

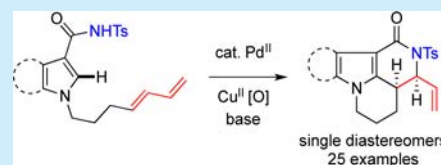
Palladium(II) Catalyzed C–H Functionalization Cascades for the Diastereoselective Synthesis of Polyheterocycles

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Supporting Information

ABSTRACT: C–H activation offers huge potential in the generation of complex structures from simple starting materials. Herein we report the development of a highly diastereoselective palladium(II) catalyzed C–H functionalization cascade to produce novel, unsaturated polyheterocycles from simple diene-tethered heterocyclic starting materials. The reaction is applicable to both indole and pyrrole based substrates and tolerates a wide range of functional group substitutions around the heteroaromatic core. The polyheterocyclic products are formed as single diastereoisomers, with two new stereocenters formed in a single step.



Nitrogen-containing heterocycles such as indole are not only prevalent in natural products¹ but are also of interest to pharmaceutical and agrochemical industries.² Thus, the functionalization of such heterocycles is a highly desirable goal in organic synthesis. In recent years the direct functionalization of C–H bonds has come to represent a convenient, atom-economic transformation in the construction of new C–C and C–N bonds³ and provides rapid access to medicinally relevant structures.⁴ While great progress has been made in the functionalization of *N*-heterocycles⁵ and olefins,⁶ the 1,2-difunctionalization of 1,3-dienes remains relatively uncommon.⁷

We have previously reported investigations into palladium-catalyzed cascade reactions proceeding through an intermediate π -allyl palladium complex. Initially we reported the 1,2-carboamination of electron poor dienes.^{7d} Subsequently we extended this methodology to heterocyclic systems such as **1** (Scheme 1A), where a pendant diene undergoes palladium-catalyzed cyclization to give intermediate **2**, followed by trapping

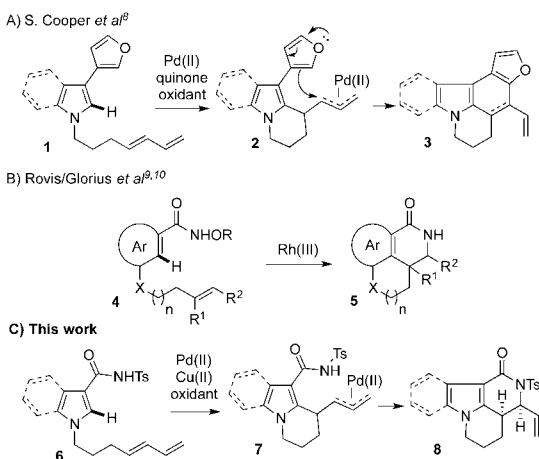
with the heterocyclic nucleophile to give polyheterocyclic compounds **3**; such structures may be useful toward the synthesis of the *Stemona* alkaloid ring system.⁸ Recently both Rovis⁹ and Glorius¹⁰ demonstrated the use of rhodium(III) catalysis in the synthesis of pharmacologically active polycyclic structures such as **5** (Scheme 1B). This useful cascade sequence was achieved from *O*-hydroxamic acid ethers **4** where the preformed N–O bond served as an internal oxidant for the Rh(I)/Rh(III) redox cycle.

Following on from our previous work (Scheme 1A) and in a complementary but mechanistically distinct approach to Scheme 1B, we now report a novel Pd(II) catalyzed sequence to polyheterocycles via a C–H activation/nucleophile trapping cascade sequence from diene substituted heterocycles (Scheme 1C). The methodology has an operational advantage in that a Cu(II) oxidant is used rather than the purification limiting quinone oxidants we and others have previously used.

To begin our investigations we screened various precatalysts, quinone-based oxidants, solvents, and additives against a small range of heterocyclic substrates (Scheme 2, 9–11). However, under the conditions screened no desired cascade products **12** were observed. In the case of the urea substrate **9** some Heck-type cyclization products were obtained in <10% yield, indicating that the initial C–C bond-forming step was feasible but that redox of Pd⁰ was ineffective. This also suggested that the pendant nucleophile/directing group was too weakly nucleophilic, and/or that the length of the tether may have been impeding the desired cascade. Efforts were therefore focused on the *N*-tosyl amide substrate **13**, as such nucleophiles are known to be effective in the trapping of π -allyl complexes.¹¹ With a range of precatalysts and quinone-based oxidants, no reaction was observed, which was surprising given our previous experience (Scheme 2).

Pleasingly, on screening other oxidants we found that use of Cu(OAc)₂ (3 equiv) in conjunction with Pd(OAc)₂ (10 mol %)

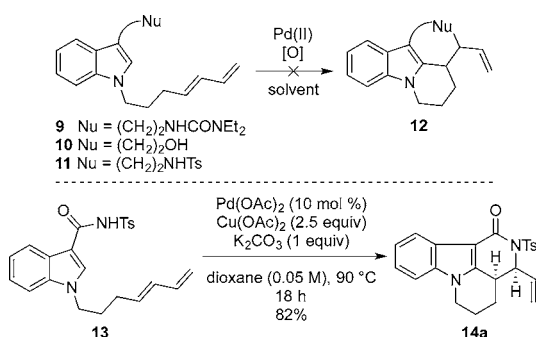
Scheme 1. Synthesis of Polyheterocyclic Compounds through Transition Metal Catalyzed Cascade Sequences



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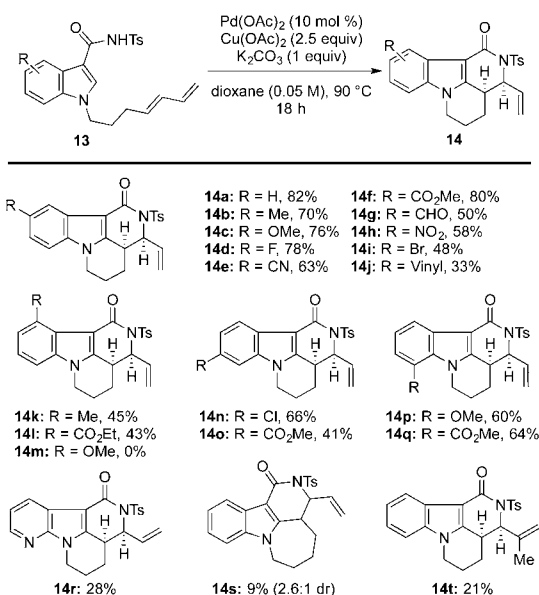
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Scheme 2. Attempted Cyclization Substrates and Optimization Studies of NHTs Amide Substrate 13



in DMF, with 1 equiv of K₂CO₃, resulted in a 47% yield of the desired cyclization product **14a** as a single diastereomer.¹² Control reactions performed to clarify the roles of the metals/reactants demonstrated that the absence of Pd(OAc)₂ gave no product **14a**, suggesting that Pd(OAc)₂ is the precatalyst required for C–H activation. Exclusion of Cu(OAc)₂ gave only trace quantities of **14a**, confirming Cu(OAc)₂ is the likely reoxidant in the sequence. However, the inability of alternative oxidants to affect catalytic turnover hinted at a more complex catalytic process.¹³ Exclusion of base (K₂CO₃) resulted in a much slower reaction and a reduction in yield (50%, by ¹H NMR) of **14a**. Crucially, a solvent swap to dioxane gave the product in an 82% yield and these conditions (10 mol % Pd(OAc)₂, 2.5 equiv of Cu(OAc)₂) were therefore used going forward in the exploration of reaction scope.

Using the optimized conditions an investigation of reaction scope was undertaken, with an initial focus on the effect of substitution around the indole ring (Scheme 3, examples **14a–q**). All the compounds were isolated as single diastereomers (with the syn configuration), clearly showing excellent

Scheme 3. Indole Based Substrate Scope^a

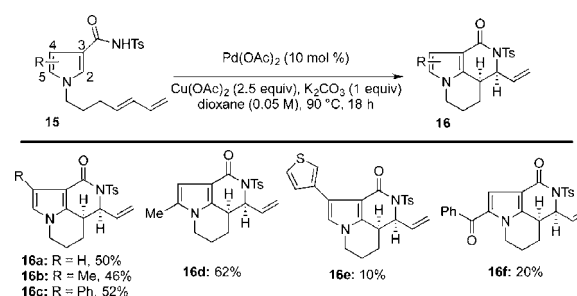
^aReaction conditions: Starting material (0.5 mmol), Pd(OAc)₂ (10 mol %), Cu(OAc)₂ (2.5 equiv), anhydrous 1,4-dioxane (10 mL, 0.05 M), N₂ atmosphere, 90 °C, 18 h. All yields are isolated yields as single diastereomers unless stated otherwise.

diastereoselectivity during the key ring-forming steps. Starting with the 5 position, both electron donating groups (Scheme 3, examples **14b,c**) and withdrawing groups (Scheme 3, examples **14d–h**) appeared to be well tolerated, giving cyclized products in moderate to excellent yields. The reduced yields for aldehyde **14g** and nitro-indole **14h** may be due to substrate solubility issues. Pleasingly the cascade sequence also tolerates halides, such as bromo-substituted **14i** and chloride **14n**. An electron withdrawing substituent in the 4-position (**14l**) was tolerated, as was a weakly donating group (**14k**), albeit in reduced yield. This may be due to a steric clash between the substituent and the *N*-tosyl amide causing twisting of this potential directing group (vide infra) from the key indole C2 hydrogen. With the electron donating 4-methoxy group (**14m**), none of the cyclized product was observed. We suspect this is a combination of steric factors and delocalization of electron density to the 2-position of the indole ring potentially deactivating the indole C2 position.¹⁴ Further substitution around the ring in the 6 and 7 positions (examples **14n–q**) were also well tolerated. This excellent functional group tolerance enables the rapid assembly of polycyclic indole containing molecules with functional handles for further derivatization. The 7-azaindole (**14r**) also gave cyclized product, albeit with a diminished yield.

Extension of the diene chain from 3 to 4 methylene units was less successful, and the 7-membered system **14s** was obtained in very low yield with notably poor stereoselectivity (2.6:1 dr). Similarly, introduction of a methyl group to the alkyl portion of the tether led to an inseparable mixture of isomers in greatly reduced yield (see Supporting Information, p 44). Methyl substitution at C2 of the diene (**14t**) gave cyclized product in poor yield, and substitution at C3 of the diene inhibited the reaction completely.

These examples all suggest a very delicate balance of factors for cyclization and that entropic and steric factors are important in the bond forming processes of the two cyclization events involved in the cascade (vide supra).

Following success with the indole-based substrates, we sought to expand the cascade sequence to include alternative heterocyclic cores. Pleasingly, a range of pyrroles were amenable to the reaction conditions, and without further optimization gave a range of cyclized products. Yields were generally reasonable for the simpler substrates but dropped considerably with more complex systems (Scheme 4). For example, the parent system gave cyclized product **16a** in moderate yield, again as a single diastereomer. Both 4-alkyl (**16b**) and 4-phenyl (**16c**) examples

Scheme 4. Pyrrole Based Substrate Scope^a

^aReaction conditions: Starting material (0.5 mmol), Pd(OAc)₂ (10 mol %), Cu(OAc)₂ (2.5 equiv), anhydrous 1,4-dioxane (10 mL, 0.05 M), N₂ atmosphere, 90 °C, 18 h. All yields are isolated yields as single diastereomers unless stated otherwise.

gave cascade cyclization products in similar yields as single diastereomers. Methyl substitution in the 5-position gave cyclized product **16d** in 62% yield. Unfortunately addition of a thiophene ring at the 4-position of the pyrrole ring gave **16e** with a significant reduction in yield, possibly due to sulfur catalyst deactivation and/or competing thiophene C–H activation. Surprisingly, the addition of an electron-withdrawing group also caused a significant drop in yield for **16f**. This was unexpected due to the observed tolerance of such groups in the indole substrates, although in this case there may be competing C–H activation at the 4-position.

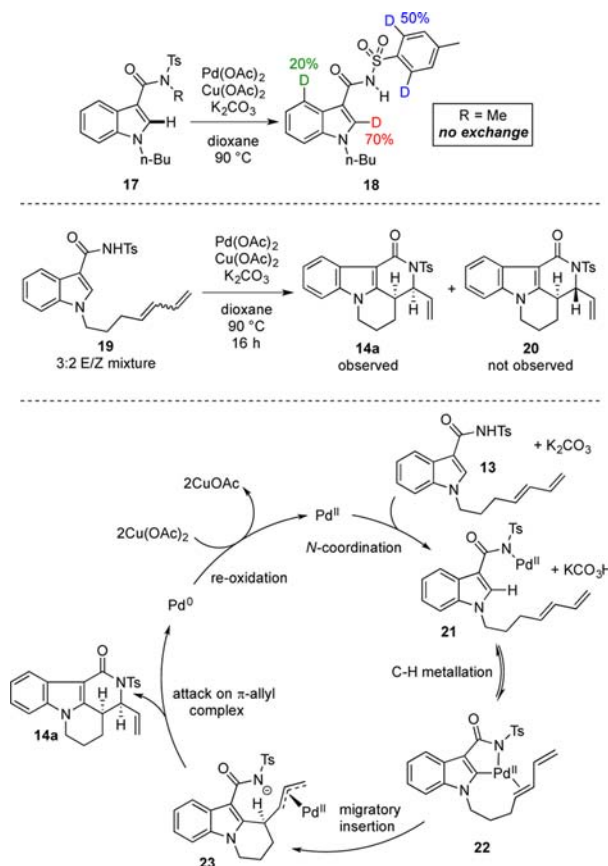
Some preliminary investigations into the mechanism have been performed. Initially, the modified substrate **17** ($R = H$) was synthesized, substituting the tethered diene for a simple *n*-butyl group. This should impart similar electronic effects to the indole ring as the diene tether, though be unable to cyclize. When **17** was exposed to standard conditions with the addition of 3 equiv of D_2O , D -incorporation was observed (**18**) at three locations, all proximal to the *N*-tosyl amide group. The greatest incorporation was at the 2-position (the usual site of C–H functionalization), with 70% incorporation. Incorporation of D was also observed on the tosyl ring at the ortho positions, and minor incorporation was observed at the 4-position of the indole ring. This evidence suggests that the *N*-tosyl amide is acting as an efficient directing group in a reversible metalation step.¹⁵ Exposing the *N*-methyl derivative (**17**, $R = Me$) to identical conditions gave no D -incorporation, further strengthening this argument. In order to ascertain the influence of diene geometry on the diastereoselectivity of the reaction, we subjected 3:2 *cis/trans* mixture of substrate **19** to the cascade sequence which surprisingly gave only the diastereomer **14a** with none of isomer **20** observed (Scheme 5).

On the basis of these observations we can propose the following plausible catalytic cycle using substrate **13** as an example (Scheme 5). Under the influence of base the *N*–Pd(II) amide **21** is formed, which then undergoes C–H insertion by a concerted metalation-deprotonation (CMD) mechanism¹⁶ to form the Pd(II) complex **22**. This is supported by the 4-methoxy substituted example (Scheme 3, **14m**) where no reaction was observed. Here it could be argued that the electron donating OMe group deactivates the C2 indole position and disfavors metalation by a CMD process. This then undergoes migratory insertion leading to the π -allyl complex **23**, which is followed by C–N bond formation to give the product **14a**. The Pd(0) is then reoxidized to Pd(II) by the $Cu(OAc)_2$. The cyclization of **22** to **23** by migratory insertion would appear to be strongly influenced by entropic (Scheme 3, entry **14s**) and steric (Scheme 3, entries **14t**) factors. It is important to note that the syn product was always observed in the cyclization of **21** to **14a**, regardless of diene geometry (**19**, Scheme 5). It is possible that the syn isomer is thermodynamically favored, perhaps via a reversible, Tsuji–Trost-like addition of Pd(0) to an initially formed mixture of syn/anti (**14a/20**) products.

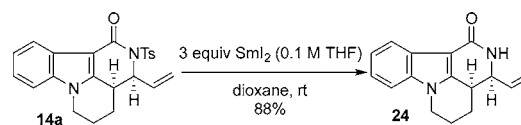
Finally, in order to broaden the synthetic utility of this cascade sequence, we investigated the removal of the tosyl group from the amide. Sulfonamides are excellent nitrogen protecting groups but can be difficult to remove, often requiring very harsh and unselective conditions. Pleasingly we were able to demonstrate that the tosyl group in **14a** can be cleanly removed to give the amide **24** in 88% yield using SmI_2 in dioxane (Scheme 6).¹⁷ Neither the indole ring nor alkene were reduced in the process.

In conclusion, we have developed a novel complexity-building reaction, where simple starting materials undergo a palladium-

Scheme 5. Preliminary Mechanistic Studies



Scheme 6. Deprotection of NTs Group with SmI_2



catalyzed diastereoselective ring annulation cascade. The exceptional diastereoselectivity, along with excellent functional group tolerance, allow for the rapid generation of a range of polyheterocyclic compounds containing functional handles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02947.

Synthesis procedures, additional spectral and characterization data, including 1H and ^{13}C NMR (PDF)

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Notes

The authors declare no competing financial interest.

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