Pd-Catalyzed Cascade Reactions of Aziridines: One-step Access to Complex Tetracyclic Amines

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ABSTRACT: Combined palladium catalysis and thermal cycloaddition is shown to transform tricyclic aziridines into complex, stereo-defined tetracyclic products in a single step. This highly unusual cascade process involves a diverted Tsuji-Trost sequence leading to a surprisingly facile intramolecular Diels-Alder (IMDA) reaction. The starting materials are accessible on multigram scales from the photochemical rearrangement of simple pyrroles. The tetracyclic amine products can be further elaborated through routine transformations, highlighting their potential as scaffolds for medicinal chemistry.

Nitrogen-containing heterocycles are among the most prominent structural motifs within bioactive molecules, showing a wide range of activity, including anti-cancer, anti-bacterial, anti-viral and those acting on the CNS.1,2 Compounds rich in sp3 character are known to perform favorably within the clinic, where their enhanced three-dimensionality leads to improved selectivity.3 Methodologies to access N-containing, complex 3D scaffolds are therefore a key objective for synthetic chemists, potentially allowing rapid access to high value lead compounds.4 Cascade reactions represent an ideal route to such compounds, necessarily adding significant complexity in a single transformation.5 Synthetic photochemistry has a long history of creating highly complex molecules.6 These products are frequently reactive, thus proving versatile intermediates in synthesis.6,7 Catalytic modification of such products continues to harbor interest, forming conformationally constrained, saturated heterocycles. We have previously shown tricyclic aziridines 2, formed directly from pyrroles 1,8 are particularly versatile intermediates in this respect (Scheme 1a).9,10 Herein, we report an efficient single step approach to the hitherto unreported ring system 6 via a novel 3-part cascade process.

Previous Pd0-mediated ring-expansion/cycloaddition of 2 with dipolarophiles gave access to 5-membered rings such as 4,10 and we were interested to determine whether extension to 6-membered rings was possible. We therefore considered whether bifunctional reagent 8 could function as both mild nucleophile and electrophile, enabling formation of 10 (Scheme 2). Surprisingly however, reaction of 2 (R = CO2tBu) gave N-alkylated product 11, where diene formation and desilylation had occurred. As dienes are key synthetic building blocks,11 we decided to investigate the scope of this reaction.
Replacing 8 with allyl acetate converted 2 (R = CO₂Bu) to allylated product 12a in a much-improved 87% yield (Table 1). These conditions also proved applicable to aziridines 2b (R = COMe) and 2c (R = CONHEt). Nitrile 2d proved unsuccessful, possibly due to decreased steric crowding of the aziridine ring. Use of allylic bromides rather than allylic acetates also proved possible but gave reduced yields and did not remove the requirement for Pd-catalysis.

Table 1. Effect of variation of aziridine and allyl reagent.

| Entry | R         | Reagent       | Product | Yield/% |
|-------|-----------|---------------|---------|---------|
| 1a,b  | CO₂Bu     | Allyl acetate | 12a     | 87      |
| 2b,c  | COMe      | Allyl acetate | 12b     | 56d     |
| 3b,c  | CONHEt    | Allyl acetate | 12c     | 60d     |
| 4a,b  | CN        | Allyl acetate | 12d     | 0e      |
| 5d    | CO₂Bu     | None          | 13a     | 83      |
| 6a    | COMe      | None          | 13b     | 82      |
| 7a    | CONHEt    | None          | 13c     | 44      |
| 8a    | CN        | None          | 13d     | 0e      |
| 9a,f  | CO₂Bu     | None          | 13a     | 0       |
| 10a   | CO₂Bu     | None          | 13a     | 0       |

[a] Reaction performed at 70 °C. [b] Performed in the presence of 1.3 equiv. K₂CO₃. [c] Reaction performed at 30 °C. [d] Yield determined by 1H-NMR using 1,3,5-trimethoxybenzene as the internal standard. [e] Slow conversion to retro-ene product 3 was observed. [f] Performed using Pd(PPh₃)₄. [g] Performed using Pd₂(dba)₃/PPh₃.

Reaction in the absence of an allylating reagent also proved successful, forming secondary amino-dienes 13a-c in good yield (Entries 5-7). This was found to proceed most efficiently in the absence of K₂CO₃ and again nitrile 2d proved unreactive. Interestingly, these reactions proved unsuccessful when other Pd(0)/PPh₃-based systems were employed (Entries 9 & 10), suggesting a by-product of catalyst activation might play a key role in aziridine N-activation. Consistent with this, the presence of a mild Lewis or Bronsted acid was found to be essential for the reaction to occur (see SI for full details).

Scheme 3. Planned Tsuji-Trost Pathway.

Scheme 2. Planned Tsuji-Trost Pathway.

Scheme 4. Scope and limitations of the tandem ring-opening/Diels-Alder process.
The cycloaddition step was seen to occur under substantially milder conditions than similar IMDA. Indeed, substrates lacking an activated dienophile (i.e. 12a-12c) reacted at 70 °C and we chose to investigate this further. As observed above, t-Bu systems 12a proved less reactive than amide 12c ($k = 6.8 \times 10^{-6} s^{-1}$ versus $k = 5.5 \times 10^{-5} s^{-1}$, 75 °C). Use of an Eyring study (Figure 1) demonstrated this variation to be largely controlled by the enthalpy of activation, with a 20 kJ mol$^{-1}$ difference between 12a and 12c. While it is unclear whether this increase is due entirely to electronic factors or includes an additional conformational element, both values appear low when compared with those known for other IMDA reactions. Further attempts to explore the impact of the dienophile activation proved not to be possible due to appreciable formation of 6ab even at 20 °C, again emphasizing the facile nature of this IMDA process.

Based on this and the preceding results, the mechanism can be proposed (Scheme 6). Initial additive-assisted, Pd-catalyzed C-N cleavage of 2 leads to the formation of a π-allyl Pd intermediate 7. This species then undergoes direct β-hydride elimination, even in the absence of additional base, to form the intermediate diene 20. What follows is likely to be a standard Tsuji-Trost mechanism between 20 and the allyl acetate 5, with the added base present serving to ensure sufficient levels of reactive free amine 20. The lack of a significant KIE associated with this process, as determined by competition (i.e. between 17 and 2a), is consistent with the first step (C-N cleavage) being turnover limiting. This low KIE value necessarily means that a reversible β-hydride elimination cannot be ruled out. The resulting N-allylated product 12 then undergoes cycloaddition to form product 6, the rate of which is controlled by both the aziridine and allylated product 12, the rate of which is controlled by both the aziridine and allyl substituents. Although a Pd-catalyzed elimination/intermolecular DA process has been reported previously, to the best of our knowledge, this is the first example of a sequential Tsuji-Trost/IMDA cascade.

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[a] Substituted with R1 at the methylene rather than alkenyl position. [b] Performed in dioxane, 100 °C. [c] 3 equiv. of allyl acetate. [d] 3 mmol scale. [e] Intermediates 12af, 12bf and 12cf were isolated in 45%, 46% and 29% yields respectively.

Figure 1. Eyring plots and thermodynamic parameters for the Diels-Alder cyclisation to form 6aa and 6ca.
Given our previous discussion of the importance of high sp³ content within drug discovery programs, we undertook a short study to diversify products 6 through routine transformations (Scheme 7). For example, in a telescoped oxidative cleavage/reductive amination sequence, compound 6aa was efficiently transformed to tetracyclic amino ester 21, possessing orthogonal protection for further functionalization. Alternatively, selective and sequential ester hydrolysis/amide formation, gave 22 in a 47% yield overall, demonstrating potential for efficient 2D-amide library formation.

In conclusion, we have shown that stereodefined tetracycles 6 can be formed in only two steps from simple pyrroles, through initial photochemical conversion to aziridines 2. These undergo a one-pot diverted Tsuji-Trost reaction, followed by a standard Tsuji-Trost reaction affording the alylated diene, which itself undergoes a direct IMDA reaction. The mechanism of diene formation likely involves rate limiting acid-assisted C-N cleavage, followed by direct β-hydride elimination. These results underline the power of photochemical/catalytic sequences in preparing complex ring systems. Finally, we have shown that the tetracyclic amines formed from this cascade process undergo further functionalization reactions, highlighting their potential as sp³-rich scaffolds in drug discovery.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at http://pubs.acs.org/doi.
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