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A study of Heck cyclization reactions to form phenanthridine ring systems

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Abstract

A survey of conditions for the palladium catalyzed intramolecular Heck cyclization of protected amines has shown that the Herrmann–Beller palladacycle can be exploited under 'cationic' conditions to provide a robust and rapid route (<2 h) to the synthesis of single double bond isomer phenanthridines in excellent yield (76–99%). In addition, the same cyclization can be performed under 'neutral' conditions to provide phenanthridines with a double bond isomer profile suitable for exploitation in diversity-based applications. We have also shown that the highly reactive $(^{t}Bu_3P)_2Pd$ catalyst can induce cyclization at low temperatures (≤50 °C), giving similar results to the 'neutral' conditions, and offering an alternative pathway for sensitive substrates.

Keywords: Phenanthridines; Heck reaction; Natural product scaffold

1. Introduction

The phenanthridine framework **1** lies at the heart of a number of natural products including the Amaryllidaceae alkaloids such as the antiviral lycorine **2**;[1,2] and the Papaveraceae benzophenanthridine alkaloids such as the tubulin polymerization inhibitor chelidonine **3**[3] and isochelidonine **4** (Fig. 1).[4] These, and the closely related class of phenanthridones, are known to exhibit diverse biological activities,[5] and thus present excellent targets for natural product scaffold-based libraries.[6] Whilst construction of the phenanthridone core, which lies at the heart of the antibiotic pancratistatin, has received considerable attention,[5a,b] the synthesis of phenanthridines is comparatively unstudied.

We were attracted to a Heck cyclization-based approach to the phenanthridine framework as there is good precedent for *cis*-stereocontrol in formation of the 6,6-ring junction in related phenanthridone systems.[7] However, we were concerned that the conditions reported were potentially limiting in a library-based approach to the phenanthridine core due to the lengthy reaction times (typically 24–48 h) and high temperatures (typically 110–160 °C) required for the cyclization reaction. Our initial aims were thus twofold to develop conditions, which might overcome these practical problems, whilst at the same time promoting the cyclization of a range of functionalized amine precursors to allow access to a diverse library based upon the phenanthridine core unit.

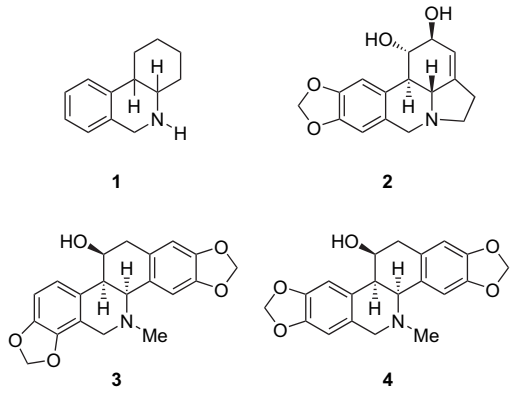

Figure 1. Phenanthridine alkaloid natural products.

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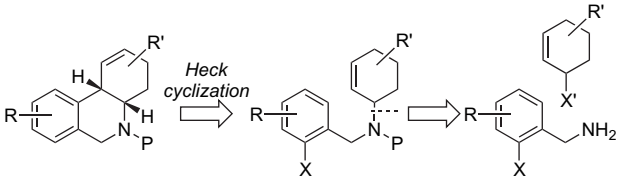
2. Results and discussion

2.1. Catalyst screening studies

To find conditions, which might be applied to the rapid synthesis of a phenanthridine library using the Heck reaction (Scheme 1), we first surveyed a range of standard catalysts. Sulfonamide **5a** (P=SO_2Me, Table 1) was found to be readily accessible through alkylation of commercially available 2-bromobenzylamine with 3-bromocyclohexene, followed by protection as the methanesulfonamide (84% yield over two steps). It provided an excellent substrate for catalyst screening studies (Table 1).



Scheme 1. A Heck cyclization-based retrosynthetic analysis of a phenanthridine library.

Using $Pd(OAc)_2/PCy_3$ under standard conditions (Table 1, entries 1–3), the intramolecular Heck cyclization of **5a** was found to proceed to completion rapidly. In related intramolecular Heck cyclization reactions of benzamides, a range of double bond isomers have been reported, including the bridgehead $\Delta^{10b,1}$ (**6a**), $\Delta^{1,2}$ (**7a**) and $\Delta^{2,3}$ (**8a**) isomers.[8,9] In this study, none of the bridgehead double bond isomer was formed, and the *cis* $\Delta^{1,2}$ isomer (**7a**) was observed as the major product,[10] along with trace amounts of the $\Delta^{2,3}$ (**8a**) and $\Delta^{3,4}$ (**9a**) double bond isomers.[11] Investigation of a range of bases at the optimum reaction temperature (140 °C) showed that DIPEA gave comparable results to those obtained in the presence of $MeNCy_2$, however, Et_3N, K_2CO_3 and 2,6-lutidine gave lower conversion levels (entries 4–7). We were pleased to observe that a switch in solvent from DMA to DMF (entry 8) resulted in similar or even enhanced reactivity with almost total conversion in only 35 min. However, at the elevated reaction temperatures required to ensure complete conversion (140–160 °C), we encountered serious problems with reproducibility, which we ascribed to catalyst decomposition and the formation of inert palladium black.[12] The capricious nature of this catalyst system led us to investigate other possible palladium sources.

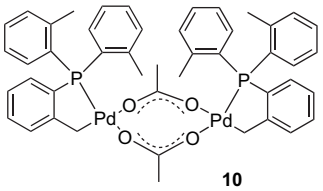
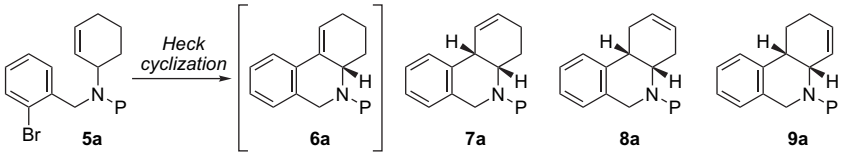


Figure 2. Herrmann–Beller palladacycle.

The Herrmann–Beller palladacycle (**10**, Fig. 2) is well-known as a highly effective source of Pd(0) for the arylation of alkenes.[13] Its reactivity at elevated temperatures has been attributed to a slow release of Pd(0) into the reaction medium, thus maintaining a constant level of the active catalytic species throughout the reaction.[14] Its use also has precedent in intramolecular cyclization reactions.[15] The application of **10** as a Pd(0) source in conjunction with the optimum base $MeNCy_2$ gave relatively rapid cyclization at a range of temperatures (130–150 °C), but led to a diminished selectivity for the $\Delta^{1,2}$ double bond isomer (entries 9–11). With the

Table 1
Catalyst screening for the intramolecular Heck cyclization reaction of sulfonamide **5a** (P=SO_2Me)



Entry	Catalyst[a]	Base (equiv)	T (°C)	t (min)	Solvent	Conversion[b] (%)	Ratio (**7a/8a/9a**)
1	$Pd(OAc)_2/PCy_3$	$MeNCy_2$ (4)	130	70	DMA	99	77:14:9
2	$Pd(OAc)_2/PCy_3$	$MeNCy_2$ (4)	140	60	DMA	99	96:2:2
3	$Pd(OAc)_2/PCy_3$	$MeNCy_2$ (4)	150	30	DMA	98	95:3:2
4	$Pd(OAc)_2/PCy_3$	Et_3N (4)	140	70	DMA	58	90:2:8
5	$Pd(OAc)_2/PCy_3$	DIPEA (4)	140	35	DMA	98	92:5:3
6	$Pd(OAc)_2/PCy_3$	K_2CO_3 (4)	140	40	DMA	87	55:27:18
7	$Pd(OAc)_2/PCy_3$	2,6-Lutidine (4)	140	—	DMA	—	—
8	$Pd(OAc)_2/PCy_3$	$MeNCy_2$ (4)	140	35	DMF	95	94:5:1
9	Herrmann–Beller (**10**)	$MeNCy_2$ (4)	130	360	DMF	85	39:38:23
10	Herrmann–Beller (**10**)	$MeNCy_2$ (4)	140	180	DMF	98	44:31:25
11	Herrmann–Beller (**10**)	$MeNCy_2$ (4)	150	110	DMF	88	52:16:32
12	Herrmann–Beller (**10**)	AgF (1)	140	180[c]	DMF	76	65:23:12
13	Herrmann–Beller (**10**)	Ag_3PO_4 (1)	140	120	DMF	99	67:18:15
14	Herrmann–Beller (**10**)	Ag_2CO_3 (1)	140	70	DMF	99	85:13:2

[a] [5 mol % Pd(0) source]/[10 mol % ligand].
[b] Conversion was determined through analysis of the ^{1}H NMR of the crude reaction mixture.
[c] No significant change was observed after 180 min, even on leaving reaction for 24 h.