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RESEARCH ARTICLE

Enantioselective Syntheses of *Strychnos* and *Chelidonium* Alkaloids via Regio- and Stereocontrolled Cooperative Catalysis.

Luke S. Hutchings-Goetz,[+] Chao Yang,[+] James W. B. Fyfe and Thomas N. Snaddon*[a]

Dedicated to Professors Philip J. Kocienski and Steven V. Ley

ABSTRACT: Herein we describe enantioselective syntheses of *strychnos* and *chelidonium* alkaloids. In the first case, indole acetic acid esters were established as excellent partner nucleophiles for enantioselective cooperative isothiourea/Pd catalyzed α-alkylation. This provides products containing indole-bearing stereocenters in high yield and with excellent levels of enantioinduction in a manner that is notably independent of the *N*-substituent. This led to concise syntheses of (–)-akuammicine and (–)-strychnine. In the second case, the poor performance of *ortho*-substituted cinnamyl electrophiles in the enantioselective cooperative isothiourea/Ir catalyzed α-alkylation was overcome by appropriate substituent choice, leading to enantioselective syntheses of (+)-chelidonine, (+)-norchelidonine and (+)-chelamine.

Introduction

Enantioselective palladium catalyzed allylic alkylation is amongst the most valuable processes available or the construction of C(sp^3)–C(sp^3) bonds.[1] Within this area, our laboratory has invested considerably in the development of cooperative isothiourea/palladium catalysis as a general platform by which to control enantioselective carbon–carbon bond formation using challenging acyclic prochiral ester pronucleophiles.[2] Our efforts have established C1-ammonium enolates as effective nucleophiles for cationic π(allyl)Pd electrophiles, where the activity and reactivity of the Pd-center can be modulated via the ancillary ligands without compromising the level of enantiocontrol.[3] This mechanistic regime is general such that C1-ammonium enolates also undergo efficient stereocontrolled reaction with other catalytically accessible electrophiles.[4,5] Most recently, we leveraged isothiourea/transition metal cooperative catalysis in the direct, regio- and stereodivergent synthesis of homoallylic amines (Figure 1a).[6] This was driven by our developing interest in the synthetic challenges surrounding stereocomplex alkaloids.

Motivated by the structural challenges posed by indole and isoquinoline alkaloids,[7] and recognizing embedded homoallylic amine substructures, we herein report enantioselective syntheses of *strychnos* and *chelidonium* alkaloids (Figure 1b & c, **1**–**2** & **4**–**6**, respectively). Each exploits the general scheme we recently presented for the synthesis of homoallylic amines,[6] and addresses challenges particular to the construction of each alkaloid class. We also report an enantioselective synthesis of indole-containing SIRT-1 inhibitor **3**.

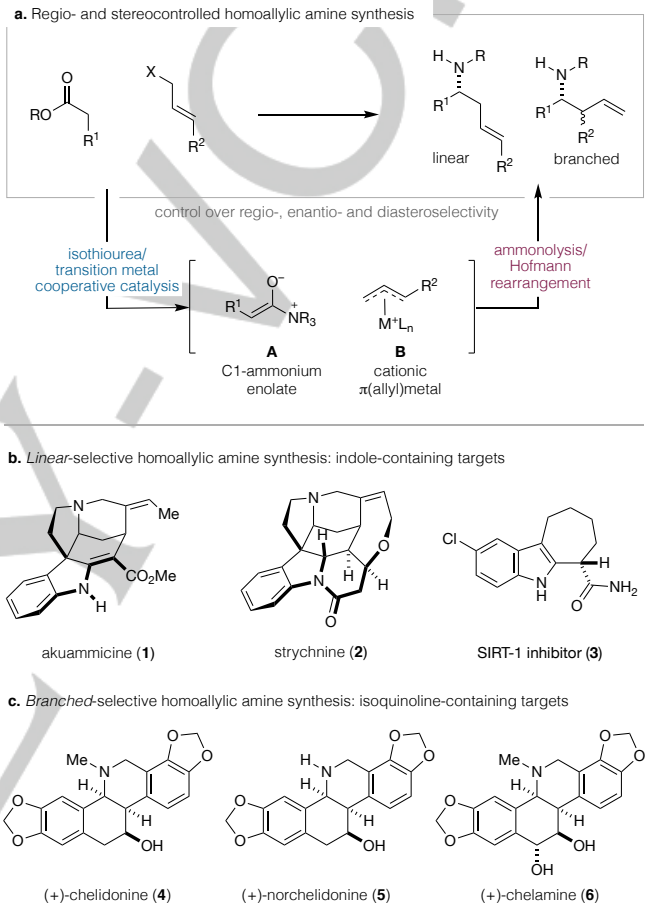

Figure 1. (a) Strategy for the regio-and stereocontrolled synthesis of homoallylic amines via cooperative catalysis. (b) Targets of this study prepared via *linear*-selective homoallylic amine synthesis. (c) Targets of this study prepared via branched-selective homoallylic amine synthesis.

Results and Discussion

1. *Strychnos* Alkaloids and SIRT-1 Inhibitor.

Indole-bearing stereocenters are ubiquitous in both naturally occurring and designed molecules, and methods for their preparation have been intensely pursued.[8-10] In particular, the Pd- and Ir-catalyzed enantioselective allylation of indoles is especially versatile (Scheme 1a).[11] However, during reactions where the indole is to remain a spectator, its nucleophilicity must

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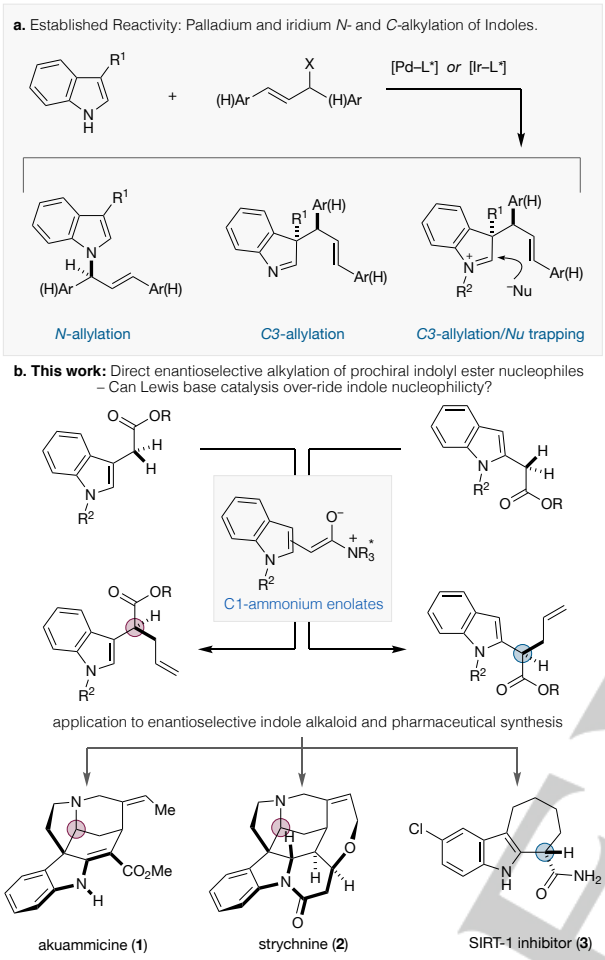
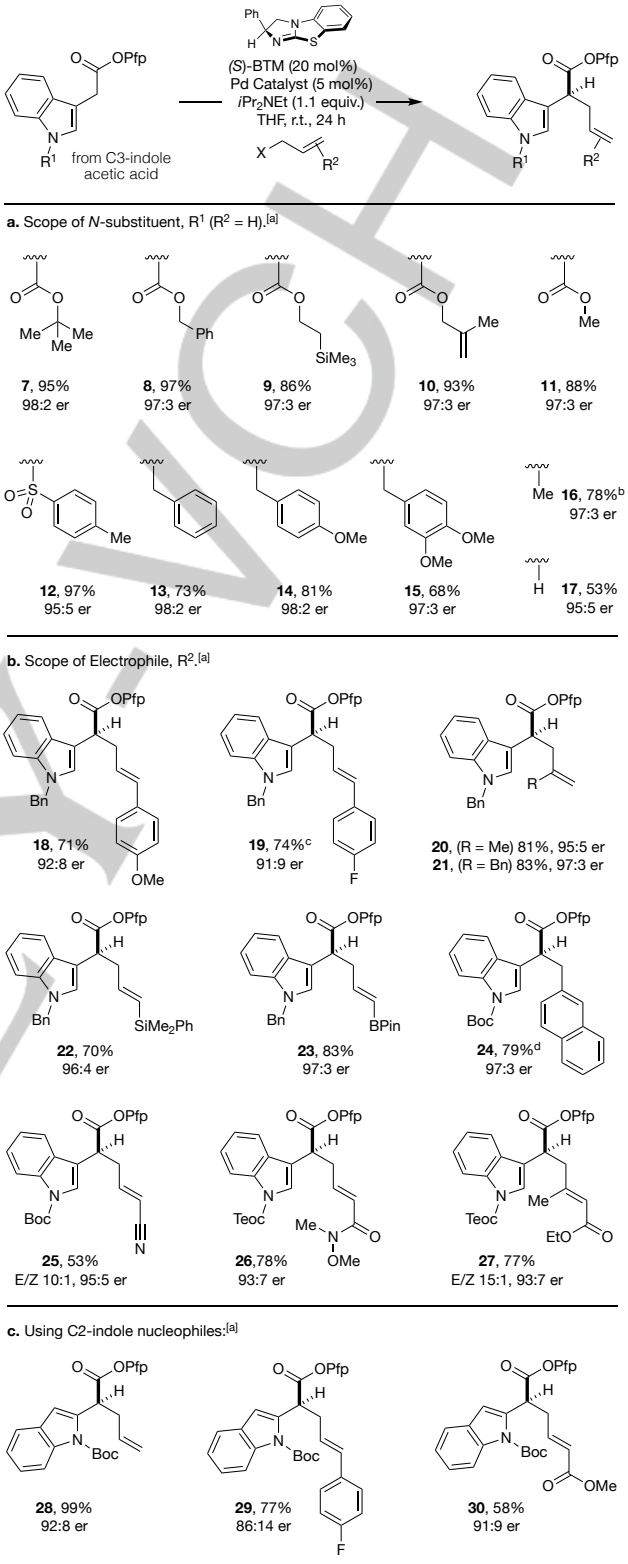
be attenuated via the attachment of an electron-withdrawing *N*-protecting group.[12]



Scheme 1. (a) Established selectivity modes of indole nucleophile during allylic alkylation. (b) Direct asymmetric allylic alkylation design to access common motifs and projected application to the syntheses of **1**–**3**.

We expected that indole-substituted prochiral nucleophiles could be effectively utilized in enantiocontrolled allylic substitution reactions (Scheme 1b). We further expected that the demonstrated affinity of isothiourea catalysts toward aryl esters could be leveraged to override the intrinsic nucleophilic proclivity of the indole itself, independent of the *N*-substituent. Herein, we describe such a protocol, which provides a straightforward and modular preparation of these valuable enantioenriched building blocks.

***N*-Substituted Indole Acetic Acid Nucleophiles.** We began by investigating the scope and effect of various C3-indole acetic acid pentafluorophenyl (Pfp) ester nucleophiles in the enantioselective Lewis base/Pd catalyzed allylic alkylation reaction (Scheme 2a). We have previously correlated the structure features of the allyl electrophile with the supporting ligand on palladium in order to engineer the necessary reactivity.[3] Accordingly, using allyl methane sulfonate as the electrophilic partner, and (*S*)-BTM[13]



Scheme 2. [a] Reactions performed on a 0.1 mmol scale. Yields are isolated following chromatography. *er* Determined by HPLC analysis in comparison to the racemate. See SI for relevant Pd catalysts [b] isolated as the corresponding propargylic amide. [c] isolated as the corresponding (4-methoxy)benzyl amide. [d] isolated as the corresponding primary amide.

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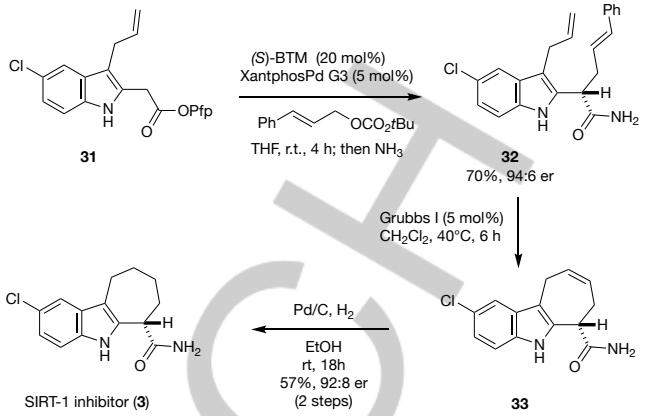
and XantphosPd G3 as the Lewis base and transition metal catalysts, respectively, a series of indole-containing nucleophiles bearing common *N*-protecting groups was assessed. In each case alkylated products were obtained in good-excellent yields and with high levels of enantioselectivity. A variety of commonly used and orthogonal carbamate protecting groups (**7**–**11**) as well as *N*-toluene sulfonate (**12**) could also be employed and gave alkylation products with similarly high levels of efficiency and enantioinduction. Furthermore, we were pleased to find that electron-rich *N*-substituents were effective, which confirmed our hypothesis that the isothiourea catalyst would override the inherent nucleophilicity of the indole; *N*-(benzyl), *N*-(4-methoxybenzyl), *N*-(3,4-dimethoxybenzyl) and *N*-Me substituted nucleophiles all gave products with the same exquisite levels of efficiency (**13**–**16**). Finally, the free unsubstituted (*N*-H) indole nucleophile also demonstrated excellent levels of enantioselectivity (**17**) but proceeded with more modest efficiency (53%). We did not observe products deriving from direct C2 or C3 indole alkylation, which confirmed that the indole nucleus was not acting as a competitive nucleophile.[11] Having established the generality of the alkylation with respect to the *N*-substituent, we turned our attention to the structural diversity of the electrophile using three orthogonally *N*-protected indole nucleophiles (Scheme 2b) (Bn, Boc, Teoc). Both cinnamyl *t*-butylcarbonate (**18**–**19**) and 2-substitued allyl sulfonate electrophiles (**20**-**21**) were efficient reactions partners, as were the corresponding silyl- and boron-substituted allyl sulfonates (**22** and **23**, respectively) and 2-naphthyl phenylphosphate (**24**). Finally, nitrile, Weinreb amide and ester-substituted allyl sulfonate electrophiles (**25**–**27**) were also tolerated. Product **27** is notable both for the incorporation of a stereodefined β,β-disubstituted acrylate motif and for excellent control over the alkene configuration (15:1 *E*/*Z*). Finally, this process could be extended to include isomeric *N*-Boc protected C2-indole nucleophiles (**28**–**30**), albeit providing products with very slightly lower levels of enantioselectivity (Scheme 2c).[14]

Having established C2-and C3-indole acetic acids are effective prochiral nucleophiles in enantioselective allylic alkylation reactions, we sought to exemplify their utility within a number of syntheses.

C2-Indole Nucleophiles: Catalytic Enantioselective Synthesis of an SIRT-1 Inhibitor. To illustrate the synthetic utility of C2-indole-substituted ester nucleophiles we targeted the potent cyclohepta[*b*]indole-containing histone deacetylase (HDAC) inhibitor **3**, which has previously been prepared by resolution of the racemate[15] and by stereospecific sigmatropic rearrangement of an enantioenriched divinylcyclopropane. [16] The functionalized C2-indole Pfp ester **31** was prepared in 4 steps from 5-chloroindole and subjected to enantioselective allylation with cinnamyl *t*-butylcarbonate (Scheme 3). Prior to work up, ammonia was bubbled through the reaction mixture, which directly provided the enantioenriched primary amide **32** in 70% yield (94:6 er). Thereafter, ring closing metathesis using Grubbs' first-generation ruthenium catalyst (**33**) followed by hydrogenation of the resulting alkene gave the (*S*)-eutomer **3** in 57% yield (2 steps).



Scheme 3. Synthesis of SIRT-1 inhibitor, **3**.

C3 Indole Nucleophiles: Catalytic Enantioselective Syntheses of Akuammicine and Strychnine. We next sought to demonstrate the synthetic utility of C3-indole-substituted ester nucleophiles within the context of indole alkaloid natural product synthesis. Akuammicine (**1**) and strychnine (**2**) are benchmark indole alkaloid targets. The latter has captivated the synthetic community since Woodward's landmark 1954 synthesis.[17] In Scheme 4a we present illustrative retrosynthetic analyses of both strychnine[17–19] and akuammicine.[20] each of which can be accessed from an appropriate enantioenriched tetracycle **C**.

Key to this was recognition that an appropriately decorated homoallylic amine (**D**) could be accessed directly from an indole-containing nucleophile (**E**) and a functionalized electrophile (**F**) using our recently reported allylic alkylation–Hofmann rearrangement strategy. However, prior to this work we had neither described nor attempted to use an indole-containing nucleophile in such a one-pot sequence, and its stability toward the strongly oxidizing conditions necessary for efficient Hofmann rearrangement were unclear. If successful, and following suitable elaboration, and appropriate amine **D** could then be merged with a one-pot sequence comprising pyrrolidine ring forming indole C3-alkylation[21] followed by DBU-catalyzed aza-Baylis–Hillman annulation, as pioneered by Andrade and co-workers, [22] resulting in a concise catalytic asymmetric synthesis of a versatile tetracycle **C**. Both (±)-**1** and (±)-**2** have been prepared in short order from (±)-**C** (P = Boc) and we sought to capitalize on this.[18q,18y] Chen and co-workers[18y] synthesized (±)-**2** via a combination of established steps[13a,e] that were streamlined to minimize purifications. Again, we sought to integrate this endgame to complete a concise enantioselective synthesis of **2**.

To begin, enantioselective (*S*)-BTM/Pd catalyzed allylic alkylation between Boc-protected indole acetic acid **34** and γ-tosylate **35** was followed by *in situ* ammonolysis of the product Pfp ester (Scheme 4b). Thereafter, the reaction was directly treated with PIFA in MeCN/H_2O and stirred at room temperature for 48 h giving the enantioenriched ammonium trifluoroacetate salt **36** in high yield and with excellent control over enantioselectivity on multigram scale (88%, 99:1 er, 5 g scale). The Hofmann rearrangement required significant optimization as elevated temperature resulted in

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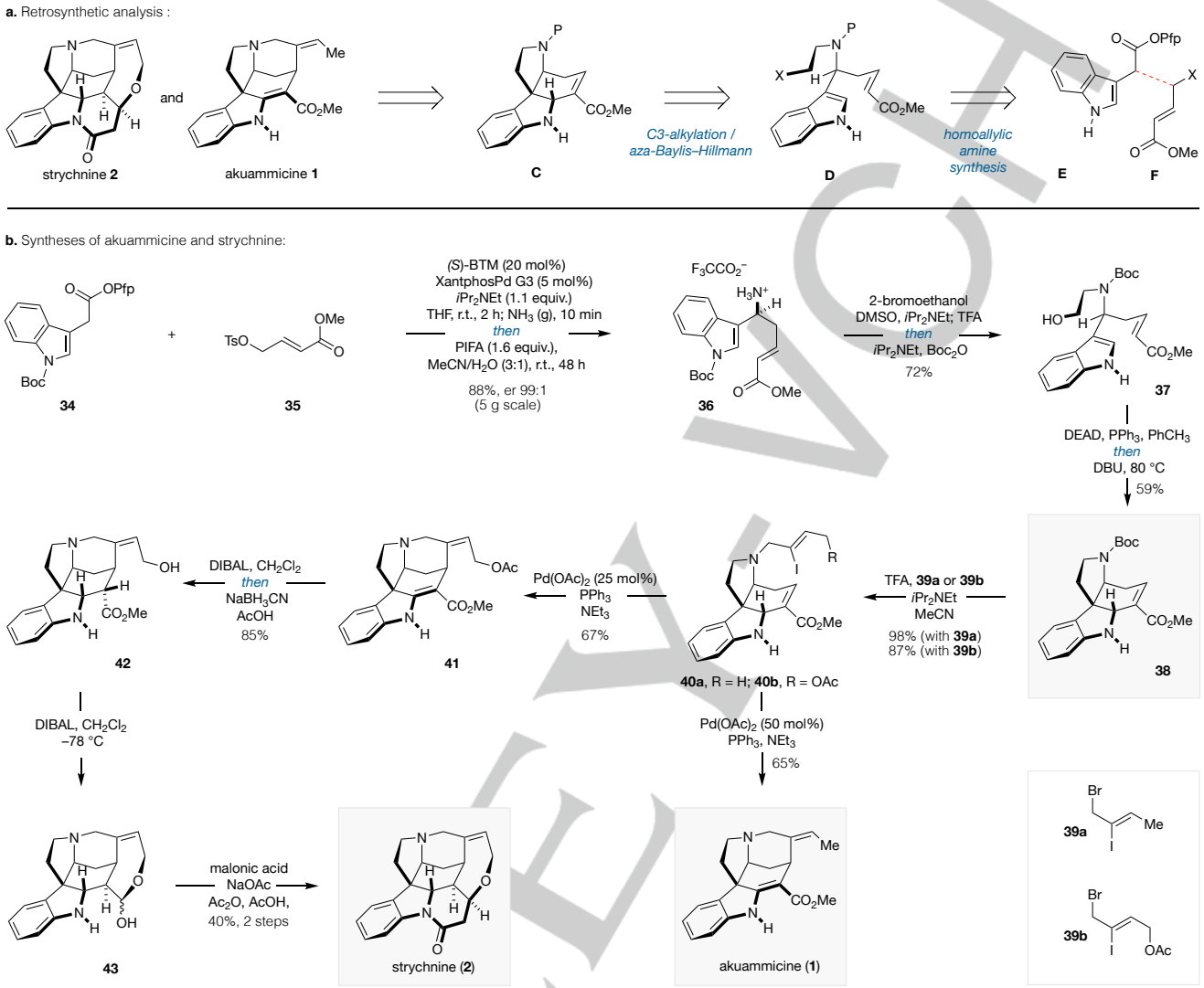

Scheme 4. .[a] Retrosynthetic analysis of akuammicine (**1**) and strychnine (**2**). [b] Synthesis routes to **1** and **2**.

poor yields of **36**, presumably via Boc deprotection and subsequent oxidative degradation of the free indole.[23] Thereafter, **36** could be directly alkylated by treatment using a combination of 2-bromoethanol and Hünig's base in dry DMSO. The solution was then directly treated with TFA to liberate the free indole, whereupon the reaction mixture was concentrated, and the residue treated with Boc_2O in Hünig's base to protect the secondary amine as the *t*-butyl carbamate **37** (72% yield, overall). Activation of the primary alcohol with PPh_3/DEAD resulted in the expected pyrrolidine ring formation via intramolecular C3-indole alkylation, and the resulting imine could be trapped *in situ* using Andrade's DBU-mediated aza-Baylis–Hillman annulation giving the *N*-Boc-protected tetracycle **38** in 59% yield[22], and in only three single-flask operations from indole acetic acid Pfp ester **34**. The literature describing the conversion of **38** (and related tetracycles) to complex indole alkaloids is vast and the path well-trodden.[18–20] Nonetheless, we sought the most economical route to the targets via the streamlining of transformations into single-flask operations, where possible. Thus, cleavage of the Boc protecting group in **38** was achieved with one equivalent of TFA in MeCN. The volatiles were removed and replaced with fresh MeCN before the solution of the crude free amine was treated with Hünig's base and bromide **39a** to give *N*-alkylated tetracycle **40a** in 98% yield. Conversion to akuammicine (**1**) was then achieved in the usual manner using Rawal's Heck cyclization (65% yield).[24] To prepare strychnine (**2**) from **38**, an identical deprotection–alkylation–Heck sequence using **39b** gave acetoxy-akuammicine **41**. Thereafter, reductive cleavage of the acetyl group using DIBAL was followed by reduction of the vinylogous carbamate using $NaBH_3CN$ in AcOH giving **42** in 85% yield. As is well-precedented the resulting ester-bearing stereogenic center is obtained with the incorrect configuration. While this is typically

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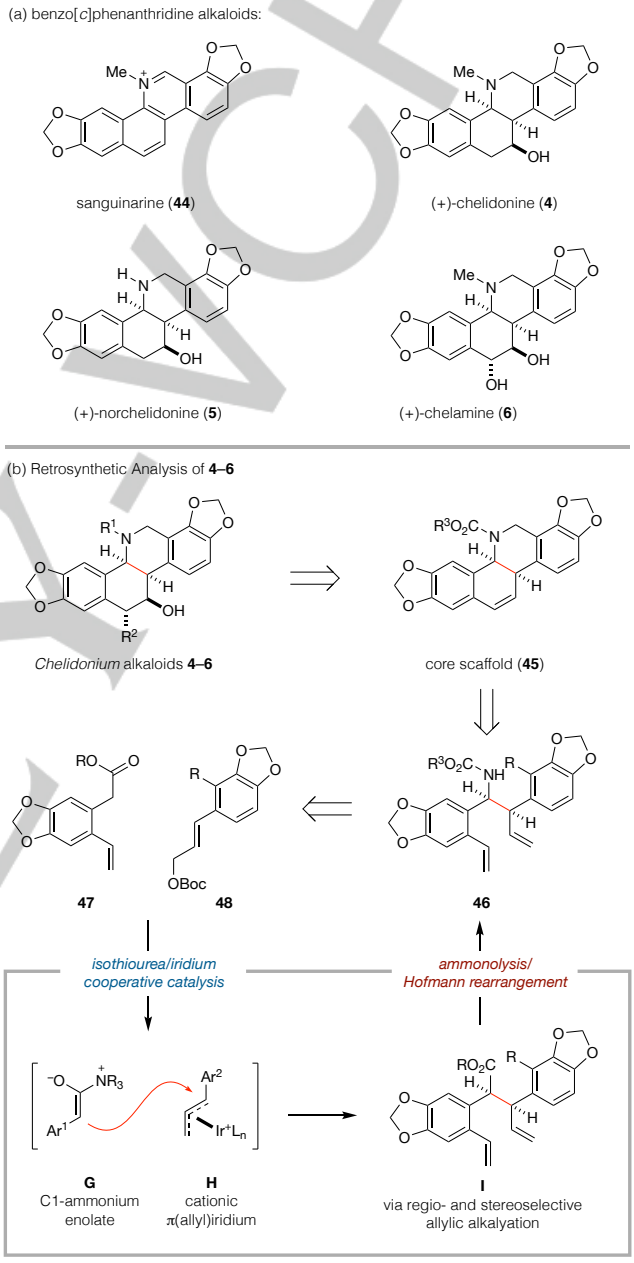
corrected via base-mediated epimerization prior to partial reduction of the ester, direct treatment of **42** with DIBAL at –78 °C using Chen's procedure accomplishes both stereochemical correction and partial reduction giving the Wieland–Gumlich aldehyde (**43**) in a single operation.[18y] Finally, conversion to strychnine (**2**) was achieved using the Anet–Robinson procedure.[25] Overall, akuammicine (**1**) and strychnine (**2**) were prepared in six and nine linear operations, respectively, from commercially-available *N*-Boc-indole-3-acetic acid. Furthermore, the lone secondary amine stereocenter installed by cooperative catalysis was used to control the stereochemistry of subsequent bond constructions.

2. Isoquinoline Alkaloids.

Chelidonium alkaloids have been extensively investigated in the context of modern medicine.[26] For example, chelidonine (**4**) has found application in experimental oncology, demonstrates considerable inhibition of tubulin polymerization, and comprises a major component of a semi-synthetic anti-tumor preparation.[27] Furthermore, simple *O*-functionalized derivatives display a multitude of biological activities that are distinct from the parent alkaloid.[28] Structurally, these alkaloids can be classified into two biosynthetically-related groups; those possessing a planar fully-aromatized benzo[*c*]phenanthridine core (e.g. **44**, Scheme 5), and those possessing the reduced hexahydrobenzo[*c*]phenanthridine congener (e.g. **4**–**6**). Both classes have attracted significant attention from the synthetic community; however, approaches to the latter have proven particularly challenging due to the contiguous stereogenic center arrays embedded within the polycyclic architectures.[29] Beginning with Oppolzer's seminal 1971 synthesis of (±)-chelidonine (**4**),[30] syntheses of *Chelidonium* alkaloids in particular have been intensely pursued. Indeed, perhaps most significant is the pioneering enantioselective Pd(II)-catalyzed arylative ring-opening of *meso*-azabicyclic alkenes reported by Lautens and co-workers, which enabled enantioselective syntheses of five alkaloids, including **4**-**6**. [31] With the exception of this ground-breaking study, and despite extensive synthesis efforts, the strategic application of catalytic asymmetric methods to address the structural and stereochemical challenges presented by these alkaloids has been limited.[32] Herein, we report enantioselective syntheses of (+)-chelidonine (**4**), (+)-norchelidonine (**5**) and (+)-chelamine (**6**) via a convergent catalysis-based synthesis strategy, which again exploits the general scheme we recently presented for the regio- and stereocontrolled synthesis of homoallylic amines.[6]

Retrosynthetic analysis of alkaloids **4**–**6** leads back to common scaffold **45**, which bears the ring-fused *syn*-vicinal stereocenter motif that is common to this family (Scheme 5b). This could be advanced to each target (i) by appropriate functionalization of the alkene, and (ii) by tailoring substitution of the nitrogen atom. Further retrosynthetic dissection of **45** corresponding to an intramolecular *N*-alkylation/ring closing metathesis sequence reveals branched homoallylic amine **46**, which could be prepared from **47** and **48** via catalytically accessible C1-ammonium enolate (**G**) and π(allyl)iridium (**H**) intermediates, respectively.[4i] However, a major challenge facing this approach concerns the identity of the *ortho* substituent R on the electrophile **48**, which is necessary to secure the regiochemical outcome of subsequent intramolecular *N*-alkylation *en route* to **45**.[33] Due to deleterious ligand–substrate interactions *ortho*-substituted cinnamyl electrophiles often exhibit poor reactivity and decreased levels of stereocontrol during iridium-catalyzed allylic functionalization reactions.[34] This feature continues to prove challenging for catalyst design.



Scheme 5. (a) selected benzo[c][phenanthridine alkaloids. (b) Retrosynthetic analysis of the *Chelidonium* alkaloids (+)-chelidonine (**2**), (+)-norchelidonine (**3**) and (+)-chelamine (**4**).

We commenced investigation of this projected structural issue via the reaction of pentafluorophenyl (Pfp) ester **49** with various cinnamyl electrophiles **50a**–**d** (Table 1) in expectation that an appropriate synthetic handle could be identified. Employing (*S*)-BTM[13] in combination with Hartwig's (*R*,*R*,*R*$_a$)-Ir catalyst (**51**)[4b,35],

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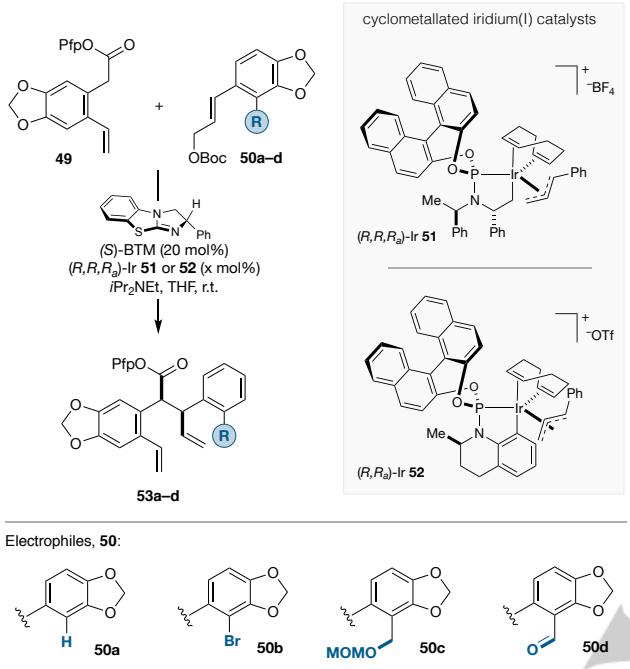
branched selective alkylation of **49** with electrophile **50a**, which possesses only H-atoms as *ortho*-substituents, gave the product

Table 1. Assessment of *ortho*-substituent on reactivity and stereoselectivity.



Entry[a]	Electrophile	Ir Catalyst (mol%)	Product d.r. [*syn*/anti][b]	Yield **53** [%][c–e]
1	**50a**	**51** (4)	15:1	88 (83)
2	**50b**	**51** (4)	4:1	15 (7)
3		**51** (8)	4:1	24 (12)
4		**52** (4)	--	--
5	**50c**	**51** (4)	--	trace
6		**51** (8)	5:1	12 (10)
7		**52** (4)	--	--
8	**50d**	**51** (4)	5:1	36 (30)
9		**51** (8)	5:1	78 (65)
10	**50d**	**52** (4)	--	--

[a] Reactions run on 0.1 mmol scale from isolated amide. [b] established by ^{1}H NMR analysis of the crude product. [c] yield calculated by ^{1}H NMR using durene as an internal standard. [d] yield of the major diastereoisomer in parentheses. [e] the enantioselectivity was not evaluated during this exploratory investigation.

53a in good yield and high diastereoselectivity as expected (Table 1, entry 1). Confirmation of the expected structural impact of larger *ortho*-substituents on the efficiency of the reaction was obtained when we evaluated bromide **50b**. Here, catalyst **51** provided the product in low conversion and modest diastereoselectivity (Entry 2). Doubling the loading of **51** resulted in a small increase yield but this was still well below synthetically useful levels (Entry 3). Next we turned to (R,R_a)-Ir catalyst **52**, which You and colleague developed specifically to accommodate *o*-substituted cinnamyl electrophiles during allylic functionalization reactions.[34b] Unfortunately, however, no alkylation of the putative intermediate C1-ammonium enolate nucleophile was observed under these conditions (Entry 4).[36] Thereafter, we moved to evaluate the MOM-protected *o*-hydroxymethylene substituent, which Lautens and colleagues used in their syntheses of the *Chelidonium* alkaloids and demonstrated that could be easily manipulated at a later stage.[31] Unfortunately, **50c** was unreactive and **53c** was produced in only trace amounts (Entries 5–6). Finally, we identified aldehyde **50d** as having higher reactivity giving the product in 36% yield as a 5:1 mixture of diastereoisomers. Increasing the loading of **51** to 8 mol% gave **53d** in 78% yield and 5:1 dr, with the major diastereomer obtained in 65% yield. With these conditions in hand we moved to merge this transformation with ammonolysis/Hofmann rearrangement to forge the necessary enantioenriched branched homoallylic amine corresponding to **46**.

Firstly, the required reaction partners could be prepared on multi-gram scale in short order (Scheme 6a). Pfp ester **49** was prepared from bromide **54** via Pd-catalyzed Suzuki reaction with potassium vinyltrifluoroborate[37] followed by methyl ester hydrolysis of **55** and EDCI-mediated esterification of the resulting crude carboxylic acid with pentafluorophenol (PfpOH). Electrophile **50d** was prepared in a single step from iodide **56** by Heck reaction with allyl *tert*-butyl carbonate under Jeffrey's conditions (Scheme 6b).[38] Thereafter, reaction of **49** and **50d** under our optimized conditions on 10 mmol scale gave **57** (following chromatographic purification) in 55% isolated yield as a single diastereosiomer and essentially a single enantiomer (>99:1 er) following ammonolysis of the Pfp ester using ammonium hydroxide[39] and reduction of the aldehyde to the corresponding alcohol (Scheme 6c).[40] Treatment of **57** with PIDA in methanol resulted in smooth Hofmann rearrangement with attendant trapping of intermediate isocyanide intermediate by the alcohol to give the methyl carbamate **58**.[41] Thereafter, the benzo[*c*]phenathridine core was assembled via a two-step bis-annulation protocol. Firstly, the primary alcohol was converted to the corresponding bromide before treatment with sodium hydride induced intramolecular *N*-alkylation giving **59** in 97% overall yield. Then, ring closing metathesis using the Grubbs second generation catalyst gave the complete benzo[*c*]phenanthridine core **60** bearing the key ring-fused *syn*-vicinal stereocenter motif. From here, conversion to **63** required epoxidation of the alkene *endo*-face.[31] This was achieved via regioselective hydrolytic trapping of bromonium ion **61** followed by low temperature treatment of the resulting bromohydrin **62** with potassium *tert*-butoxide to provide the corresponding *endo*-epoxide **63**. Epoxide **63** was then easily diversified to each target.[42] Conversion to (+)-chelidonine (**4**) was achieved in 82% by reductive epoxide opening and one-pot carbamate reduction using lithium aluminum hydride. (+)-Norchelidonine (**5**) was prepared by treating **63** with L-selectride, which resulted in reductive epoxide opening with attendant carbamate cleavage giving the corresponding secondary amine.[43] Finally, (+)-chelamine (**6**) was prepared via bismuth trichloride-mediated hydrolytic epoxide ring opening followed by carbamate reduction with lithium aluminum hydride.

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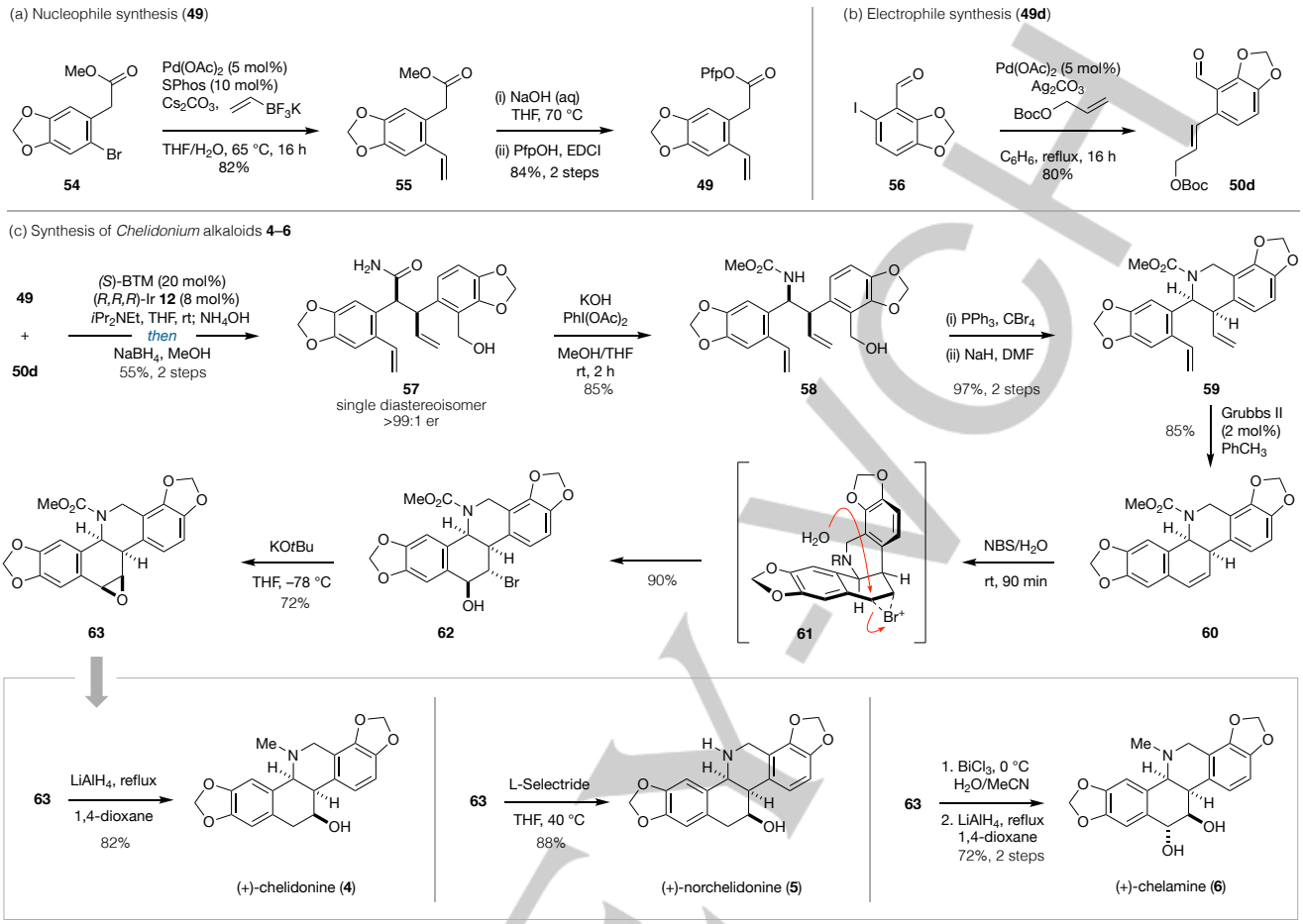

Scheme 6. (a) Preparation of ester **49**. (b) Preparation of allylic *tert*-butylcarbonate **50d**. (c) Syntheses of (+)-chelidonine (**4**), (+)-norchelidonine (**5**) and (+)-chelamine (**6**)..

Conclusion

We have described here the details to two synthesis campaigns based on a unifying catalytic strategy for the efficient synthesis of enantioenriched homoallylic amines. In the first, we developed indole acetic acids as effective pro-nucleophiles for Pd-catalyzed allylic alkylation which enabled the construction of indole-bearing stereocenters. This was exploited in the syntheses of *strychos* alkaloids **1** and **2**, and a pharmaceutical lead, **3**. In the second, we identified an *ortho*-aldehyde substituted cinnamyl electrophile as an effective electrophile in Ir-catalyzed allylic alkyation. This was exploited in the syntheses of *chelidonium* alkaloids **4**–**6**. We anticipate that partnering cooperative Lewis base/transition metal catalyzed allylic alkylation with subsequent Hofmann rearrangement will prove valuable in the synthesis of other alkaloids as well as designed analogues. Studies along these lines are continuing in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: isothiourea, C1-ammonium enolate, palladium, iridium, alkylation, enantioselective, cooperative catalysis, alkaloid

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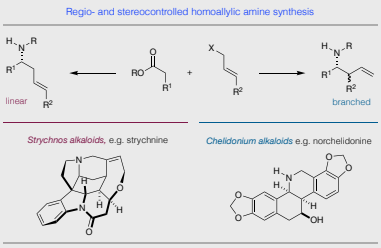

*Luke S. Hutchings-Goetz,[+] Chao Yang,[+] James W. B. Fyfe and Thomas N. Snaddon **

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Herein we describe enantioselective syntheses of *strychnos* and *chelidonium* alkaloids, via a regio and stereocontrolled isothiourea/transition metal cooperative catalysis-based synthesis of homoallylic amines. Using a linear selective protocol, we have established indole acetic acid esters as remarkably effective nucleophiles, leading to syntheses of akuammicine, strychnine and an SIRT-1 inhibitor. Using a branch-selective protocol, we have overcome structure-based