Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
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Cite this: *Chem. Sci.*, 2021, **12**, 13756

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 28th June 2021
Accepted 15th September 2021

DOI: 10.1039/d1sc03533a

rsc.li/chemical-science

A general approach to 2,2-disubstituted indoxyls: total synthesis of brevianamide A and trigonoliimine C†

Fan Xu and Myles W. Smith *

The indoxyl unit is a common structural motif in alkaloid natural products and bioactive compounds. Here, we report a general method that transforms readily available 2-substituted indoles into 2,2-disubstituted indoxyls *via* nucleophile coupling with a 2-alkoxyindoxyl intermediate and showcase its utility in short total syntheses of the alkaloids brevianamide A (7 steps) and trigonoliimine C (6 steps). The developed method is operationally simple and demonstrates broad scope in terms of nucleophile identity and indole substitution, tolerating 2-alkyl substituents and free indole N–H groups, elements beyond the scope of most prior approaches. Spirocyclic indoxyl products are also accessible *via* intramolecular nucleophilic trapping.

Introduction

Indoxyls, also known as indolin-3-ones, are important structural units in biologically active small molecules and natural alkaloids (**1–5**, indoxyl highlighted in red, Fig. 1A), and serve as versatile precursors to related N-heterocyclic compounds (*e.g.*, **6**).[1] These include the highly cytotoxic duocarmycins (*e.g.*, **3**) and the potent μ-opoid receptor agonist mitrogynine pseudoindoxyl (**4**), which have received interest from the medical community as payloads in antibody–drug conjugates or potential analgesics, respectively.[2] 2,2-Disubstituted indoxyls bear a fully substituted center at the C-2 position and represent a core challenge in the synthesis of targets such as iboluteine (**1**) and brevianamide A (**2**). While many creative methods toward 2,2-disubstituted indoxyls have issued from the synthetic community, including cyclization/trapping of 2-alkynyl aryl azides[3] or -nitroarenes,[4] aryne heteroannulation,[5] interrupted Ugi reactions,[6] and many others,[7] challenges still remain in accessing such motifs bearing two alkyl substituents at C-2, as would be required for **1–2**.

One of the most convenient ways to access 2,2-disubstituted indoxyls (**8**) is *via* dearomatization of readily available indole starting materials.[8] Broadly speaking, such reactions fall into two classes: those that begin with (or proceed *via*) a 2,3-disubstituted indole (**7**), and those that begin with a 2-substituted indole (**9**) and introduce the second substituent through an additional nucleophilic component (Fig. 1B). The former approach proceeds *via* oxidation of the disubstituted indole **7** to a 3-hydroxyindolenine (**10**), followed by Wagner–Meerwein-type 1,2-shift of the C-3 substituent to C-2 with concomitant formation of the indoxyl ketone.[9] Indeed, this approach has been widely explored, including in alkaloid total synthesis,[10] but can suffer from competing rearrangement into the 3,3-disubstituted oxindole isomer **12** (*via* transient epoxide **11**) in a manner that can be highly substrate- and condition-specific. Additionally, the preparation of the required 2,3-disubstituted indole can often be step-intensive.

Alternatively, from a 2-substituted indole (**9**), oxidation can yield an electrophilic 3-oxoindolenine (**13**) or its 2-hydroxy/alkoxyindoxyl equivalent (**14**) prior to iminium trapping with a nucleophile, often mediated by Lewis or Brønsted acids. Aside from being complementary to the prior rearrangement approach, this strategy offers the advantage of being convergent, provided sufficient generality is available for the nucleophilic and electrophilic components. While this approach has been explored,[11] a key issue in such reactions is avoiding simple dimerization of the indole fragment *via* attack of the nucleophilic indole starting material onto **13** during oxidation to yield an adduct like **15**. In fact, many methods explicitly target such dimers (or trimers) because of this problem.[12] Additionally, where cross-couplings are possible, the overwhelming majority of such methods are only suitable for 2-aryl substituted systems and/or require *N*-substitution, likely due to the instability of the corresponding 2-alkylimine/iminium intermediates (*vide infra*).[11] Though a handful of exceptions exist,[11a,h,j,m] these approaches also typically employ highly nucleophilic coupling partners like indoles or pyrroles (Mayr nucleophilicity parameter, $N = 5.5–7$)[13] presumably to ensure efficient iminium trapping. Among these methods, You and coworkers reported a notable asymmetric coupling of indoles with spiroindoxyls

Department of Biochemistry, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, Texas 75390, USA. E-mail: myles.smith@utsouthwestern.edu

† Electronic supplementary information (ESI) available. CCDC 2092889. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc03533a

that relies on a hydroxyalkyl chain as reversible iminium trap (see **16**, Scheme 1B, bottom), building off of racemic work by Kobayashi,[11a] which necessarily limits the scope to specific 2-(hydroxyalkyl) substrates (**18**).[11d]

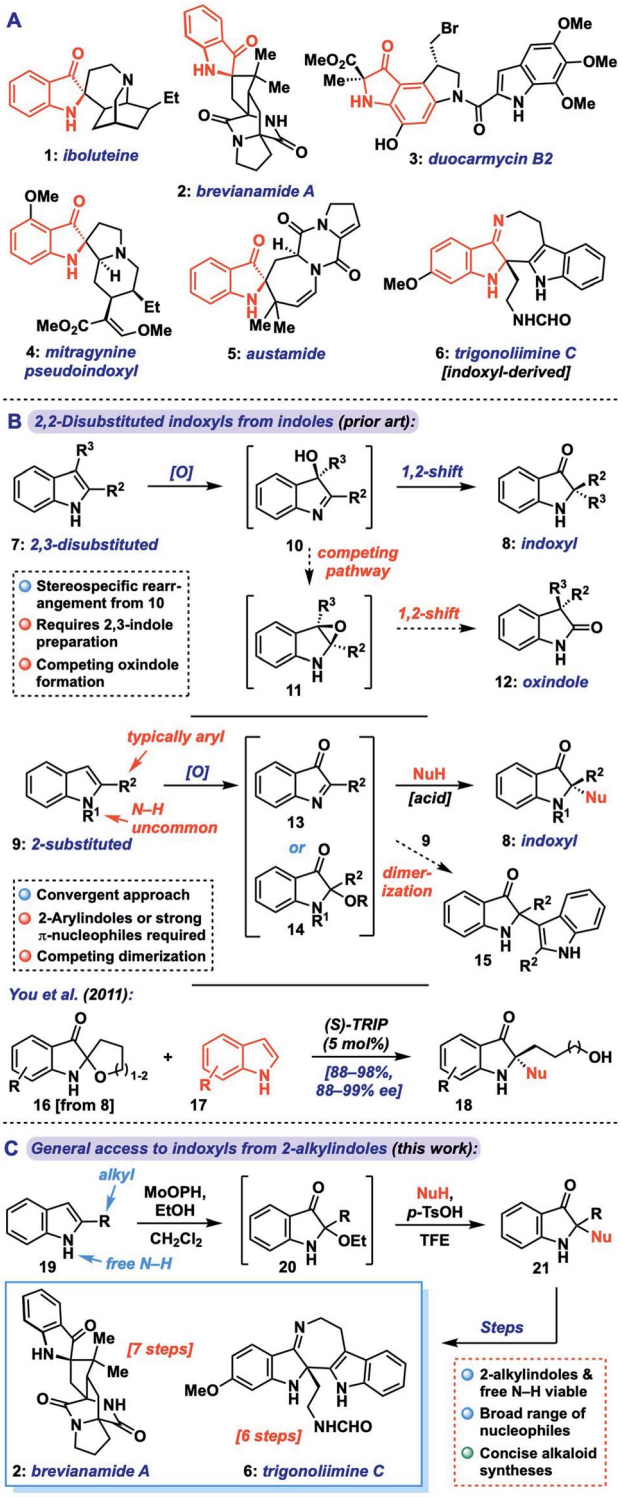


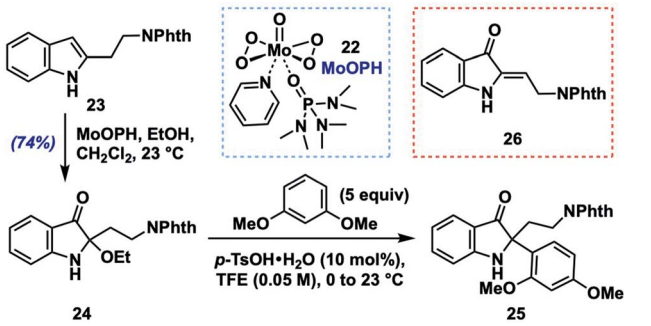
Fig. 1 (A) Bioactive indoxyl natural products. (B) Approaches to 2,2-disubstituted indoxyls *via* indole dearomatization. (C) Our general method to 2,2-disubstituted indoxyls from 2-alkylindoles and its application in alkaloid synthesis.

Thus, a general approach which can tolerate a range of 2-alkyl substituents, a broader selection of nucleophiles, and not require *N*-protection would be highly desirable. This should expedite the synthesis of complex targets such as trigonoliimine C (**6**) and is especially evident when considering application to indoxyl alkaloids such as iboluteine (**1**) or brevianamide A (**2**), neither of which incorporate a 2-aryl unit or *N*-substitution. Herein, we describe the development of a general approach that transforms readily available 2-substituted indoles into 2,2-disubstituted indoxyls *via* nucleophile coupling with a 2-alkoxyindoxyl intermediate. The method demonstrates broad scope in terms of nucleophile identity and indole substitution, tolerating 2-alkyl substituents and free indole N–H groups. The utility of our approach is highlighted in concise syntheses of the alkaloids brevianamide A (**2**) and trigonoliimine C (**6**).

Results and discussion

To begin these efforts, we sought a robust, alkyl-group-tolerant entry to an activated intermediate such as **13** or **14** from 2-alkylindoles, which are either commercially available or accessible in one step using the C–H alkylation method developed by Bach and coworkers.[14] Out of these options, we considered 2-alkoxyindoxyl intermediates to be the most feasible precursors. Although we screened several potential methods for their

Table 1 Optimization of nucleophile coupling[a]



Entry	Deviation from above	**25** (%)	**26** (%)
1	None	98 (95)[b]	0
2	HFIP as solvent	99 (98)[b]	0
3	CH_2Cl_2 as solvent	19	27
4	THF as solvent	0	85
5	CH_3CN as solvent	6	14
6	TFA as catalyst	81	0
7	TMSOTf as catalyst	56	0
8	TMSCl as catalyst	58	0
9	$TiCl_4$ as catalyst	94	0
10	$BF_3 \cdot OEt_2$ as catalyst	86	0
11	5 mol% *p*-TsOH·H_2O	56	0
12	3.0 equiv. nucleophile	(80)[b]	0
13	1.5 equiv. nucleophile	72 (63)[b]	0

[a] Reactions conducted on 0.1 mmol of **24**; ^{1}H NMR yields with 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yield.

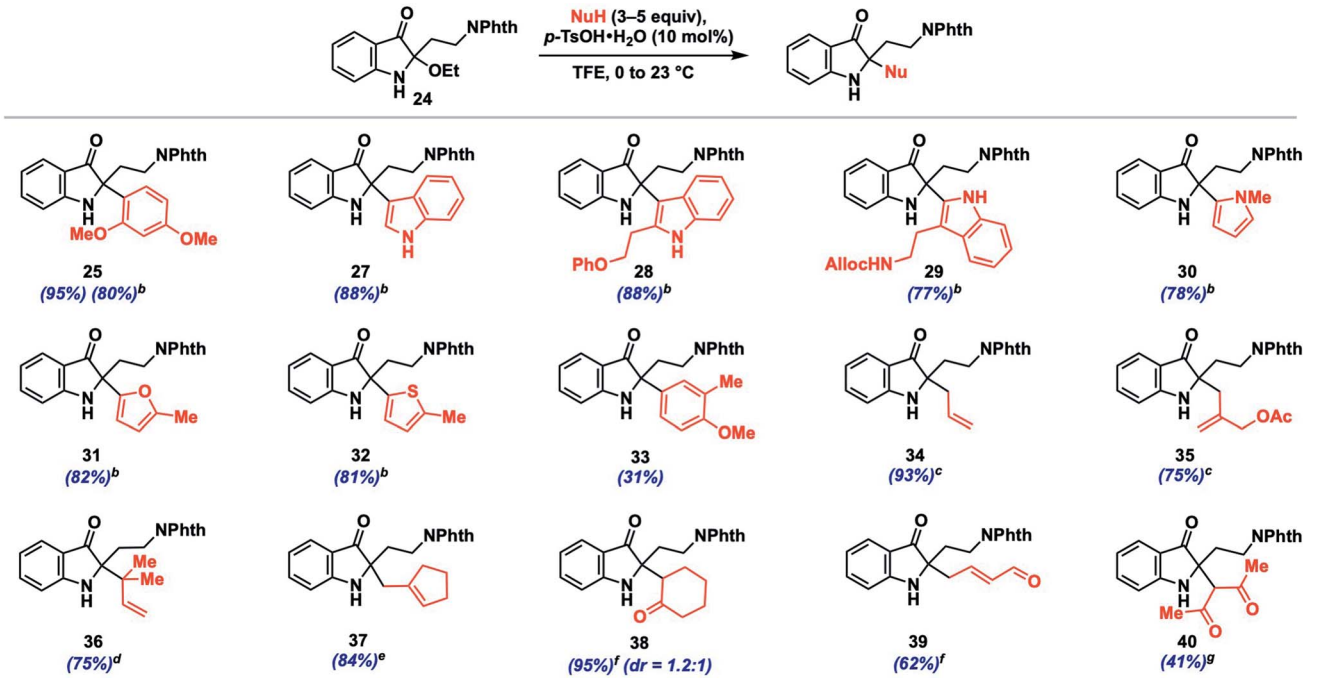
preparation,[15] we found that the most user-friendly and scalable option was to treat the indole substrate with oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)[16] (MoOPH, **22**, 2.0 equiv.) in a mixture of CH_2Cl_2 and EtOH at room temperature.

Similar oxodiperoxymolybdenum(VI) complexes had been reported for *N*-acylindole oxidations by Sakamoto[17a,b] and later by Jimenez,[17c] along with a single example of the use of **22** with a free N–H 2-alkylindole substrate.[17d] Using these mild oxidation conditions, phthalimide-containing model substrate **23** [18] was converted to N–H 2-ethoxyindoxyl **24** in 74% after rapid chromatographic purification on triethylamine-deactivated silica gel (Table 1). In general, however, N–H 2-ethoxyindoxyl compounds displayed variable stability to chromatographic purification (often more severe than **24**), which led us to develop a two-step, one-purification protocol from indole to final indoxyl product (*vide infra*); for optimizing the nucleophile coupling part of that sequence, however, we chose to utilize pure **24**.

We began by screening conditions for coupling **24** with 1,3-dimethoxybenzene (5 equiv.) as a moderately nucleophilic partner ($N = 2.48$).[13a] Initial efforts to employ a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH, 10 mol%) in several common solvents (entries 3–5) at 0 °C to room temperature showed that a key issue was simple elimination of the ethoxy group (presumably *via* an iminium ion) to give (*Z*)-enamine **26**.[19] We found, however, that the fluoroalcohol solvents 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which are known to stabilize cationic intermediates,[20] gave none of the elimination byproduct and provided excellent yields of the desired aryl coupling product **25** (HFIP: 99%; TFE: 98%; entries 1 and 2). In fact, upon screening different acids in TFE, we found that acid identity was not especially important, with several Brønsted acids and Lewis acids (entries 6–10) all providing product to varying degrees (*e.g.*, trifluoroacetic acid: 81%; $TiCl_4$: 94%). In the case of Lewis acids in TFE, we consider these as likely precursors of the corresponding Brønsted acid (*e.g.*, TfOH from TMSOTf) or perhaps able to engage in Lewis acid-assisted Brønsted acid[21] catalysis with the protic solvent (*e.g.*, $BF_3 \cdot OEt_2$). To assess whether *p*-TsOH in TFE was simply able to reprotonate any enamine **26** that formed to the iminium ion in order to funnel it to product **25**, we subjected **26** to the standard reaction conditions (entry 1). Only decomposition of **26** was noted with no **25** formed, suggesting that the TFE solvent either stabilizes the intermediate iminium ion or increases the rate of its reaction with the aryl nucleophile (or both). Efforts to employ a lower loading of nucleophile and acid catalyst (entries 11–13) showed a moderate reduction in yield with 3 equivalents of arene (80%) but a more significant drop with 1.5 equivalents of nucleophile (72%) or 5 mol% *p*-TsOH (56%). Ultimately, we settled on the use of 10 mol% *p*-TsOH in TFE as a mild, user-friendly, and relatively inexpensive set of conditions with which to explore the generality of this method.[22]

We initiated such studies by exploring the nucleophile scope using purified **24** as the iminium precursor (Table 2). Pleasingly,

Table 2 Nucleophile scope[a]



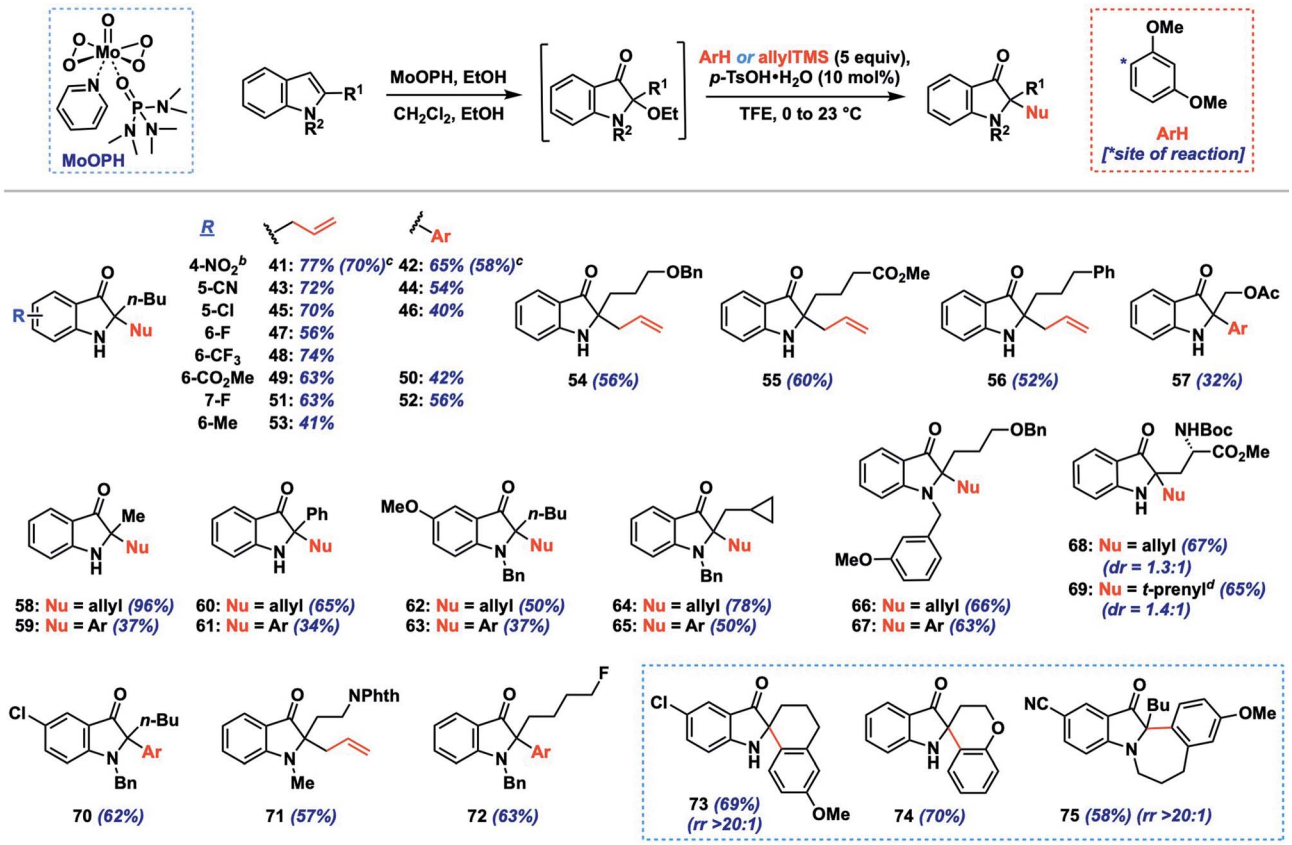
[a] Reactions conducted on 0.1 mmol of **24** using 5 equiv. of nucleophile unless otherwise noted. [b] 3 equiv. nucleophile. [c] From the corresponding allyltrimethylsilane. [d] *n*-Prenyltributylstannane as nucleophile. [e] Methylenecydopentane as nucleophile. [f] From the corresponding silylenol ether. [g] Acetylacetone as nucleophile.

the reaction tolerated a range of arene and π-nucleophiles. For highly nucleophilic arene partners ($N > 5$) like indoles and pyrrole, we found that 3 equivalents of nucleophile could be employed, while maintaining high yields (77–88%, **27–30**). Other heteroarene partners like 2-methylfuran (82%, **31**) and 2-methylthiophene (81%, **32**) were also competent under such conditions. A variety of allylations could be conducted with allylsilane, allystannane, or nucleophilic alkene partners to give olefin-containing products (**34–37**, 75–93%). The coupling efficiency with functionalized nucleophilic partners yielding **35** bearing an allylic acetoxy group (75%) or highly hindered ones which forge vicinal fully-substituted centers (75%, **36**) is noteworthy.

Additionally, we found that carbonyl nucleophiles in the form of silyl enol ethers could couple effectively, while a relatively acidic β-diketone was also a viable substrate; the products from these couplings provide versatile ketone (**38**, **40**) or enal (**39**) functionalities for further elaboration. Finally, although the nucleophile scope is greater than that observed for related indoxyl syntheses,[11,12] we did note that less nucleophilic coupling partners such as anisole ($N = -1.18$)[13b] and 2-methylanisole gave either no observed product or only a moderate yield (31%, **33**), respectively. Based on our experience, nucleophiles with $N > 1$ tended to react effectively unless steric factors became dominant (see ESI† for unsuccessful partners).

Next, we explored the tolerance of the method toward different indole substituents using 1,3-dimethoxybenzene and allyltrimethylsilane as representative nucleophiles (Table 3). As mentioned above, the stability of the intermediate 2-ethoxyindoxyl to purification was variable, so the nucleophile coupling reaction was performed on this crude intermediate following work-up to provide a convenient two-step, one-purification transformation. Using an *n*-butyl group as a model 2-alkyl substituent, the method tolerated a range of substituents on the indole nucleus, including electron-withdrawing (*e.g.*, CN, NO_2, CF_3, halogen, **41–52**; 56–77%, 2 steps) and electron-donating (Me, OMe, **53**, **62–63**), though the efficiency for the latter systems was lower (37–50%, 2 steps). Substrates bearing *N*-substitution in the form of benzyl or methyl groups also performed well in the chemistry (**62–67**, **70–72**; 37–78%, 2 steps), and were on average slightly higher yielding compared to their N–H congeners. Side-chains containing benzyloxy (**54**, **66–67**), acetoxy (**57**), phenyl (**56**), cyclopropane (**64–65**), and fluoro (**72**) functionality were well tolerated, as was a simple 2-methyl substituent (**58–59**; 37–96%, 2 steps). A substrate containing an acid sensitive Boc-protected

Table 3 Indole scope[a]



[a] Reactions conducted on 0.1 mmol of indole; yields are over 2 steps. [b] 5 equiv. MoOPH. [c] 4.0 mmol scale. [d] Using *n*-prenyltributylstannane as nucleophile; 1.0 mmol scale.

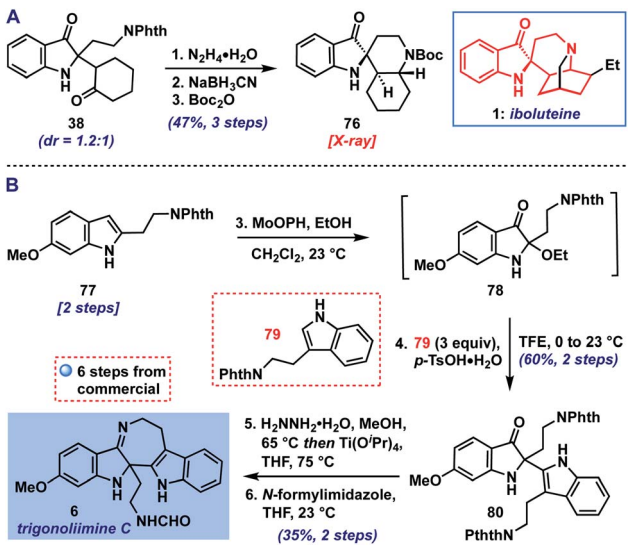
amino acid moiety also survived the coupling conditions, providing products **68** and **69** in good yields (65–67%, 2 steps) but with low diastereoselectivity (dr = 1.3–1.4 : 1).

Although not extensively explored here, given our focus on 2-alkylindole systems, we did demonstrate that 2-phenylindole could be converted to indoxyls **60** and **61** in moderate yield (34–65%, 2 steps) using our protocol. Additionally, more complex spirocyclic products (**73–74**) could be generated in good yield (69–70%, 2 steps) by incorporating nucleophilic arenes into the side-chain, while a fused 7-membered indoxyl was formed *via* cyclization of an *N*-tethered methoxyarene (**75**, 58%). Finally, larger-scale preparations of products **41** and **42** (0.88 g, 4.0 mmol) proceeded in only slightly lower yields than our screening results (70 *vs.* 77%, 58 *vs.* 65%, respectively), suggesting that the reaction can provide useful quantities of indoxyl products if required.

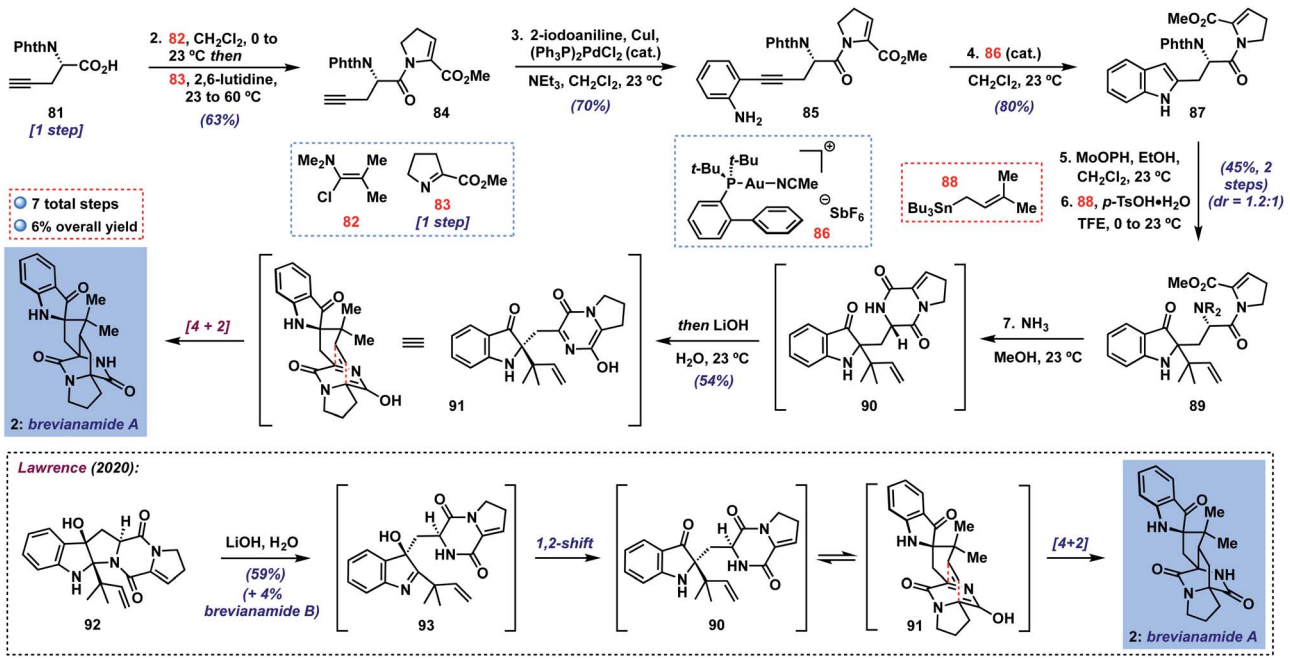
With the scope of the method defined, we returned to our original goal of its application to complex molecule synthesis (Scheme 1). As an initial test, we targeted the preparation of the core structure of indoxyl-containing *Iboga* alkaloids like iboluteine (**1**)[23] represented by spirocyclic Boc-amine **76**. We were able to access this polycyclic indoxyl from cyclohexanone adduct **38** *via* a deprotection/reductive amination/protection sequence (Scheme 1A). The two initial steps appeared to converge the mixture of diastereomers of **38** to one observable product, presumably *via* epimerization α-to the ketone or imine. The final structure and stereochemistry of **76** were confirmed by X-ray crystallographic analysis.

Next, we set our sights on the synthesis of trigonoliimine C (**6**), an indole alkaloid isolated from the leaves of *Trigonostemon lii*[24] that displays moderate anticancer activity (Scheme 1B).[25d] Trigonoliimine C (**6**) has been the subject of three prior total syntheses by the groups of Tambar, Movassaghi, and Ramana, wherein its imine motif was accessed *via* intramolecular indoxyl-amine condensation.[25] Our synthesis of **6** began with the advancement of indole **77** (prepared in two steps from commercial materials, see ESI†) to 2-ethoxyindoxyl intermediate **78**, followed by coupling with protected tryptamine **79** [26] (3 equiv.). This provided the indole addition product **80**, a known precursor to **6**,[25b] in 60% yield over the two steps (0.5 mmol scale). Thus, following the reported 2-step sequence,[25b,c] we completed our synthesis of trigonoliimine C (**6**) in a total of 6 steps (longest linear sequence).

Finally, we targeted the preparation of the more challenging brevianamide A (**2**) (Scheme 2), a bicyclo[2.2.2]diazaoctane alkaloid isolated from the fungus *Penicillium brevicompactum* in 1969 and shown to possess antifeedant activity against a number of crop pests.[27] Though many illuminating biogenetic studies and syntheses of targets in this family have been reported over the last four decades,[28] the total synthesis of brevianamide A has only very recently been achieved by Lawrence and coworkers (inset, Scheme 2).[29] These authors described an elegant biomimetic approach to **2**, involving a 1,2-shift to putative indoxyl **90** from transient 3-hydroxyindolenine intermediate **93** (*cf.* **10** → **8**, Fig. 1B), followed by a tautomerization/intramolecular [4 + 2] sequence. Overall, their approach provides a short 7-step synthesis of this natural product and its minor diastereomer, brevianamide B. For our part, we hoped to access **90** in a complementary fashion without the need for C-3/C-2-migration by utilizing a 2-substituted indole precursor. Thus, beginning with *N*-protected amino acid **81** [30] (one step from commercial L-propargylglycine), we could couple its carboxylic acid with imine **83** [29,31] *via* activation with Ghosez's reagent[32] (**82**) under modified literature conditions[33] in 63% yield; here, heating the mixture of imine **83** and putative acid chloride proved crucial to achieving reasonable yields of enamide **84**. Next, a Sonogashira coupling with 2-iodoaniline delivered 2-alkynyl aniline **85** (70%), which could be smoothly cyclized to indole **87** using JohnPhosAu(MeCN)SbF_6 (**86**) in CH_2Cl_2 at room temperature in 80% yield.[34] With **87** in hand, the stage was set for our key transformation to indoxyl **89**. In the event, oxidation yielded the expected 2-ethoxyindoxyl intermediate which was stable enough for partial chromatographic purification in this case. Subsequent treatment with prenylstannane **88** under the usual conditions generated the desired product **89** as a mixture of diastereomers (dr = 1.2 : 1) in 45% yield over the two steps. It is noteworthy that our method is able to tolerate the presence of multiple functionalities in **87** and that reverse prenylation occurs efficiently despite forming two adjacent fully-substituted centers. Although separation of each diastereomer could in principle lead to a single enantiomer of brevianamide A, we elected to advance the diastereomeric mixture together since, in a racemic sense, the diastereomers would converge to the same intermediate at the stage of heterodiene **91**. Thus, treatment with NH_3 in MeOH[29] was able to deprotect the phthalimide and cyclize to diketopiperazine **90**, which was stable enough to be purified on silica gel if desired.[35] We found, however, that simply concentrating the reaction mixture and subjection to Lawrence's conditions[29] (LiOH in H_2O) in the same pot was sufficient to deliver brevianamide A (**2**) in 54% yield, completing a 7-step total synthesis of this complex alkaloid. In our hands, we were unable to isolate any brevianamide B (formed *via* [4 + 2] on the opposite heterodiene



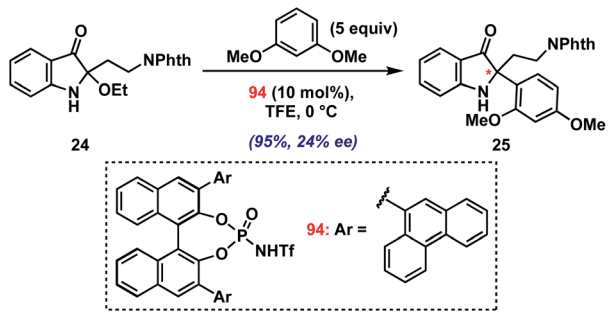
Scheme 1 (A) Synthesis of iboluteine core structure (**76**). (B) Total synthesis of trigonoliimine C (**6**).



Scheme 2 7-step total synthesis of brevianamide A (**2**).

face), though we did note very small amounts by ^{1}H NMR or LC-MS analysis of the crude reaction mixture. As expected, our final sample of **2** displayed only minor enantioenrichment on the basis of its optical rotation (~9% ee expected based on the 1.2 : 1 dr of **89**).

As a final test of the potential of the present method, we conducted preliminary investigations into an asymmetric variant.[36] Initial screens using several chiral Brønsted and Lewis acid catalysts in the coupling of model 2-ethoxyindoxyl **24** with 1,3-dimethoxybenzene have yielded proof of concept (Scheme 3; see ESI† for screening details). Namely, using BINOL-derived *N*-triflyl phosphoramide **94** (10 mol%) in TFE at 0 °C, we have been able to isolate product **25** in excellent yield (95%) with modest enantioselectivity (24% ee). The low level of asymmetric induction is likely due to the requirement for a fluoroalcohol solvent for productive reaction with 2-alkylindole substrates, which presumably interferes with hydrogen bonding/ion-pairing between the chiral catalyst and the iminium intermediate. Future studies will seek to improve upon this result.



Scheme 3 Preliminary asymmetric indoxyl synthesis.

Conclusions

In summary, we have developed an operationally simple method for the conversion of 2-substituted indoles to 2,2-disubstituted indoxyls that is characterized by a broad substrate scope in terms of both indole and nucleophile partners. Our method provides convenient and relatively unique access to such heterocycles with 2,2-dialkyl substitution and free N–H groups, properties which should make it appealing for medicinal chemistry applications. We have showcased its utility in concise total syntheses of trigonoliimine C (6 steps) and brevianamide A (7 steps), being amongst the shortest approaches to these targets reported to date. Future studies will focus on the use of aerobic oxidation and asymmetric catalysis to provide an efficient, enantioselective route to such motifs. Our hope is that the tools communicated here will inspire further exploration of 2,2-disubstituted indoxyls as medicinal agents.

Data availability

Data for all compounds in this manuscript are available in the ESI,† which includes experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. Crystallographic data for compound **76** have been deposited under CCDC 2092889.

Author contributions

F. X. and M. W. S. conceived the project. F. X. conducted the experimental studies and M. W. S. directed the research. M. W. S. composed the manuscript with input from F. X., and F. X. compiled the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by UT Southwestern through the W. W. Caruth Jr. Scholarship and the Welch Foundation (I-2045). We thank the Tambar, Ready, Qin, DeBrabander, Chen, and Falck groups (UT Southwestern) for generous access to equipment and chemicals, as well as helpful discussions. We are grateful to Dr Feng Lin, Dr Eric Weaver (UT Arlington), and Dr Vincent Lynch (UT Austin) for assistance with NMR studies, high-resolution mass spectrometry, and X-ray crystallographic analysis, respectively.

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