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Copper-Catalyzed Ring Expansion of Vinyl Aziridines under Mild Conditions

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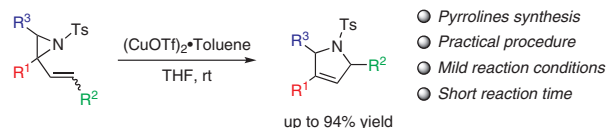Jean-Marc Campagne*

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- Pyrrolines synthesis
- Practical procedure
- Mild reaction conditions
- Short reaction time

up to 94% yield

In expression of our respect to Professor Barry M. Trost on the occasion of his 80th birthday.

Abstract   Vinyl aziridines are versatile starting materials toward ring-expansion transformations. Such processes are widely used to give various medium or larger N-heterocycles of synthetic interest. This letter describes a copper-catalyzed ring expansion of vinyl aziridines to 3-pyrrolines by using a Cu(I) salt [(CuOTf)$_2$·toluene or Cu(MeCN)$_4$·PF$_6$]. In particular, this transformation occurs under mild conditions (THF, rt).

Key words   ring expansion, vinyl aziridines, pyrrolines, copper catalysis, heterocycles

Ring expansion of small-sized carbo- and heterocycles is among the most widely used transformations toward medium (or larger) carbo- and heterocycles.[1] Due to the presence of both a highly strained three-membered heterocycle and an activated double bond, vinyl aziridines are an extraordinary source of reactivity, and are therefore valuable building blocks in organic synthesis.[2–4] Consequently, we have been interested in exploring possibilities for performing ring-expansion processes with vinyl aziridines under mild and practical conditions toward novel useful building blocks. Moreover, N-heterocycles are highly valued and widely used in medicinal chemistry, revealing much promise for industrial purposes.[5]

Building on our previous work in the area of palladium-catalyzed [3+2]-cycloadditions of vinyl aziridines **1** with cyclic sulfoxyimines,[4] we were drawn to the potential use of silyl enol ethers **2** in the presence of Lewis acids to form the corresponding five-membered lactams **3** (Scheme 1) bearing a quaternary center.

When the reaction was attempted with model compound **1a** and the silyl enol ether **2a** in the presence of 5 mol% of Cu(OTf)$_2$ at room temperature in dichloromethane, the expected compound **3a** could not be observed in the
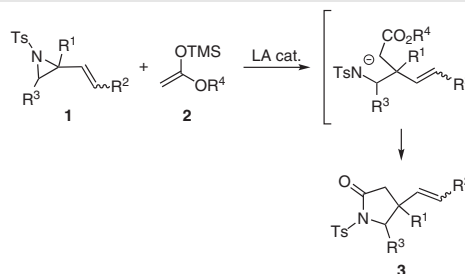

Scheme 1   Envisaged reactions of vinyl aziridines **1** with silyl enol ethers **2**
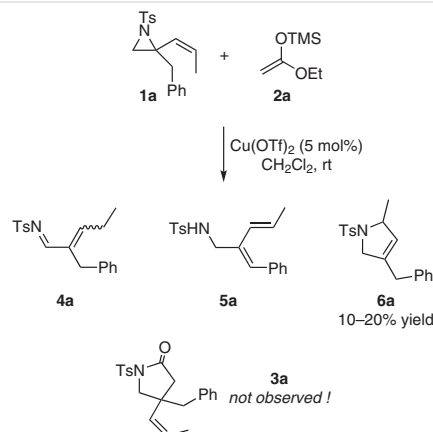
Scheme 2   Attempted reaction of vinyl aziridine **1a** with silyl enol ether **2a** under copper catalysis

crude material. Instead, along with the rather predictable elimination compounds **4a** and **5a**, pyrroline **6a** was isolated from the reaction mixture in low yields (10–20%) (Scheme 2).

The copper-catalyzed ring expansion of vinyl aziridines to 3-pyrrolines is a known reaction, originally described by Njardarson and co-workers in 2008 (Scheme 3).[6] However these reactions required the presence of an unusual copper complex, bis(hexafluoroacetylacetonato)copper [Cu(hfacac)$_2$], under relatively harsh conditions (toluene, 150 °C).[7] As shown in Scheme 3, various substituted 3-pyrrolines could be efficiently obtained under these reaction conditions; the reaction mechanism was also unveiled.[6c]
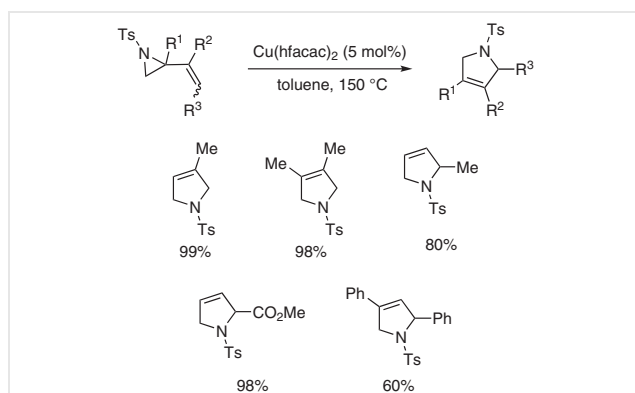
Scheme 3 Some examples of vinyl aziridine rearrangements under Njardarson's conditions[6a]

The very mild conditions (Scheme 2) in which **6a** was formed in our reaction prompted us to reinvestigate the reaction conditions (Table 1) towards the exclusive, or at least, main formation of pyrroline **6a**. Interestingly, in the absence of silyl enolate **2a**, the pyrroline **6a** was not observed (Table 1, entry 2). Suspecting an in situ Cu(II) → Cu(I) reduction in the reaction process,[8] we investigated the use of Cu(I) salts in the absence of silyl enolate **2a**. Whereas various Cu(I) salts proved unsuccessful in catalyzing the reaction (entries 3–5), we were delighted to observe the clean formation of **6a** in the presence of 10 mol% of (CuOTf)$_2$·toluene (entry 6) at room temperature in THF.[9] To exclude the possibility of an organic acid-catalyzed transformation, we ran a trial in the presence of 5 mol% of TFA; in this case, no reaction was observed (entry 7).

After optimizing of the basic rearrangement reaction with vinyl aziridine **1a**, we examined its general scope. For
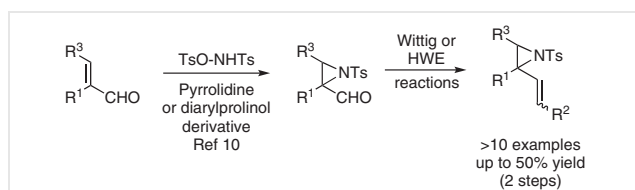
Scheme 4 Synthesis of vinyl aziridines **1**. For additional details, see Supporting Information.

Table 1 Pyrroline **6a** Synthesis from Vinyl Aziridine **1a**: Optimization Study[a]

Entry	Solvent	Cat. (5 mol%)	(**4a** + **5a**)/**6a**[b]	Yield (%) of **6a**
1[c]	CH$_2$Cl$_2$	Cu(OTf)$_2$	70:30	10
2	CH$_2$Cl$_2$[d]	Cu(OTf)$_2$	100:0	–
3	THF	[(i-Pr)CuCl]	NR[e]	–
4	THF	[(Ph$_3$P)$_3$CuF]	NR	–
5	THF	CuTC[f]	NR	–
6	THF	(CuOTf)$_2$·toluene	<5: >95	60
7	THF	TFA	NR	–

[a] Reactions conditions: **1a** (0.05 mmol), catalyst (5 mol%), solvent (0.5 mL), rt, argon atmosphere, 12 h.
[b] Determined by ^{1}H NMR of the crude product.
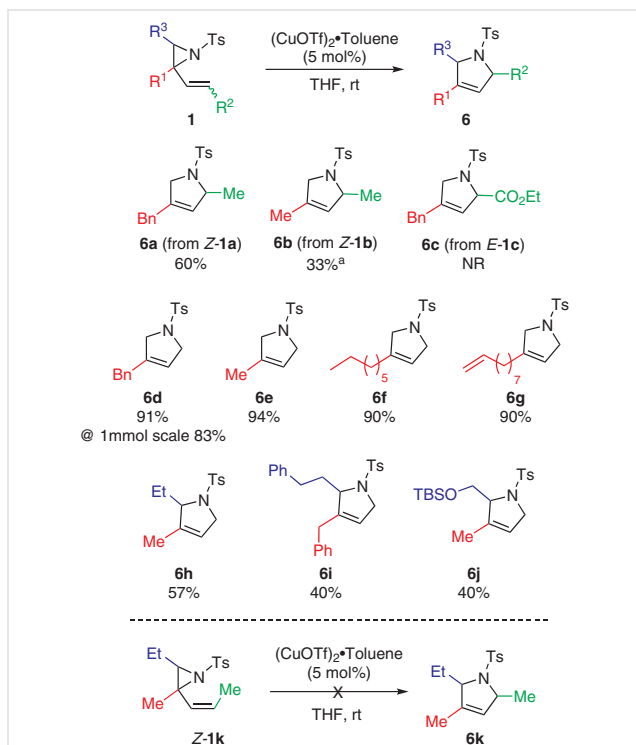[c] With silyl enolate **2a** (1.5 equiv).
[d] Or THF.
[e] NR = no reaction.
[f] TC = thiophene-2-carboxylate.

this purpose, a small collection of vinyl aziridines **1** were prepared by following a sequence involving an organocatalyzed aziridination/Wittig reaction (Scheme 4).[6,10] The expected substrates needed for the ring-expansion transformation were obtained in moderate-to-good yields.
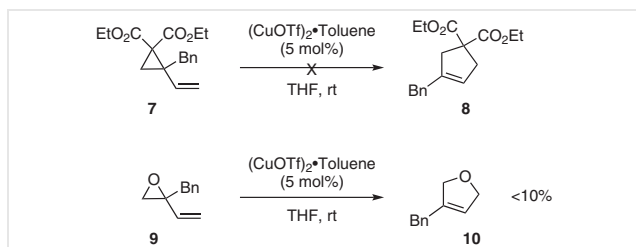
As shown in Scheme 5, various mono- and disubstituted pyrrolines **6** were isolated in good yields. In the presence of both R^1 and R^2 groups in the starting vinyl aziridine, pyrrolines **6a** and **6b** were obtained in yields of 60 and 33%, respectively. Notably, no reaction was observed when an electron-withdrawing group (R^2 = CO$_2$Et; compound **6c**) was present, and for which Njardarson's conditions are efficient.[6] From monosubstituted aziridines **1d–g**, the corresponding pyrrolines **6d–g** were obtained in yields of 60–94%. Of note, the presence of functionalized side-chains was well tolerated (**6g** and **6j**). The rearrangement of vinyl aziridine **1d** was also performed at a 1 mmol scale (as opposed to 0.14 mmol) to give the expected pyrroline **6d** in a comparable isolated yield of 83%. The ring expansion of vinyl aziridines **1h–j** with substituents at the R^3 position was next investigated. In this case, pyrrolines **6h–j** were formed in moderate to good yields of 40–57%. From these results, we can deduce that hindrance around the NTs functional group (the R^2 and R^3 groups) has a deleterious effect on the ring-expansion process, as the expected compounds were isolated in lowers yields (<60%). In these cases, the reactions were complete according to TLC monitoring, but were accompanied by the formation of unidentified byproducts. This trend was reinforced when substrate **1k** was submitted to the ring-expansion conditions, as none of the trisubstituted pyrroline **6k** was formed. In contrast, pyrrolines monosubstituted at R^1 were obtained in excellent yields (≤94%). Interestingly, Cu(MeCN)$_4$·PF$_6$ could also be used as catalyst for the synthesis of **6b**, **6d**, and **6i**, affording similar yields (32, 90, and 40%, respectively).

Starting from the enantiomerically enriched vinyl aziridine (*Z*)-**1a** (80% ee),[10] the corresponding pyrroline **6a** was obtained in 62% yield in a racemic form (Scheme 7).

Scheme 7 Rearrangement of enantiomerically enriched vinyl aziridine (*Z*)-**1a**

These results, including the racemization of enantiomerically enriched vinyl aziridines, are in full accordance with Njardarson's observations. Mechanistic studies performed by Njardarson and co-workers highlighted a copper(I) insertion into the C–N bond to give an allylcopper intermediate, ultimately leading, to the pyrroline **6** after reductive elimination (Scheme 8; left-hand pathway).[6c] An alternative mechanistic scenario (Scheme 8; right-hand pathway) involving copper coordination and subsequent heterolytic rupture of the C–N bond, followed by the attack of the *N*-tosyl anion, cannot be totally excluded under our reaction conditions.
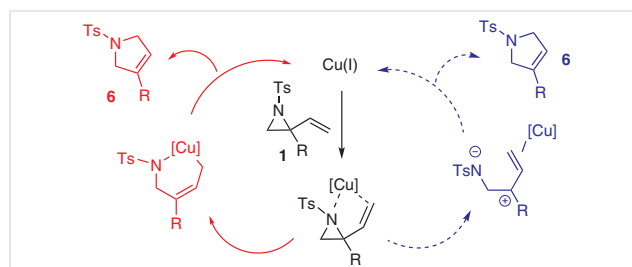
Scheme 8 Proposed mechanistic scenarios

These mechanistic insights prompted us to test the use of palladium salts in these ring-opening aziridine reactions. In a model reaction with (*Z*)-**1a**, we eventually found that, under aza-Wacker conditions,[12] the corresponding pyrrole **11** could be obtained in an unoptimized 50% yield (Scheme 9).[13]

Scheme 9 Aza-Wacker-type rearrangement of (*Z*)-**1a**

In conclusion, we have developed a practical protocol[14] for the synthesis of 3-substituted pyrrolines from accessible vinyl aziridines. The ring-expansion process takes place under Cu(I) catalysis. In particular, mild conditions (THF, rt) are sufficient to accomplish the rearrangements. In the

Scheme 5 Scope of the rearrangement of vinyl aziridines **1**. *Reagents and conditions*: **1** (0.14 mmol), (CuOTf)₂·toluene (5 mol%), THF (0.7 mL), rt, 2 h. Isolated yields after purification by silica gel column chromatography are reported. NR = no reaction. ᵃ Pyrroline **6b** was, for an unknown reason, very difficult to purify.
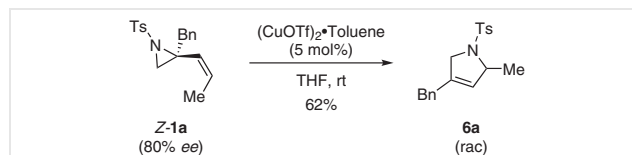
Thanks to an easy access to 2-substituted vinyl cyclopropanes,[11] a related reaction of the vinylcyclopropane **7** was next attempted under the same reaction conditions, but with no success (Scheme 6). The rearrangement of vinyl epoxides had been previously reported by Njardarson [Cu(hfacac)₂ (5 mol%), toluene, 150 °C].[6d] We therefore attempted a rearrangement of vinyl epoxide **9** in the presence of (CuOTf)₂ at room temperature, but the reaction led to an intractable mixture of products, and dihydropyran **10** could not be isolated.

The mild conditions used in this transformation (THF, rt) prompted us to check the reaction stereospecificity.
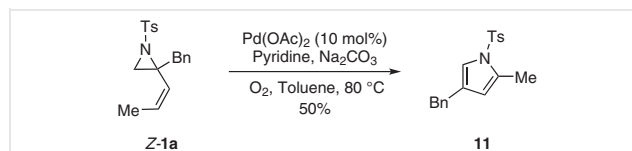

Scheme 6 Attempted copper-catalyzed rearrangements of vinylcyclopropane **7** and epoxide **9**

presence of R² and R³ groups (steric hindrance around the NTs functionality), yields ranged from 33 to 60%, whereas 3-pyrrolines (R² = R³ = H) were isolated in higher yields (>90%). Further investigations will be carried in an attempt to understand the correlation (if any) between conversion and steric encumbrance, and also to broaden the actual scope. The present procedure might be an efficient method for the synthesis of 3-pyrrolines, which are useful building blocks in both organic and medicinal chemistry. Moreover, the Wacker-type reactions disclosed are currently under investigation.

Funding Information

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706007.

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(14) **4-Benzyl-2-methyl-1-tosyl-2,5-dihydro-1***H***-pyrrole** (**6a**): **Typical Procedure**
A flame-dried 10 mL flask equipped with a stirrer bar was charged with vinyl aziridine **1a** (46 mg, 0.14 mmol, 1.00 equiv), (CuOTf)₂·toluene (3.5 mg, 0.007 mmol, 0.05 equiv), and THF (0.7 mL), and the mixture was stirred for 2 h under argon at rt. The solvent evaporated under reduced pressure, and the crude product was purified by chromatography [silica gel, pentane–EtOAc (100:0 to 70:30)] to give a pale-yellow solid; yield: 28 mg (60%); mp 80–83 °C.
FTIR (neat): 1402, 1355, 1178, 1163, 1090, 993, 945, 858, 840, 765, 664 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.65–7.63 (m, 2 H), 7.27–7.20 (m, 5 H), 7.01–6.99 (m, 2 H), 5.19–5.17 (m, 1 H), 4.48–4.46 (m, 1 H), 4.04–3.90 (m, 2 H), 3.33–3.23 (m, 2 H), 2.43 (s, 3 H), 1.38 (d, J = 6.40 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 143.2, 137.6, 137.1, 134.8, 129.6 (2 C), 128.5 (2 C), 128.5 (2 C), 127.4 (2 C), 126.5, 126.3, 63.4, 56.6, 35.1, 22.9, 21.5. HRMS-ASAP: m/z [M + H]⁺ calcd for $C_{19}H_{22}NO_2S$: 328.1371; found: 328.1381.

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