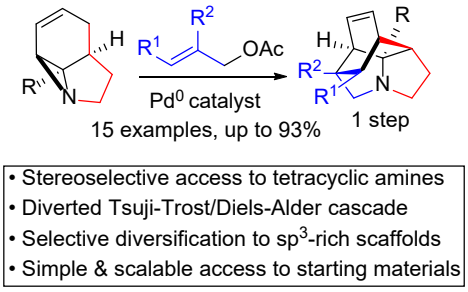
Pd-Catalyzed Cascade Reactions of Aziridines: One-step Access to Complex Tetracyclic Amines

Jonathan P. Knowles,*‡‡ Hannah G. Steeds,‡† Maria Schwarz,† Francesca Latter† and Kevin I. Booker-Milburn*†

†School of Chemistry, University of Bristol, Cantock's Close, Bristol, UK, BS8 1TS

‡Department of Applied Sciences, Northumbria University, Newcastle upon Tyne, UK, NE1 8ST

KEYWORDS aziridines, Diels-Alder, domino reactions, palladium, Tsuji-Trost

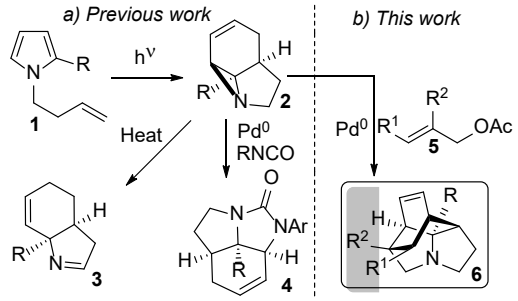


ABSTRACT: Combined palladium catalysis and thermal cycloaddition is shown to transform tricyclic aziridines into complex, stereo-defined tetracyclic products in a single step. This highly unusual cascade process involves a diverted Tsuji-Trost sequence leading to a surprisingly facile intramolecular 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 sp^3 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]

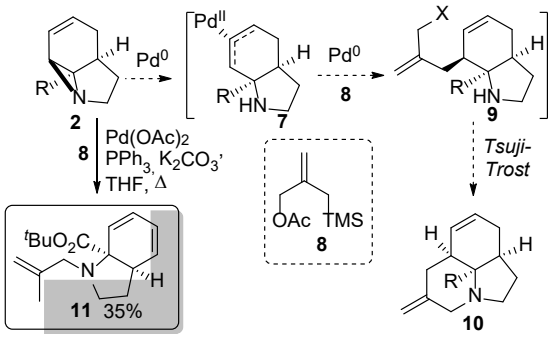
Synthetic photochemistry has a long history of creating highly complex molecules.[6] These products are frequently reactive, thus proving versatile intermediates in synthesis.[6,7] Catalytic modification of such products continues to harbor interest, forming conformationally constrained, saturated heterocycles. 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.

Scheme 1. Previous and current photochemical/catalytic sequences to form complex structures.[9,10]



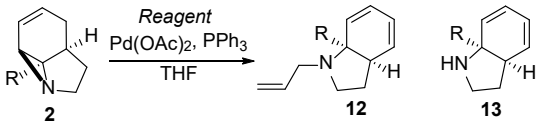
Previous Pd^0-mediated ring-expansion/cycloaddition of **2** with dipolarophiles gave access to 5-membered rings such as **4**,[10] and we were interested to determine whether extension to 6-membered rings was possible. We therefore considered whether bifunctional reagent **8** could function as both mild nucleophile and electrophile, enabling formation of **10** (Scheme 2). Surprisingly however, reaction of **2** (R = $CO_2{}^t$Bu) 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.

Scheme 2. Planned Tsuji-Trost Pathway.



Replacing **8** with allyl acetate converted **2** (R = $CO_2{}^tBu$) 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.[12] 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.

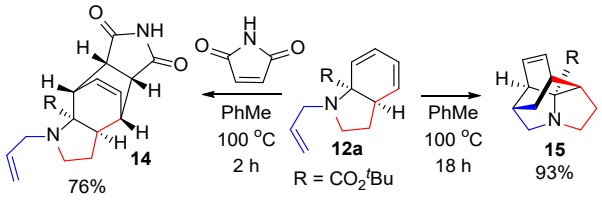


Entry	R	Reagent	Product	Yield/%
1[a,b]	$CO_2{}^tBu$	Allyl acetate	**12a**	87
2[b,c]	COMe	Allyl acetate	**12b**	56[d]
3[b,c]	CONHEt	Allyl acetate	**12c**	60[d]
4[a,b]	CN	Allyl acetate	**12d**	0[e]
5[d]	$CO_2{}^tBu$	None	**13a**	83
6[a]	COMe	None	**13b**	82
7[a]	CONHEt	None	**13c**	44
8[a]	CN	None	**13d**	0[e]
9[a,f]	$CO_2{}^tBu$	None	**13a**	0
10[a,g]	$CO_2{}^tBu$	None	**13a**	0

[a] Reaction performed at 70 ºC. [b] Performed in the presence of 1.3 equiv. K_2CO_3 [c] Reaction performed at 30 ºC [d] Yield determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard. [e] Slow conversion to retro-ene product **3** was observed.[9] [f] Performed using $Pd(PPh_3)_4$. [g] Performed using $Pd_2(dba)_3/PPh_3$.

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 K_2CO_3 and again nitrile **2d** proved unreactive. Interestingly, these reactions proved unsuccessful when other Pd(0)/PPh_3-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 Brønsted acid was found to be essential for the reaction to occur (see SI for full details).

Scheme 3. Inter- and intramolecular Diels-Alder reactions of 12a.

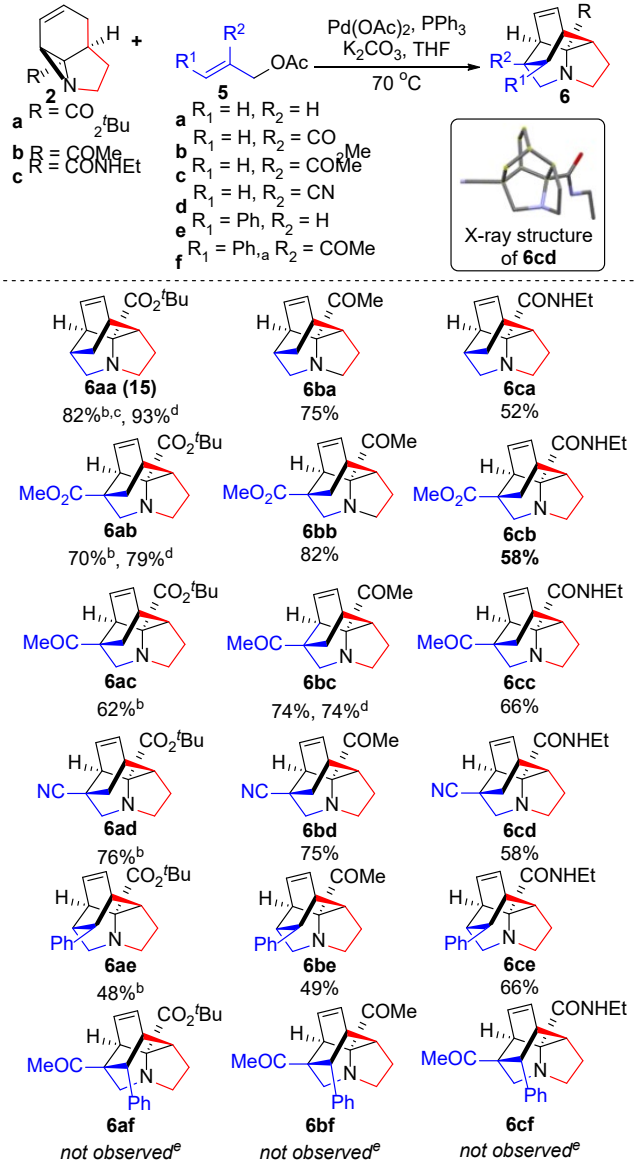


We then turned our attention to exploiting the dienyl component of these cyclic dienes **12**. Diels-Alder reaction of *N*-allyl derivative **12a** with maleimide formed the expected adduct **14** (Scheme 3). However, we were intrigued to isolate trace amounts of the IMDA product **15**, which was unexpected given the unactivated nature of the dienophile. Simply heating **12a** led to formation of **15** in an excellent 93% yield, demonstrating rapid access to a complex unreported, ring-system (3 steps from pyrrole **1a**[13]).

To explore this further we expanded the range of allylating reagents and moved to performing the ring-opening/cycloaddition sequence in a single step. This proved highly successful, with use of an electron-withdrawing functionality at the 2-position of component 5 being well tolerated and accelerating the Diels-Alder reaction (Scheme 4). One-pot reaction of **2a** required refluxing in dioxane to effect full conversion in the Tsuji-Trost reaction, however the less sterically hindered aziridines **2b** and **2c** were found to react fully in THF. Importantly, scale-up of these reactions proved facile, with **6aa**, **6ab** and **6bc** being formed in equal or increased yield on a 3 mmol scale.

Reactions of 3-substituted tether **5e** also proved successful, with high regiocontrol for the linear allylated intermediate combining with high *E*-selectivity to yield a single stereoisomer. However, attempted reactions of disubstituted allyl acetate **5f** was less successful, with only the allylated diene intermediate being obtained. This likely reflects an increased steric demand, where the phenyl substituent of the *E*-alkene would need to adopt an unfavorable *endo*-cyclic position in the transition state.

Scheme 4. Scope and limitations of the tandem ring-opening/Diels-Alder process.



[a] Substituted with R^1 at the methylene rather than alkenyl position. [b] Performed in dioxane, 100 ºC. [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.

The cycloaddition step was seen to occur under substantially milder conditions than similar IMDA.[14] 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 system **12a** proved less reactive than amide **12c** (k = 6.8 x 10^{-6} s^{-1} versus k = 5.5 x 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.[15] 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.

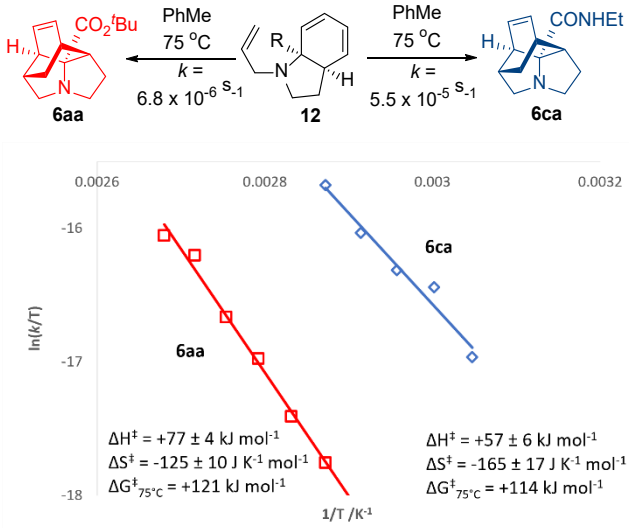
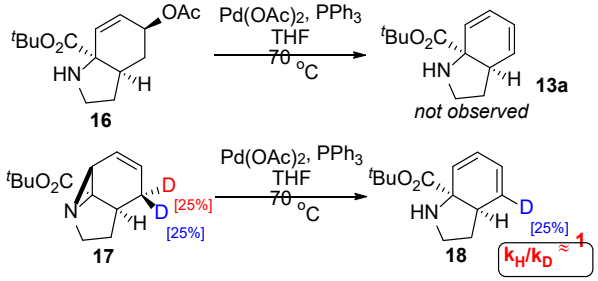


Figure 1. Eyring plots and thermodynamic parameters for the Diels-Alder cyclisation to form **6aa** and **6ca**.

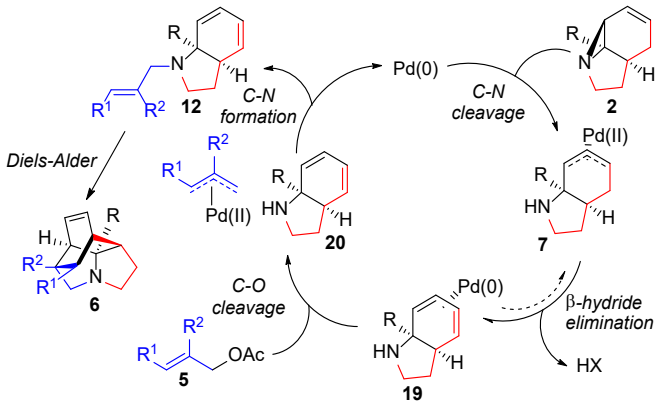
To explore the role of acetate observed in Table 1 (Entries 9 & 10; see also SI) compound **16** was prepared and submitted to the reaction conditions;[13] however, diene **13a** was not observed, ruling this out as a potential intermediate (Scheme 5). Deuterated substrate **17** was also submitted to the reaction conditions, leading to the formation of **18** by cleavage of a single C-D bond. The kinetic isotope effect associated with this process was investigated through a competition reaction with **17** and **2a**, which showed essentially no difference in reaction rate (see SI for details).

Scheme 5. Mechanistic and isotopic labelling studies.



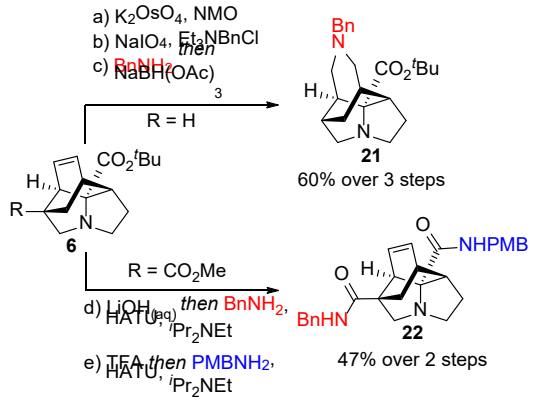
Based on this and the preceding results, the mechanism can be proposed (Scheme 6). Initial additive-assisted, Pd-catalyzed C-N cleavage of **2** leads to the formation of a π-allyl Pd intermediate **7**. This species then undergoes direct β-hydride elimination, even in the absence of additional base, 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.[16] The resulting *N*-allylated product **12** then undergoes cycloaddition to form product **6**, 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,[17] to the best of our knowledge, this is the first example of a sequential Tsuji-Trost/IMDA cascade.[18,19]

Scheme 6. Proposed mechanism.



Given our previous discussion of the importance of high sp^3 content within drug discovery programs,[3] we undertook a short study to diversify products **6** using 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.

Scheme 7. Functionalization of tetracyclic scaffolds.



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 allylated 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 sp^3-rich scaffolds in drug discovery.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, spectral and analytical data, copies of ^1H and ^{13}C NMR spectra for new compounds and Crystallographic Data of **6cd** (PDF)

AUTHOR INFORMATION

Corresponding Authors

Jonathan P. Knowles – *Northumbria University, Newcastle upon Tyne, UK, NE1 8ST*; orcid 0000-0001-5110-4131; Email: jonathan.p.knowles@northumbria.ac.uk

Kevin I. Booker-Milburn – *School of Chemistry, University of Bristol, Cantock's Close, Bristol, UK, BS8 1TS*; orcid 0000-0001-6789-6882; Email: K.Booker-Milburn@bristol.ac.uk

Authors

Hannah G. Steeds – *School of Chemistry, University of Bristol, Cantock's Close, Bristol, UK, BS8 1TS.*

Maria Schwarz – *School of Chemistry, University of Bristol, Cantock's Close, Bristol, UK, BS8 1TS.*

Francesca Latter – *School of Chemistry, University of Bristol, Cantock's Close, Bristol, UK, BS8 1TS.*

Author Contributions

‡These authors contributed equally.

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ABBREVIATIONS

CNS, Central Nervous System; IMDA, Intramolecular Diels-Alder reaction, NMO, *N*-methylmorpholine; HATU, 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*] pyridinium 3-oxid hexafluorophosphate; TFA, Trifluoroacetic acid.

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