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A microwave assisted intramolecular-furan-Diels–Alder approach to 4-substituted indoles†

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Abstract

The key steps of a versatile new protocol for the convergent synthesis of 3,4-disubstituted indoles are the addition of an α-lithiated alkylaminofuran to a carbonyl compound, a microwave-accelerated intramolecular Diels–Alder cycloaddition and an *in situ* double aromatization reaction.

The indole moiety is a ubiquitous structural motif that is found in a wide array of naturally occurring alkaloids and designed therapeutic agents. Interestingly, a relatively uniform fraction of ~4% of all pharmaceuticals, high-throughput screening samples, as well as natural products, contain an aromatic or partially saturated indole core (Fig. 1).[1] Accordingly, the search for efficient protocols for the synthesis of substituted indoles has remained an important research topic for over a century.[2] As part of a program aimed at the synthesis of Ergot alkaloids,[3,4] we have investigated suitable methodologies for the late-stage introduction of a 4-substituted indole ring system. Padwa and co-workers have developed an intramolecular Diels–Alder furan cycloaddition reaction that provides substituted indolines from *N*-homoallylic 2-aminofurans.[5,6] We envisioned that the addition of an α-lithiated alkylaminofuran, **1**, to an α,β-unsaturated carbonyl compound, **2**, followed by the *in situ* cycloaddition and dehydrative aromatization of **6**, would allow an extension of this methodology to the direct preparation of 4-substituted indoles, **7** (Scheme 1).

The preparation of lithium reagent **1** was accomplished by transmetalation of stannane **10** (Scheme 2), which was readily obtained from known iodide **8**[7] and Boc-protected 2-aminofuran **9**[8] in the presence of sodium hydride. We next explored conditions for the addition of **10** to α,β-unsaturated carbonyl compounds. Transmetalation with n-butyllithium in THF occurred only sluggishly at −100 °C, and decomposition was found to be the major pathway at 0 °C. However, at −78 °C, transmetalation was complete within 15 min, and upon treatment with an excess of cinnamaldehyde, the expected addition product, **11**, was obtained in 66% yield.

After establishing a viable route to homoallylic furanyl amines, we turned our attention to the intramolecular Diels–Alder cascade indole formation process. Initially, alcohol **11** was heated in toluene at reflux. After 48 h, gradual decomposition of the starting material was observed. In contrast, when **11** was heated in *o*-dichlorobenzene under microwave irradiation for 30 min at 170 °C, complete consumption of the starting material was observed, and 4-phenylindole

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(**12**) was isolated in 72% yield, presumably according to the mechanism shown in Scheme 1. Indeed, this process proceeded concomitantly with thermal Boc deprotection.[9] In an effort to shorten the reaction time, temperatures were varied, and optimal conditions were found to involve microwave heating of furan derivatives for 20 min at 180 °C. Under these conditions, **12** was obtained in 79% yield from **11** (Table 1, entry 1). The success of the microwave conditions *vs*. standard heating is likely to be a consequence of the much faster heating process and the higher temperatures in the pressurized reaction vial, which can easily be accomplished with current microwave reactors.

This annulation strategy is quite tolerant of functional groups. Initially, we varied the 4-aryl substituents from simple electron-rich (entries 2 and 4) to electron-deficient arenas (entry 3), observing a slight increase in yield to 83% in the case of the 4-fluoro aryl substituent. *Para*- and *meta*-substituted arenes with ester-functionalized side chains behaved analogously to the methyl group (entries 5 and 6). The use of a tosyl-protected indole ring in substrate **23** provided the corresponding 3,4′-bisindole **24** (entry 7).

When symmetric bisfuran **25** was subjected to the Diels–Alder cascade process, diannulated products **26** and **27** were obtained exclusively in a 7 : 4 ratio, with no monocyclization being observed (entry 8). Interestingly, in this case, the major product still contained a single Boc protecting group. The formation of a monoprotected derivative of an otherwise symmetrical bisindole could potentially be advantageous for selective functionalizations and desymmetrizations. Alternatively, re-subjecting this compound to thermal reaction conditions (microwave irradiation at 180 °C, 20 min) cleanly removed the residual Boc functionality to afford fully deprotected species **27** in 89% yield after chromatographic purification.

The introduction of alkenyl and alkyl groups in position 4 of the newly formed indole ring was also possible (entries 9–12). Propenyl derivative **29** was isolated in 69% yield in a 7 : 1 ratio of *E* : *Z* isomers, while the efficiency of the process was slightly reduced for cyclopropyl compound **31** (48% yield) and isopropyl indole **33** (36% yield). In spite of the lower yield observed for **31**, the successful use of a cyclopropane-substituted compound in this reaction sequence is noteworthy.

We were also interested in expanding the scope of this reaction to 3,4-disubstituted indoles, derived analogously from additions of lithium reagent **1** to α,β-unsaturated ketones. Specifically, *tert*-alcohol **34** was obtained by the treatment of **1** with 5 equiv. of 2-cyclohexene-1-one. The exposure of **34** to the standard microwave conditions provided cyclohexane-annulated indole **35** in 84% yield. Tricycle **35** is representative of the core heterocycle of many Ergot alkaloids.

In conclusion, we have developed a new method for the convergent and rapid preparation of 4-monosubstituted and 3,4-disubstituted indoles featuring the microwave-assisted Diels–Alder cyclization of furans. The cascade process is quite tolerant of functional groups and associated substitution patterns. This strategy is a convenient alternative to the common transition metal-mediated coupling processes for the synthesis of these heterocycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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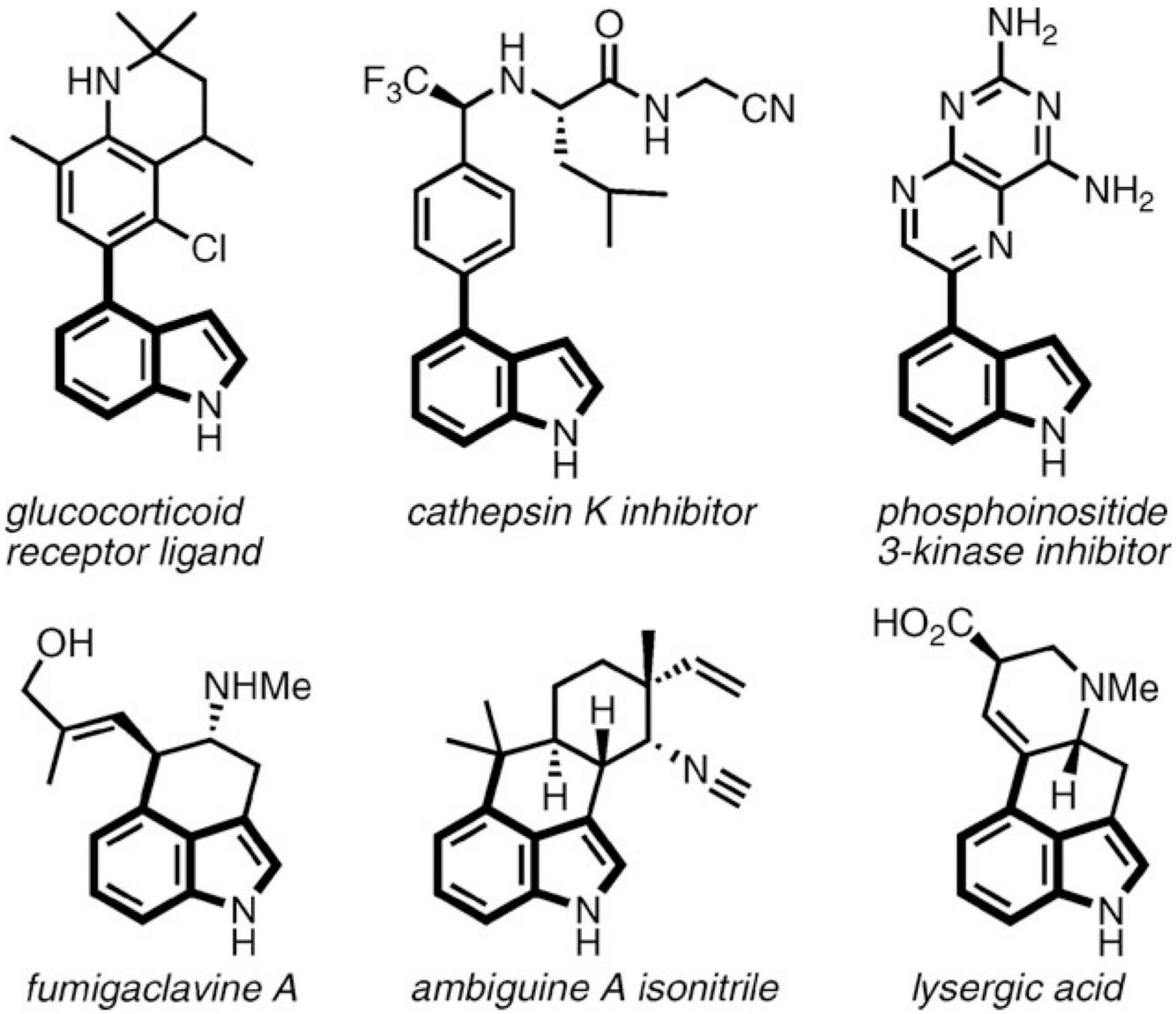
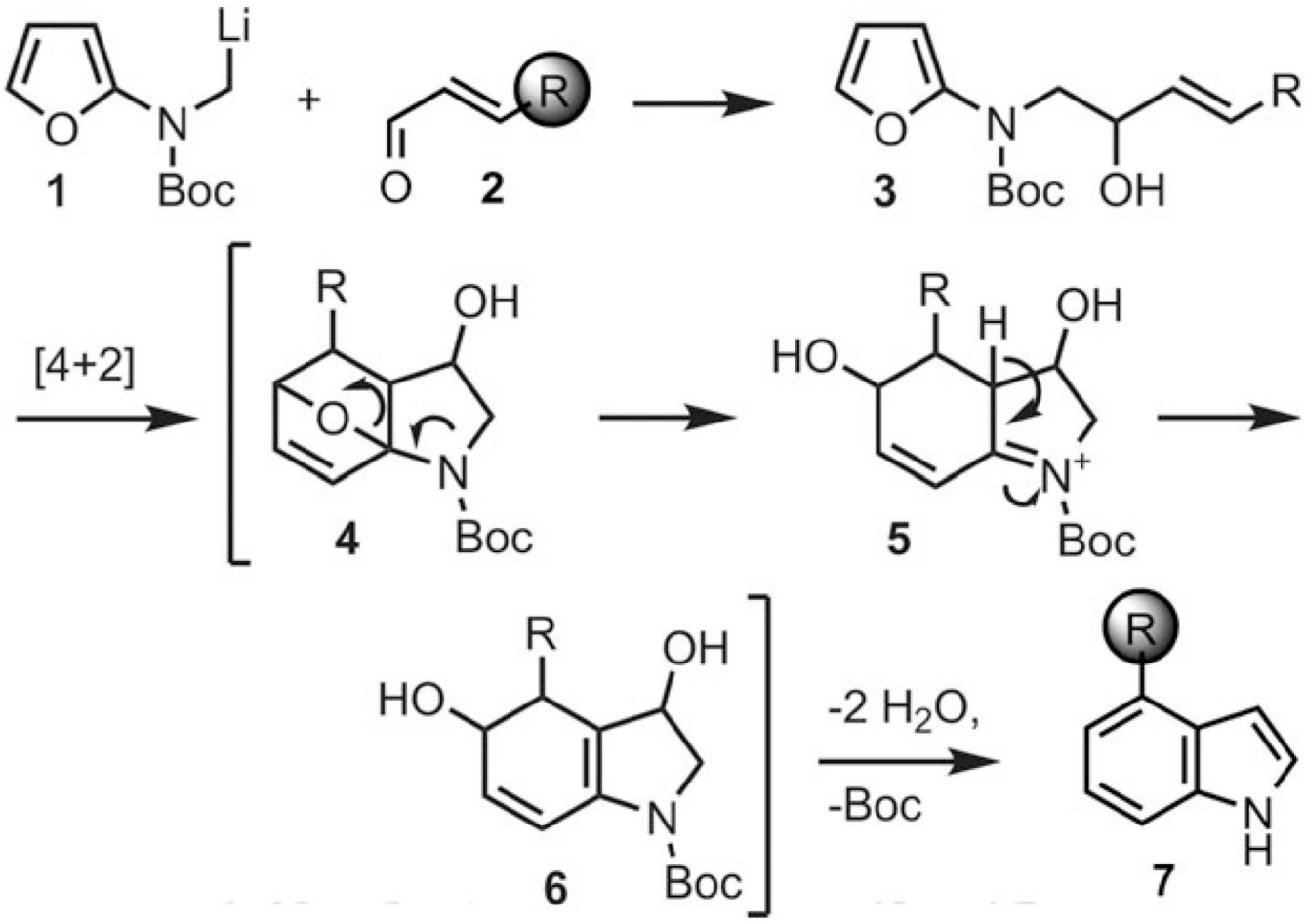
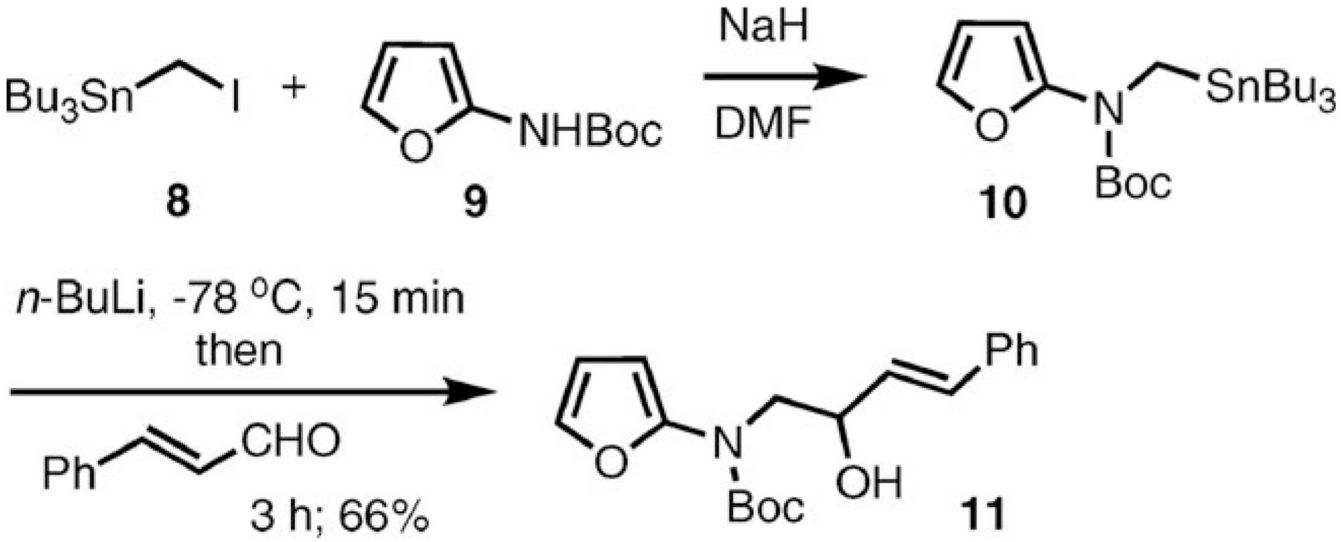


Fig. 1.
Representative synthetic and natural products with 4-substituted indole scaffolds (outlined in bold).[1]



Scheme 1.
Proposed indole synthesis.



Scheme 2.
The preparation of furanyl stannane **10**, and a typical transmetalation and aldehyde addition reaction.

Table 1

Scope of the microwave-accelerated intramolecular Diels–Alder indole formation cascade reaction

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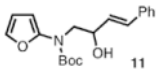
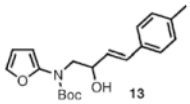
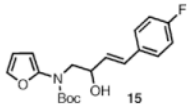
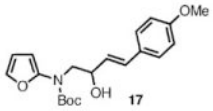
1	 11
2	 13
3	 15
4	 17

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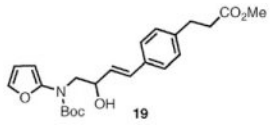
5	 19

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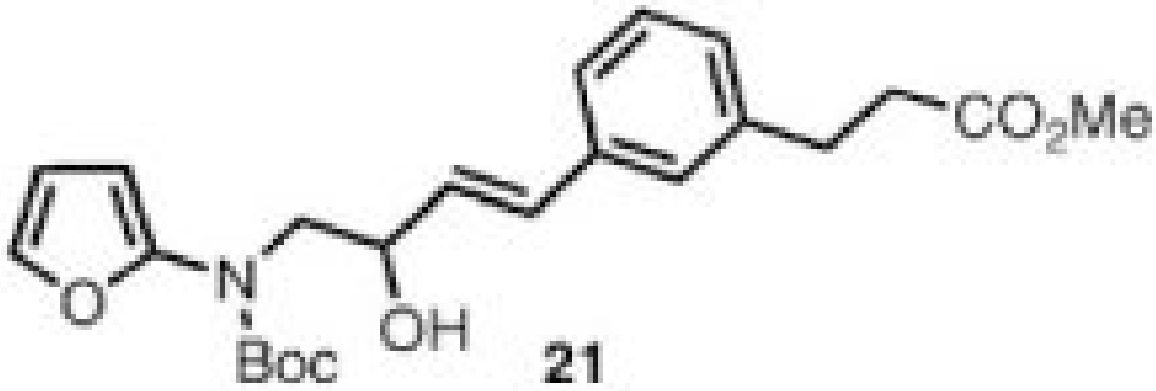
6	 21

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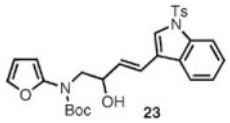
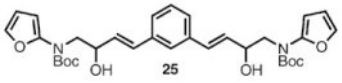
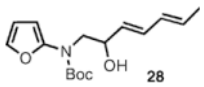
7	 23
8	 25
9	 28

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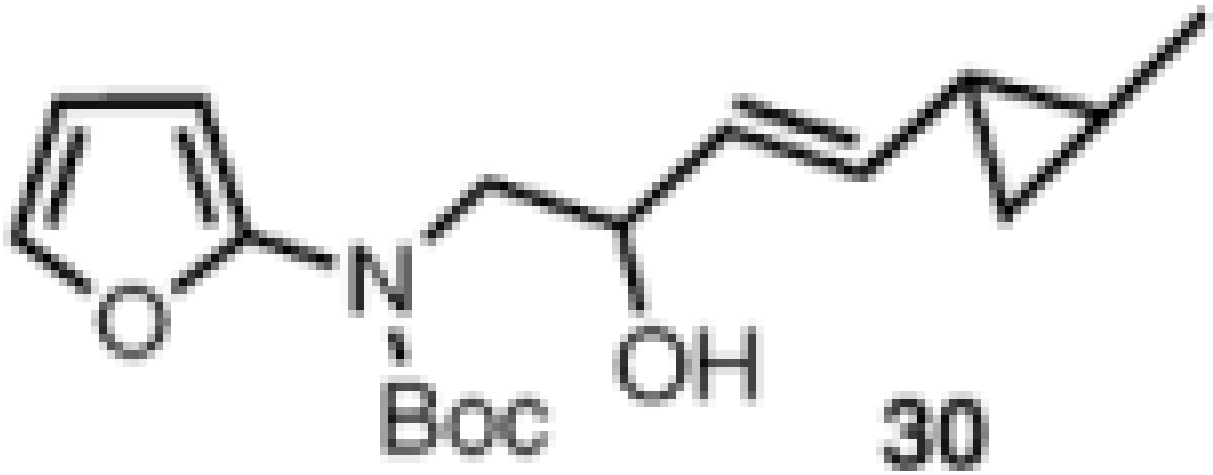
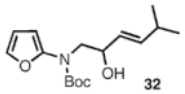
10	 30
11	 32

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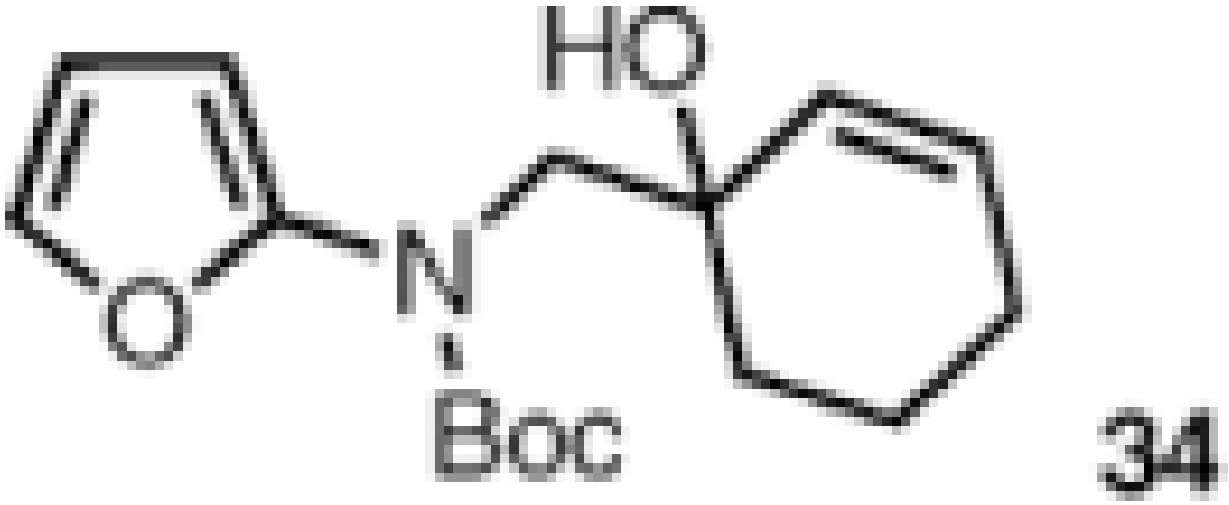
12	 34