# Amidopalladation of Alkoxyallenes Applied in the Synthesis of an Enantiopure 1-Ethylquinolizidine Frog Alkaloid

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The rare 1-ethylquinolizidine (e.g., **1**, eq 1) and 8-ethylindolizidine alkaloids[1] are present in minor quantities in skin extracts of poisonous frogs of the genera *Dendrobates* and *Mantella*.[2] Although some approaches have led to the first syntheses of such alkaloids and have provided definitive structural proof,[3] general asymmetric access to these biologically relevant molecular scaffolds is lacking. We designed a synthetic route to these structural motifs in enantiopure form, based on the cationic cyclization of allylic *N,O*-acetals such as **2**, which again may be derived from the corresponding amino acid derivatives **3** via a Pd-catalyzed amidopalladation of alkoxyallenes.[4,5] Here, we wish to disclose the latter reaction in more detail, including a mechanistic proposal, and demonstrate its versatility via application in the asymmetric synthesis of the 1-ethylquinolizidine framework.



quinolizidine 233A
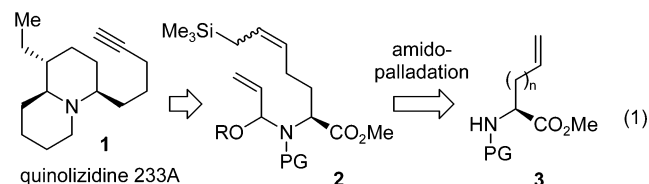
Pd-catalyzed nucleophilic additions onto allenes have been studied extensively,[6] but the use of alkoxyallenes[7] in such processes received notably less attention.[8] Reaction of *N*-nucleophiles with alkoxyallenes would provide a catalytic and unique way (basic conditions!) to synthesize *N,O*-acetals, and thus widen the field of catalytic reactions with alkoxyallenes. Allylglycine-derived amides served as the substrates for probing the amidopalladations with benzyloxyallene (**4a**, Table 1). Intriguingly, secondary amines, carbamates, and amides (entries 1−3) did not react under conditions that were successful for secondary alcohols,[4] while the phosphoramidate **3d** provided the desired product as a single regioisomer in an isolated yield of 55% at 60 °C. Gratifyingly, the use of sulfonamides **3e** and **3f** gave excellent yields of 85% and 84% at room temperature. Recognizing that the acidity of the nucleophile might be a key factor in the amidopalladation,[9] DBU (p$K_{aH}$ 24−25 in MeCN)[10] was used as the base for the less acidic amides. Indeed, the desired products were now observed for both Cbz- and Boc-protected allylglycine at 60 °C, resulting in 50% (**5b**) and 67% (**5g**) isolated yields. Analogous reactions with methoxyallene (**4b**) provided similar good results. In comparison, phenoxyallene (**4c**) gave a significant drop in yield to 69% and 55% for **3e** and **3f**, respectively, which might be due to the somewhat lower stability of the acetals **7a** and **7b**.

The use of DBU as the base also allowed regular amides to react in the amidopalladation (Table 2). For example, *N*-methylacetamide

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**Table 1.** Amidopalladation with Protected Allylglycine Methyl Esters
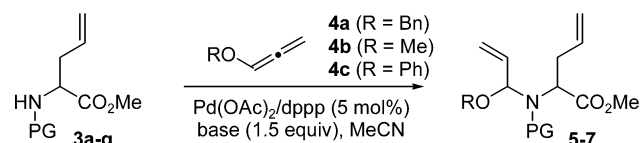


| entry | substrate | PG | alkoxyallene | base, T (°C), t (h) | product (%) |
|---|---|---|---|---|---|
| 1 | **3a** | Bn | **4a** | TEA, Δ, 24 | **5a** (0) |
| 2 | **3b** | Cbz | **4a** | TEA, Δ, 24 | **5b** (0) |
| 3 | **3c** | COCCl₃ | **4a** | TEA, Δ, 24 | **5c** (0) |
| 4 | **3d** | PO(OPh)₂ | **4a** | TEA, 60, 6 | **5d** (55) |
| 5 | **3e** | Ts | **4a** | TEA, rt, 2 | **5e** (85) |
| 6 | **3f** | Ns | **4a** | TEA, rt, 2 | **5f** (84) |
| 7 | **3b** | Cbz | **4a** | DBU, 60, 6 | **5b** (50) |
| 8 | **3g** | Boc | **4a** | DBU, 60, 16 | **5g** (67) |
| 9 | **3d** | PO(OPh)₂ | **4b** | TEA, 60, 16 | **6a** (52) |
| 10 | **3f** | Ns | **4b** | TEA, rt, 16 | **6b** (82) |
| 11 | **3e** | Ts | **4c** | TEA, rt, 16 | **7a** (69) |
| 12 | **3f** | Ns | **4c** | TEA, rt, 16 | **7b** (55) |

**Table 2.** Amides and Lactams
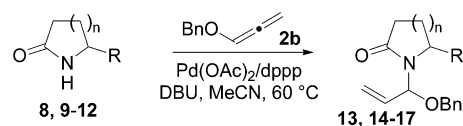


| entry | substrate | t (h) | product (%) |
|---|---|---|---|
| 1 | **8**: *N*-methylacetamide | 64 | **13** (21) |
| 2 | **9**: n = 1, R = H | 24 | **14** (77) |
| 3 | **10**: n = 1, R = CH₂CCH | 16 | **15** (72, dr 3:1) |
| 4 | **11**: n = 2, R = H | 24 | **16** (41) |
| 5 | **12**: n = 3, R = H | 24 | **17** (14) |

(**8**) was converted into the corresponding *N,O*-acetal **13** in 21% yield. The five-membered lactams **9** and **10** gave good yields of the corresponding acetals, while lower yields were observed for the lactams **11** and **12**.

Two competing mechanisms may account for the difference in reactivity between the various amides (Scheme 1).[11] In case of the more acidic sulfonamides, path A may take place.[12] The sulfonamide pronucleophile[13] may oxidatively add to Pd(0)[14] to form a Pd-hydride species, which can react with the allene to form the intermediate π-allyl complex **18**. Reaction with the amide moiety from within the coordination sphere will then lead to the product **19**. In case of less acidic amides, the protonated tertiary amine base (R₃NH⁺) may oxidatively add to Pd(0), followed by reaction with the allene to result in the π-allyl complex **20** (path B). The deprotonated amide (**21**) can then attack either after ligand exchange

**Scheme 1.** The Proposed Mechanism
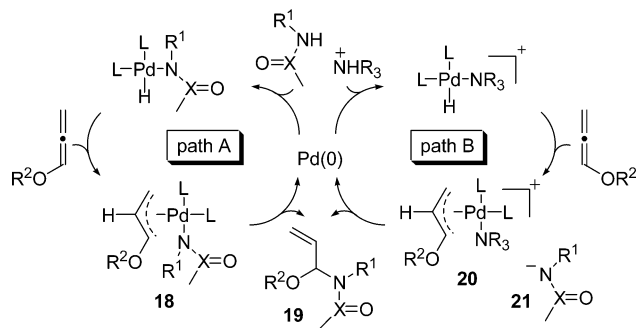


or via external attack to form the product **19** and regenerating Pd-(0). This would also explain why more vigorous conditions and longer reaction times are required.

Having established straightforward access to the required *N,O*-acetals, we investigated its application in the synthesis of the 1-ethylquinolizidine framework. In doing so, we focused on the construction of the enantiopure 1-ethylquinolizidine amino alcohol **27** (Scheme 2), because it is known that this intermediate in racemic form can be elaborated to quinolizidine 233A (**1**).[3c] In an analogous fashion, 1-*epi*-207I (**28**) may be prepared from **27**.

**Scheme 2.** Synthesis of the Enantiopure Key Synthon **27**[a]
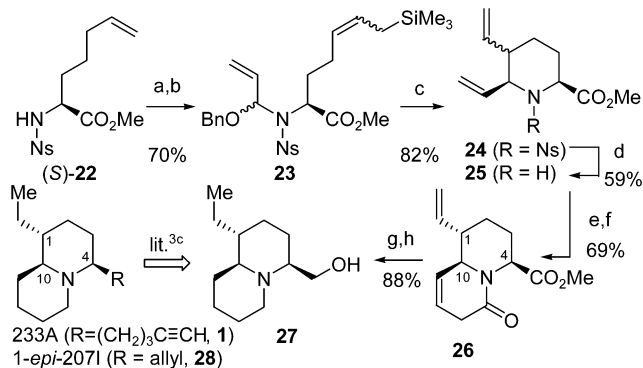


[a] Reaction conditions: (a) ATMS, Hoveyda−Grubbs cat. (5 mol %), CH$_2$Cl$_2$, reflux, 16 h (87%). (b) Benzyl propadienyl ether, Pd(OAc)$_2$/dppp (5 mol %), Et$_3$N, MeCN, room temperature, 16 h (80%). (c) Sn(OTf)$_2$ (2 mol %), CH$_2$Cl$_2$, 0 °C to room temperature, 2 h (82%). (d) PhSK (2.5 equiv), MeCN, 50 °C, 6 h (59%). (e) 3-Butenoyl chloride (1.05 equiv), 2,6-lutidine, CH$_2$Cl$_2$, 0 °C, 2 h (83%). (f) Second-generation Grubbs cat. (5 mol %), CH$_2$Cl$_2$, reflux, 4 h (83%). (g) PtO$_2$ (cat.), H$_2$, MeOH, 2 h (100%). (h) LiAlH$_4$, THF, 70 °C, 20 h (88%).

Thus, enantiopure protected 2-amino-6-heptenoic ester[15] (**22**) was treated with the Hoveyda−Grubbs[16a] catalyst and allyltrimethyl-silane (ATMS) to give the desired product in 87% yield via an unusual double bond isomerization,[17] followed by cross-metathesis with ATMS. Amidopalladation with benzyl propadienyl ether gave the allylic *N,O*-acetal **23** in 80% yield. Crucial CC-bond formation took place by treatment with a catalytic amount of Sn(OTf)$_2$ (2 mol %), leading to fast formation of the desired cyclized target **24** as a mixture of two diastereoisomers. Thiophenolate-mediated sulfonamide cleavage[18] in MeCN at 50 °C afforded the free amine **25** as a 86:14 mixture of *trans/cis*-isomers. Elaboration to the desired bicyclic target consisted of amine acylation with 3-butenoyl chloride, followed by ring-closing metathesis of the triene using the second-generation Grubbs[16b] catalyst. This afforded **26** as a

separable mixture of the two diastereoisomers in a combined yield of 69% (two steps), of which the major diastereoisomer was obtained as a crystalline solid ($[\alpha]_D$ −216.2 (*c* 0.5, EtOH)). The X-ray crystal structure determination of this pure diastereoisomer of **26** unequivocally proved the 4,10-*cis*-relationship and the 1,10-*trans*-configuration.[19] Hydrogenation of the pure *trans*-diastereoisomer, followed by hydride reduction, led to the enantiopure key building block **27** in 88% yield. This eight-step (five catalytic, starting from (*S*)-**22**) synthesis of the amino alcohol **27** − a key synthon in the synthesis of the poisonous frog alkaloid quinolizidine 233A and derivatives − shows the usefulness of the new Pd-catalyzed amidation of alkoxyallenes that can be applied to a wide range of amide substrates. Currently, we are conducting further research toward application of the *N,O*-acetals in other types of reactions and natural product syntheses.

**Supporting Information Available:** Experimental procedures, and spectroscopic and analytical data (PDF). Crystallograpic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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