as a geminal acceptor/donor (effectively a 1,1-dipole) instead of the typical vicinal acceptor/donor; the net result would be the formation of a five-membered ring as opposed to the six-membered ring created with traditionally employed acceptors.[11–12] Also, cognizant of the ability of the *N*-aziridinyl imine to function as a carbene precursor (Scheme 1, path B) a competing pathway that could lead to *N*-fused indoline **2** had to be considered.[13]



Scheme 1. General strategy.

In this manuscript, we report a general catalytic protocol of non-carbonyl-stabilized rhodium carbenoid C–H insertions enabling rapid synthesis of *N*-fused indolines and complex heterocycles. The ability of hydrazone **1a** to cyclize to tricycle **2a** through C(sp^3)–H bond functionalization was first examined (Table 1). Upon screening Lewis and Brønsted acids, only varying amounts of starting material and decomposition were observed. However, when heating the reaction ($\geq$70 °C) in the absence of a promoter, the carbene pathway was evident by the formation of the desired product **2a** (by C–H insertion) along with aldehyde **3a**, cyclopropanes **4a**,[14] and dimerization products (azine **5a** and alkenes **6a**; Table 1, entry 1). It was then found that the cyclopropanes could be selectively formed (**4a**, *trans*/*cis* ratio of 1.6:1) by intermolecular scavenging of the carbene intermediate upon addition of an excess of styrene (Table 1, entry 2). Optimistic about the possibility of mediating the carbene reaction[15] with rhodium,[16–17] a catalyst screen was performed. It was gratifying to see that the product distribution changed significantly to predominantly form the C–H insertion product (Table 1, entry 3) in contrast to a recent report of tosyl hydrazone decomposition, which exclusively formed alkenes through dimerization.[13e] Steric effects of dirhodium(II) carboxamidates proved to be beneficial (Table 1, entry 4 versus entries 5 and 6). Additional experiments with [Rh_2(cap)$_4$] (cap = caprolactamate) probing higher dilution, increased catalyst loading, and slow addition of the substrate resulted in negligible improvement in formation of the C–H insertion product **2a** (Table 1, entries 7–9). The catalyst of choice was determined to be [Rh_2(5*S*-MEPY)$_4$] (5*S*-MEPY = methyl-2-oxopyrrolidine-5(*S*)-carboxylate) on the basis of its slight superiority in terms of selectivity for C–H insertion and yield (Table 1, entry 6, 51 %), albeit affording racemic product.[18–19] Since this

[a] S. J. Mahoney, Prof. Dr. E. Fillion
Department of Chemistry, University of Waterloo
200 University Avenue West, Waterloo, Ontario
Canada N2L 3G1 (Canada)
Fax: (+1) 519-746-0435
E-mail: efillion@uwaterloo.ca

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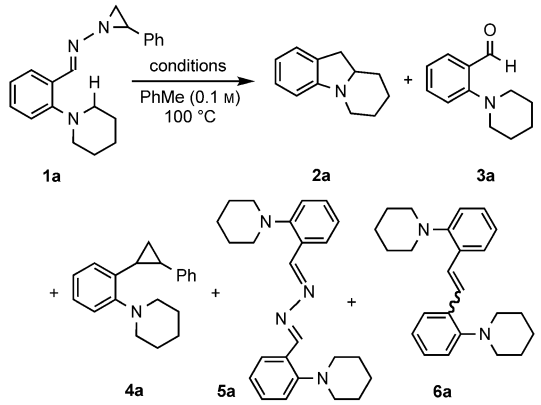
Table 1. Evaluation of reaction parameters.



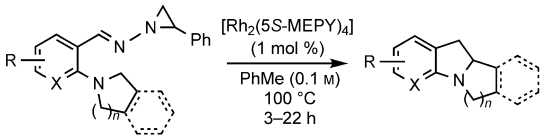
Entry	Conditions	t [h]	Ratio[a] **2a/3a/4a/5a/6a**
1	–	5	24:5:64:4:3
2	styrene (10 equiv)	4	0:0:100 (78%):0:0
3	$[Rh_2(OAc)_4]$ (1 mol%)	5	81:5:0:14:0
4	$[Rh_2(acam)_4]$ (1 mol%)	5	46:4:35:2:13
5	$[Rh_2(cap)_4]$ (1 mol%)	5	93 (49%):4:0:3:0
6[b]	$[Rh_2(5S\text{-MEPY})_4]$ (1 mol%)	5	95 (51%):4:0:1:0
7[c]	$[Rh_2(cap)_4]$ (1 mol%)	5	93 (43%):4:0:3:0
8	$[Rh_2(cap)_4]$ (2 mol%)	5	96 (51%):2:0:2:0
9[d]	$[Rh_2(cap)_4]$ (1 mol%)	17	89 (40%):7:0:4:0

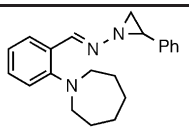
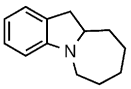
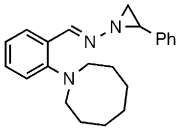
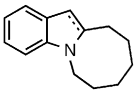
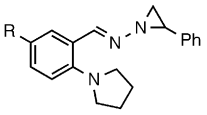
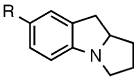
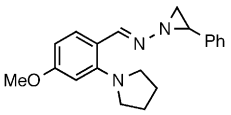
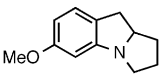
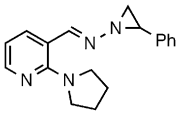
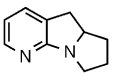
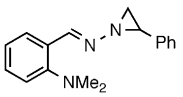
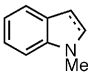
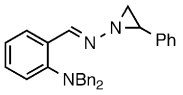
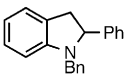
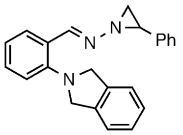
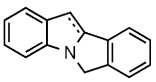
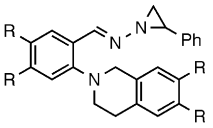
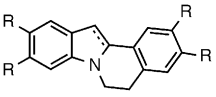
[a] Determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures; values in parentheses correspond to isolated yield of respective component after chromatography. [b] Enantiomeric ratio of 54:46 determined by chiral HPLC on Chiralpak OD-H column, see the Supporting Information for details. [c] PhMe (0.05 M). [d] Syringe pump addition of **1a** over 9 h. acam = acetamide.

promising result was already competitive or an improvement to most of the known alternative methods of forming related *N*-fused indolines,[13,20–24] which include tosylhydrazone decomposition in the presence of base,[13] radical cyclization onto indoles,[20] intramolecular benzyne trapping,[21] [1,6] hydride shift/cyclization,[22] intramolecular palladium-catalyzed reactions,[23] and aryl trifluoromethyl activation,[24b] the scope of the present rhodium carbenoid reaction was further investigated (Table 2). Alternative cyclic amine ring sizes all yielded superior results (Table 2, entries 1–3). The reaction also proceeded in moderate yields with a sampling of electron-rich and electron-deficient aromatics (Table 2, entries 4–7). In addition, insertion into 1° and 2° C–H bonds of acyclic amines was also successfully realized (Table 2, entries 8–9). Furthermore, tetracyclic *N*-fused indolines were also amenable to synthesis and found to readily undergo oxidation to the indole (Table 2, entries 10–12). Complete regioselective insertion into the benzylic C–H bond was obtained in the formation of the dibenzopyrrocolines (Table 2, entries 11 and 12), of which the latter contains the oxygenated core of the natural product cryptaustoline and related alkaloids.

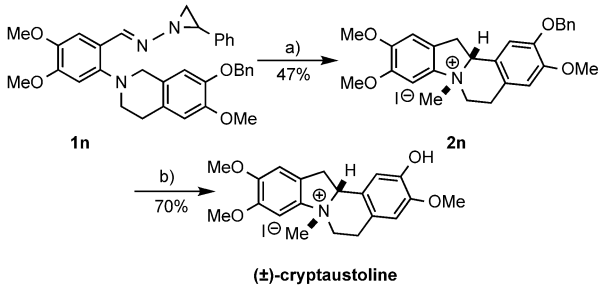
Having successfully executed a facile synthesis of model compound **2m**, an expedient total synthesis of (±)-cryptaustoline was pursued (Scheme 2).[25] Under the optimized reaction conditions, readily obtained precursor **1n** gave the desired *N*-fused indolinium **2n** as a single regioisomer in moderate yield following direct methylation of the crude product to minimize the aforementioned facile oxidation. The remaining two steps to complete the total synthesis were per-

Table 2. Substrate scope.



	Substrate **1**	Product **2**	Yield [%][a]
1		**1b** 	**2b** 84
2		**1c** 	**2c** 65 (14)
			
3	R = H	**1d** R = H	**2d** 74
4	R = NO_2	**1e** R = NO_2	**2e** 83
5	R = OMe	**1f** R = OMe	**2f** 79
6		**1g** 	**2g** 68
7		**1h** 	**2h** 66
8		**1i** 	**2i** 50 (4)
9		**1j** 	**2j** 68
10		**1k** 	**2k** 33 (17)
			
11	R = H	**1l** R = H	**2l** 56 (17)
12[b]	R = OMe	**1m** R = OMe	**2m** 53 (22)

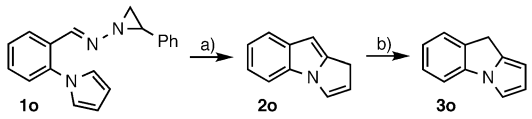
[a] Isolated yields of the indoline and indole (in parentheses) after chromatography; indolines were found to be racemic by chiral HPLC analyses, see the Supporting Information for details. [b] Reaction was performed under Ar.



Scheme 2. a) 1) $[Rh_2(5S\text{-MEPY})_4]$ (1 mol%), PhMe (0.1 M), 100 °C, under Ar; 2) MeI (excess), MeOH, 23 °C. b) 1) HCl (12 M), PhH, 100 °C; 2) KI (excess), EtOH, 75 °C.

formed according to Kametani's procedure,[21b] which consisted of benzyl deprotection under acidic conditions followed by counterion exchange to give (±)-cryptaustoline.

An extension of the developed reaction conditions was demonstrated in which pyrrole substrate **1o** reacted smoothly in the presence of catalyst to give **3o** in high yield, following facile isomerization of initially formed **2o** (Scheme 3).[26–27]



Scheme 3. a) $[Rh_2(5S\text{-MEPY})_4]$ (1 mol%), PhMe (0.1 M), 100 °C; b) silica gel, CH_2Cl_2 (0.1 M), 23 °C (83% over two steps).

In conclusion, a direct entry into *N*-fused indolines that culminated in an expedient total synthesis of racemic cryptaustoline has been described. This synthesis was found to be dependent on the ability of a rhodium carboxamidate catalyst to mediate the formation of the non-carbonyl-stabilized carbenoid. Future efforts will be directed at extending the scope of the reaction and transformations of *N*-aziridinyl imines under rhodium catalysis.

Experimental Section

Compound **1a** (305 mg, 1.00 mmol, 1 equiv) and toluene (10 mL, 0.10 M) were placed into 20 mL sample vial with a magnetic stirrer bar and stirred at 23 °C, until the mixture became homogenous (≈1 min). Complex $[Rh_2(5S\text{-MEPY})_4]$ (7.7 mg, 0.010 mmol, 2 mol% Rh) was added, and then the vial was immersed into a preheated 100 °C oil bath. The reaction progress was monitored by TLC (EtOAc/hexanes, 1:5), and after 5 h the crude reaction mixture was passed through a thin pad of silica gel (washed with EtOAc) and concentrated. A ^{1}H NMR spectrum of the crude product was recorded to determine the selectivity. Then the mixture was purified by flash chromatography (SiO_2, CH_2Cl_2/hexanes, 1:9) to afford *N*-fused indoline **2a** (88 mg, 0.51 mmol, 51%).

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Keywords: carbenoids · C–H insertion · hydrazones · nitrogen heterocycles · rhodium

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