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Indole Synthesis by Palladium-Catalyzed Tandem Allylic Isomerization – Furan Diels-Alder Reaction

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A Pd(0)-catalyzed elimination of an allylic acetate generates a π-allyl complex that is postulated to initiate a novel intramolecular Diels-Alder cycloaddition to a tethered furan (IMDAF). Under the reaction conditions, this convergent, microwave-accelerated cascade process provides substituted indoles in moderate to good yields after Pd-hydride elimination, aromatization by dehydration, and *in situ N*-Boc cleavage.

Indole heterocycles have an exceptional legacy in organic and biological chemistry. The indole is a privileged scaffold for pharmaceuticals, and its frequent presence in alkaloids and biopolymers has inspired numerous synthetic methods (Fig. 1).[1,2] Most indole preparations start with an aniline, followed by ring fusion to generate the pyrrole moiety; in contrast, convergent syntheses that assemble both benzene and pyrrole rings are quite rare.[3] Kanematsu and coworkers applied this strategy to generate indolines from Diels-Alder reactions of allenic dienamides,[4] and Padwa and coworkers pioneered the use of the intramolecular Diels-Alder cycloaddition to 2-amidofurans (IMDAF) in the synthesis of indoline natural products.[5] Our group further extended this approach to the direct preparation of indoles and 5-hydroxyindoles by introducing a different retrosynthetic disconnection and an *in situ* water elimination step (Fig. 2).[6,7,8] Heating of a secondary or tertiary alcohol, obtained by combining a lithiated alkylamidofuran with an α,β-unsaturated aldehyde or ketone, in a microwave reactor to 180-200 °C initiates a cascade process that results in the elimination of 1 to 2 equiv of H_2O and the fragmentation of the Boc-protective group to provide the desired aromatic heterocycles (Fig. 3). Depending on the level of unsaturation, IMDAF intermediate **2** aromatizes after ether bridge opening to allylic alcohol **4**, double dehydration and a retro-ene Boc-thermolysis[9] to give indole **5**. Alternatively, if starting material **1** contains an alkyne, **2** leads to bisallylic alcohol **6**, and dehydration of phenol **7** generates 5-hydroxyindole **8**. The mechanistic analysis of this transformation inspired us to consider alternative disconnections to accomplish an equivalent, convergent indole synthesis.

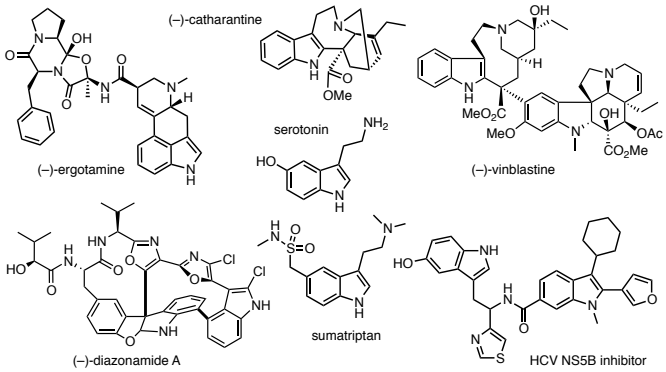

Fig. 1. Selected alkaloids and pharmaceuticals with 3-alkylated indole scaffolds.

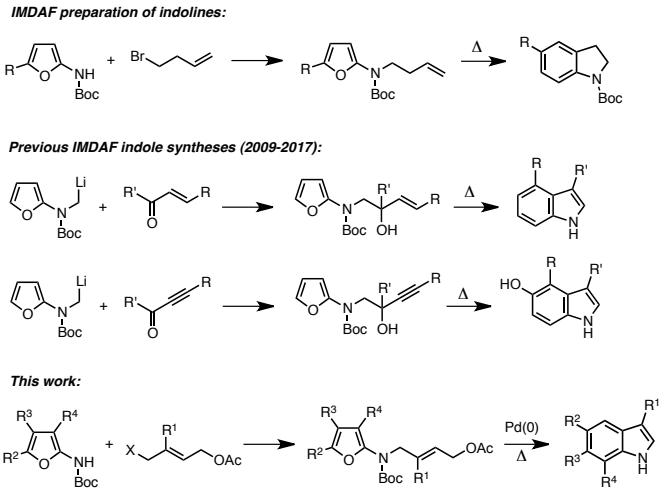

Fig. 2. Use of intramolecular Diels-Alder cycloadditions to furans for indoline and direct (non-oxidative) indole syntheses.[6,7,8]

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Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data, and NMR spectra of the products (PDF). See DOI: 10.1039/x0xx00000x

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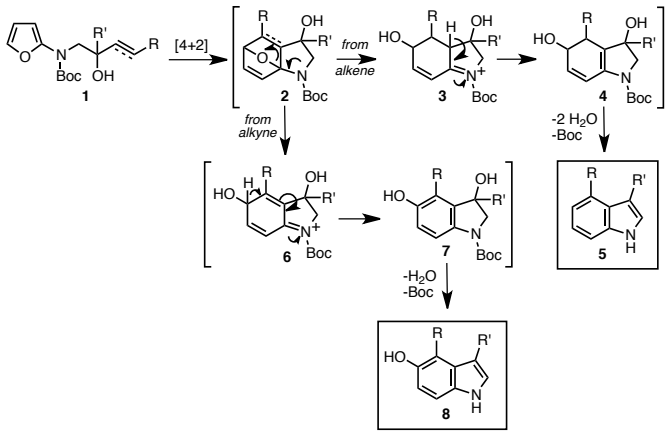


Fig. 3. Suggested reaction mechanisms for indole ring formation from allylic and propargylic amido alcohols **1**.[6,7,8]

Since the preparation of the amido alcohol **1** required the use of a tributylstannane-derived reactive organolithium reagent, we were interested in extending the scope of this new IMDAF indole synthesis by a transposition of the allylic carbon-oxygen bond as shown in **11**,[10] thus enabling the use of a simple S_N2-reaction for *N*-alkylation and combination of building blocks **12** and **13** (Fig. 4). Activation of **11** and isomerization of the alkene into the desired homoallylic position versus the Boc-amine was going to be accomplished by means of π-allyl palladium complex **10**.[11]

Results and Discussion

Mesylate **14** and *N*-Boc-2-aminofuran **12** were combined to afford a model system, (*Z*)-allylic acetate **15**, for the study of this transformation (Scheme 1). On exposure of **15** in a concentration of 1.0 M in NMP to 5 mol % of $Pd(PPh_3)_4$ and 20 mol % of PPh_3 under microwave irradiation conditions, starting material and five distinct new products were identified: the desired indole **9**, the (*E*)-allylic acetate **11**, the deallylated *N*-Boc-2-aminofuran **12**, the isomerized allylic acetate **16**, and the ester elimination product, diene **17**. Below 100 °C, mainly isomerization products **11** and **16** were formed. At temperatures between 100 °C and 150 °C, elimination products **12** and **17** were prominent. For example, at 100 °C, 6% starting material **15**, 27% isomerized compound **11**, 9% terminal alkene **16**, and 33% diene **17** were isolated, whereas 130 °C produced 22% of **11**, 43% of **17**, and 21% of **12**. Finally, at 180 °C for 20 min, 19% of the desired indole **9** was isolated. Moreover, under otherwise identical conditions, the trisubstituted (*E*)-alkene **19** provided skatole **20** in 45% yield.

Based on these encouraging preliminary data, we selected the conversion of **19** to **20** for a more extensive screen of ligand conditions, a decision that was guided in part by the assumption that the 3-methyl substituent on indole **20** was representative for the 3-alkylated indole natural products and biologically active compounds we were most interested in (Fig. 1). While the use of 20 mol % of the more electron-rich and more air-stable alkyl phosphine PBn_3 in place of PPh_3 increased the yield dramatically to 74%,[12] other alkyl phosphines such as P(*n*-Bu)$_3$ and P(*t*-Bu)$_3$ actually lowered the yield significantly, or failed to provide product (Table 1, Entries 1-4).

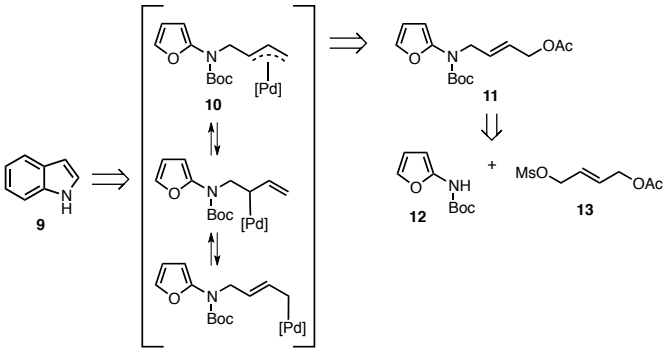
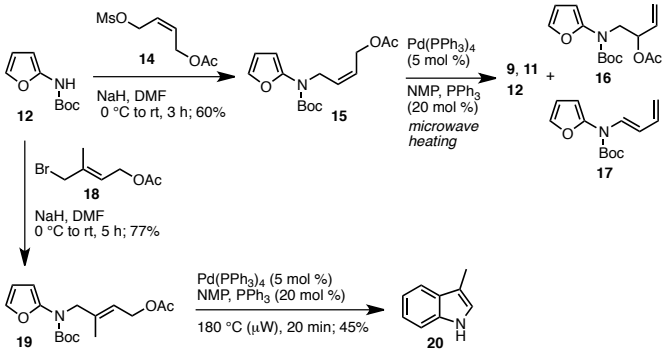


Fig. 4. Retrosynthetic strategy to generate indoles from Boc-aminofuran **12** and allylic mesylate **13**.



Scheme 1. Exploratory studies for the Pd-catalyzed cascade conversion of allylic acetates to indoles.

Table 1. Isolated yields for the formation of skatole **20** in a 0.1 M solution of furan **19** in NMP in the presence of $Pd(PPh_3)_4$ (5 mol %) and ligand (20 mol %) under microwave irradiation at 180 °C for 20 min.

Entry	Ligand	Yield	Entry	Ligand	Yield
1	PPh_3	45%	6	dppp	40%
2	PBn_3	74%	7	dppb	59%
3	P(*n*-Bu)$_3$	25%	8	P(OEt)$_3$	71%
4	P(*t*-Bu)$_3$	0%	9	P(O*i*-Pr)$_3$	83%
5	dppe	48%	10	P(OPh)$_3$	27%

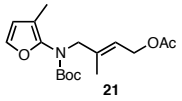
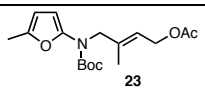
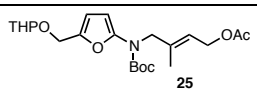
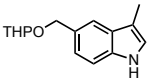
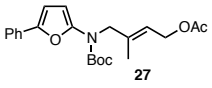
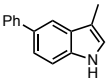
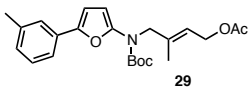
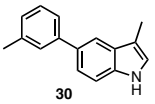
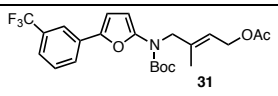
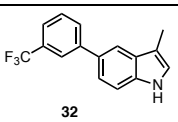
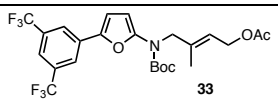
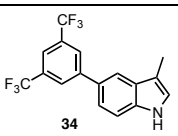
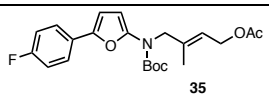
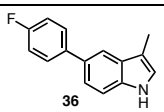
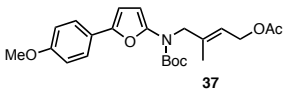
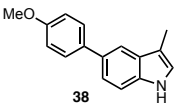
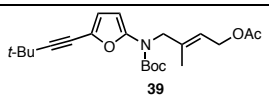
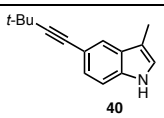
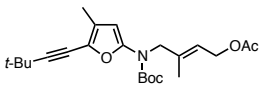
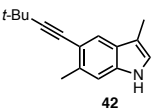
Diphosphine ligands, i.e. dppe, dppp, and dppb,[13] delivered quite consistent yields in the 40-60% range (Entries 5-7). Overall, however, alkyl phosphites proved to be superior for the preparation of **20**, since P(OEt)$_3$ gave the indole in 71% yield, and P(O*i*-Pr)$_3$ produced 83% (Entries 8 and 9).[14] Triphenylphosphite was inferior as a ligand, furnishing only

27% of product (Table 1, Entry 10), and thus supporting the overall observation that both the electron density and the steric size of the palladium ligands had a major influence on the reaction outcome. Finally, we also varied palladium loadings, and found that 5 mol % of $Pd(PPh_3)_4$ was indeed optimal, and that the use of $Pd_2(dba)_3$, $PdCl_2$, or $Pd(OAc)_2$ resulted in a decrease in turnover efficiency.[15] We also briefly explored a conventional thermal conversion of **19** to **20** under the optimized time, temperature, catalyst and ligand conditions; but, to our surprise, only recovered starting material. The mechanistic relevance and generality of this observation remains to be addressed in future studies of this reaction, in particular since the analogous, transition metal free conversion of **1** to **5** generally occurred with comparable efficiency under both conventional thermal and microwave conditions.[6,7,8] Finally, using Wilkinson's catalyst, $Rh(PPh_3)_3Cl$, in the presence of phosphite ligands led to partial recovery of starting material in addition to unidentified decomposition products both at 150 °C and 180 °C.

The optimized reaction conditions (5 mol % $Pd(PPh_3)_4$, 20 mol % $P(OiPr)_3$, microwave irradiation at 180 °C for 20 min in 0.2 M solution of substrate in NMP) were applied to determine the scope of this cascade Tsuji-Trost π-allyl-palladium formation/ IMDAF reaction/ aromatization sequence. Alkyl and aryl substitutions on the furan were compatible with indole formation; with the highest yields arising from mildly electron-donating functionalities. For example, the 3-methylated furan **21** provided the 3,7-dimethylated indole **22** in 86% yield (Table 2, Entry 1). Moving the methyl substituent into the furan 5-position as in **23** did not influence the outcome of the reaction, but the THP-ether at this position in **25** led to a noticeable drop in the yield of the isolated 5-functionalized indole **26** to 59% (Entry 2 and 3). The presence of strongly electron-withdrawing trifluoromethyl groups had only a slightly detrimental effect on the isolated yield. While 5-phenyl furan **27** provided 5-phenyl indole **28** in 77% (Entry 4) and the *meta*-toluene analog **29** was converted in 87% yield (Entry 5), the corresponding trifluoromethylated **31** gave indole **32** in a lower yield of 41% (Entry 6). Additional trifluoromethyl groups, as in **33** (Entry 7), however, did not further decrease the isolated yield. Also, *para*-fluorinated **35** gave indole **36** in an acceptable yield of 66% (Entry 8), equivalent to the 64% conversion of *para*-methoxy furan **37** to indole **38** (Entry 9).

An alkyne substitution at the furan C-5 position was briefly explored with substrate **39**, which gave 5-alkynylindole **40** in a moderate yield of 52% (Entry 10). However, with an additional substituent at C-4, the trisubstituted furan **41** produced only 27% of the isolated indole **42** (Table 2, Entry 11). The conversions of alkynylfurans also led to a noticeably larger number of side products than the other substrates, suggesting the possibility for thermal decomposition of starting materials and/ or products under the reaction conditions.

Table 2. Pd(0)-catalyzed cascade formation of indoles from furans. Conditions: NMP, 5 mol % $Pd(PPh_3)_4$, 20 mol % $P(OiPr)_3$, microwave irradiation at 180 °C for 20 min; 0.2 M furan concentration.

Entry	Furan	Indole	Yield
1	 **21**	 **22**	86%
2	 **23**	 **24**	84%
3	 **25**	 **26**	59%
4	 **27**	 **28**	77%
5	 **29**	 **30**	87%
6	 **31**	 **32**	41%
7	 **33**	 **34**	48%
8	 **35**	 **36**	66%
9	 **37**	 **38**	64%
10	 **39**	 **40**	52%
11	 **41**	 **42**	27%

Originally, our design of this new reaction sequence was based on the mechanistic hypothesis that the π-allyl species **44**, formed by the Pd(0)-catalyzed elimination of allylic acetate **43**, was capable of an IMDAF reaction either directly or by virtue of the σ-bonded allylic palladium complex **45** (Fig. 5). However, it is entirely feasible that a Friedel-Crafts type intramolecular attack on the electron-rich furan ring leads to the transient palladium-complex **46**, which, upon reductive elimination, results in the bicyclo[5.2.1] π-complex **47**.[16]

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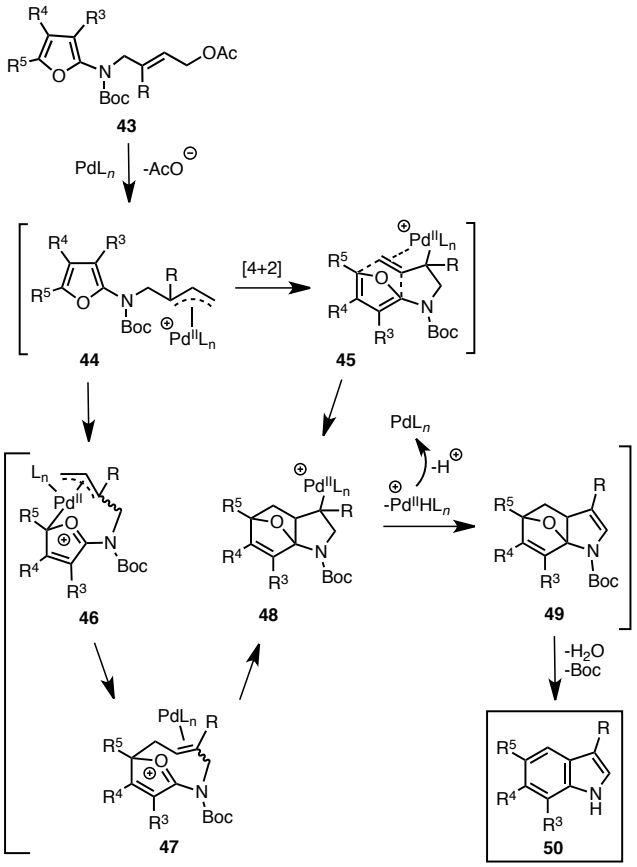

Fig. 5. Possible reaction mechanisms for indole formation from allylic acetate **43**.

Both pathways converge mechanistically in the formation of the intermediate σ-complex **48**, which, after elimination of palladium hydride, forms the ether-bridged **49**. The latter compound has already been shown[6,7] to readily aromatize to indole **50** under thermal conditions after water and Boc-group eliminations.

Conclusions

Based on a mechanistic hypothesis, we have developed a tin- and organolithium-free variant of our IMDAF indole synthesis. This new approach takes advantage of the reactivity of an intermediate π-allyl palladium complex and provides the desired heterocycles in a convergent fashion in moderate to high yields from readily available starting materials. The scope of the cascade reaction was demonstrated to extend to 5-, 6-, and 7-substituted indoles bearing alkyl-, alkynyl-, aryl-, and heteroatom-functionalized side chains. The use of microwave heating allows for a rapid and convenient access to these synthetically and biologically useful scaffolds. Further applications and mechanistic studies that address possible concerted [4+2] or alternative stepwise Friedel-Crafts-type reaction manifolds will be reported in due course.

Acknowledgements

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Notes and references

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