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# Nitrogen atom insertion into indenes to access isoquinolines†

Patrick Finkelstein, Julia C. Reisenbauer, Bence B. Botlik, Ori Green, Andri Florin and Bill Morandi *

We report a convenient protocol for a nitrogen atom insertion into indenes to afford isoquinolines. The reaction uses a combination of commercially available phenyliodine(III) diacetate (PIDA) and ammonium carbamate as the nitrogen source to furnish a wide range of isoquinolines. Various substitution patterns and commonly used functional groups are well tolerated. The operational simplicity renders this protocol broadly applicable and has been successfully extended towards the direct interconversion of cyclopentadienes into the corresponding pyridines. Furthermore, this strategy enables the facile synthesis of $^{15}N$ labelled isoquinolines, using $^{15}NH_4Cl$ as a commercial $^{15}N$ source.



## Introduction

Isoquinoline is an important aromatic *N*-heterocycle scaffold with numerous applications in medicinal chemistry,[1–6] materials science,[7–9] and as a ligand in catalysis.[10–13] Traditionally, this heterocycle has been synthesised through the assembly of pre-oxidised building blocks and amines,[14–16] or oxidation of di- or tetrahydroisoquinoline,[17,18] among other methods.[19–21] A strategically different approach is the introduction of the key nitrogen atom at a later stage of a synthetic route, using a pre-decorated carbocyclic framework. A classical strategy to accomplish this task relies on the stepwise oxidative cleavage of an indene skeleton, usually through ozonolysis, followed by condensation with an amine (Scheme 1A).[22–24] Recently, more direct methods have emerged, such as an electrochemical approach using gaseous ammonia as the nitrogen source,[25] but which is only compatible with electron-rich indenes bearing additional aryl and alkyl substitutions on the double bond. Finally, an osmium nitride was shown to stoichiometrically react with 3-phenyl-1*H*-indene, which, after a subsequent step gave 1-phenylisoquinoline.[26] However, the need for stoichiometric metal and the synthesis of the starting osmium nitride limits synthetic applications. These challenges highlight the demand for a synthetically useful and practical approach to directly transform indenes into isoquinolines.[27]

Our group has recently reported a nitrogen atom insertion method into silyl-protected indoles, affording either quinazolines or quinoxalines in a single step.[28] In our proposed mechanism we postulated nitrogen lone pair participation in the fragmentation of an *N*-iodonium-aziridine intermediate. We surmised that indenes, which possess an acidic C–H moiety in place of the indole nitrogen atom, could possibly engage in a similar process through isoelectronic reactive intermediates (Scheme 1B). If successful, this would result in a simple and efficient conversion of indenes into isoquinolines.

Here, we report the direct nitrogen atom insertion into a broad range of indenes and cyclopentadienes, employing commercially available phenyliodine(III) diacetate (PIDA) as the oxidant and ammonium carbamate as the nitrogen source. We also report an extension of this protocol to enable the formation of isotopically labelled isoquinoline structures using commercially accessible $^{15}NH_4Cl$ (Scheme 1C).

## Results and discussion

We chose 3-phenyl-1*H*-indene **1a** as our model substrate and started our study by using two equivalents of phenyliodine(III)-bis(trifluoroacetate) (PIFA) as the oxidant and four equivalents of ammonium carbamate as the nitrogen source. The combination of a hypervalent iodine compound and an ammonia source—proposed to generate an iodonitrene *in situ*—has been used successfully in several transformations in recent years.[28–31] Our hypothesis was validated by observing the formation of the desired 1-phenylisoquinoline product **1b** (Table 1, entry 1) in methanol at 0 °C after 10 minutes in 77% yield (as determined by $^1$H-NMR analysis of the crude reaction mixture, for more details see ESI†). However, further increasing the amount of oxidant and ammonia source did not improve the yield (Table 1, entry 2). We continued by investigating the remaining

*Laboratorium für Organische Chemie, ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland. E-mail: bill.morandi@org.chem.ethz.ch*

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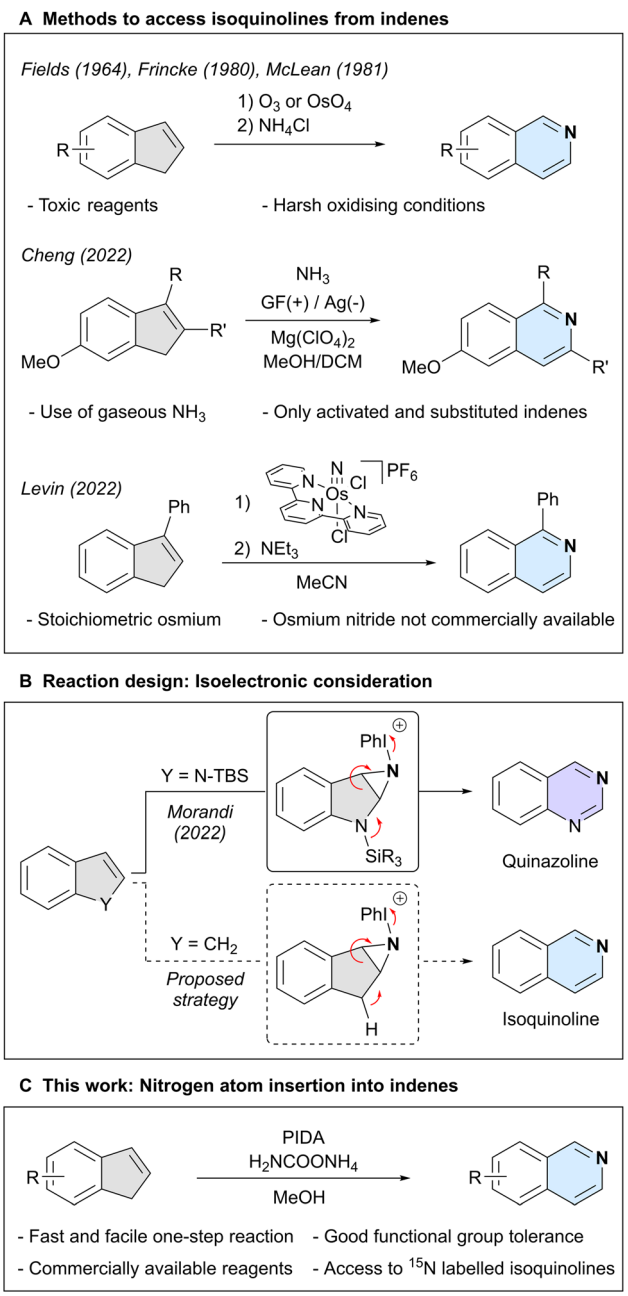
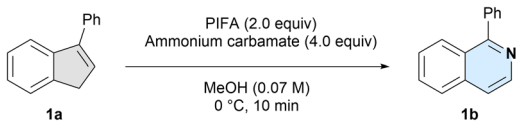



Scheme 1 Context of this work.

parameters of the reaction, starting with different ammonia sources and observed that these also led to the desired product, albeit in lower quantities (Table 1, entries 3–4). The reaction also proceeded in aprotic solvents such as MeCN (Table 1, entry 5), providing a potential alternative for substrates that are incompatible with protic conditions. Changing the oxidant had the largest net positive effect, with both bis(*tert*-butylcarbonyloxy)iodobenzene and PIDA increasing the NMR yield to over 90% (Table 1, entries 6–7). Finally, 2 equivalents of PIDA in combination with 4 equivalents of ammonium carbamate in MeOH at 0 °C proved to give the highest yield for our transformation. Other parameters such as the temperature (0 °C *vs.*

Table 1 Selected optimisation data for the nitrogen atom insertion into indenes[a]



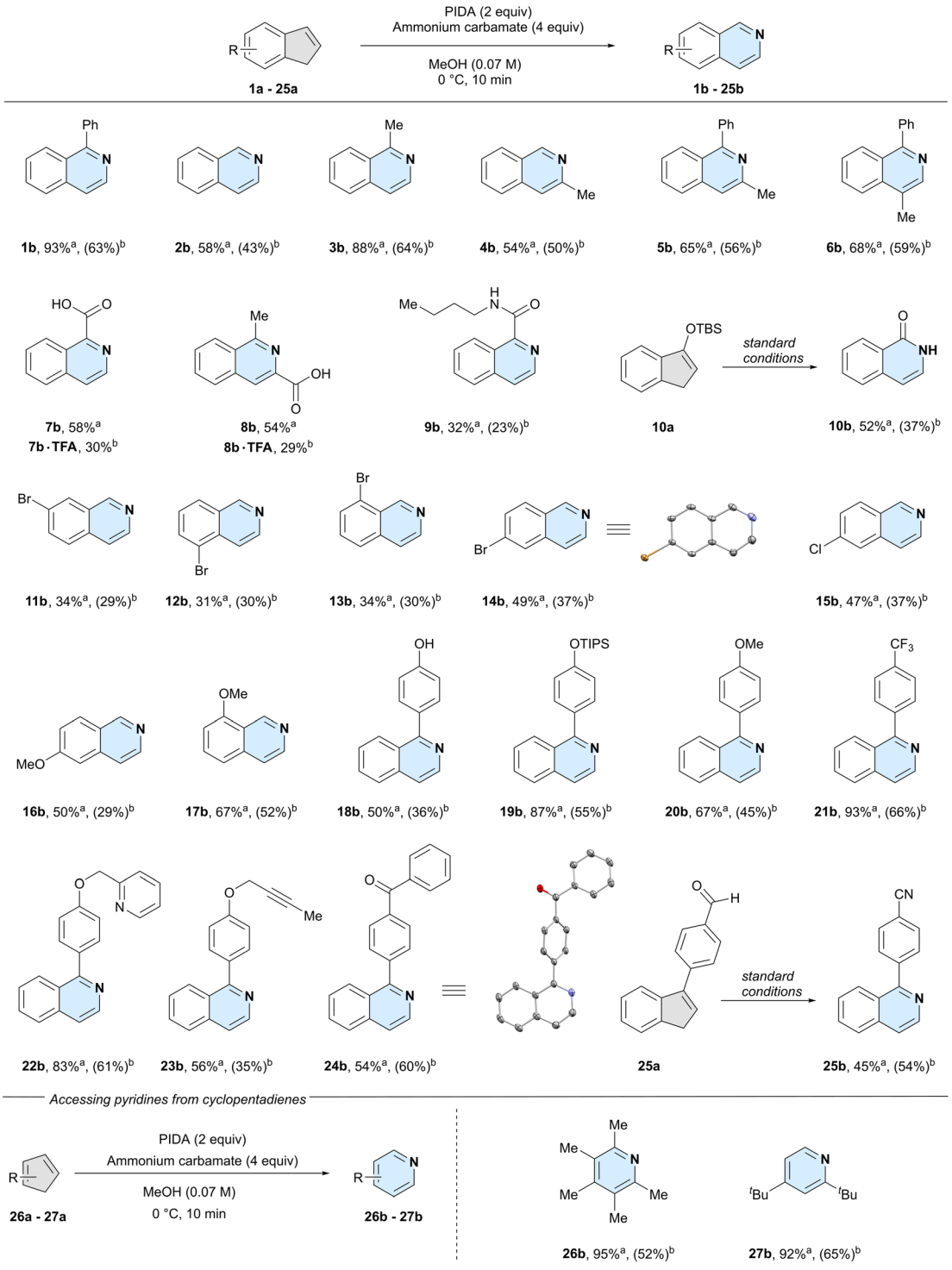

| Entry | Deviation from above | Yield[b] of **1b** [%] |
|---|---|---|
| **1** | None | 77 |
| **2** | PIFA (4.0 equiv.), ammonium carbamate (6.0 equiv.) | 72 |
| **3** | Ammonium formate instead of ammonium carbamate | 46 |
| **4** | Ammonium acetate instead of ammonium carbamate | 70 |
| **5** | MeCN instead of MeOH | 62 |
| **6** | Bis(*tert*-butylcarbonyloxy)iodobenzene instead of PIFA | 91 |
| **7** | PIDA instead of PIFA | 93 |
| **8** | 1-mmol scale, PIDA (2.5 equiv.) instead of PIFA | 77, (63)[c] |

[a] Reaction conditions: indene (0.05 mmol), PIFA (0.10 mmol), ammonium carbamate (0.20 mmol), methanol-$d_4$ (0.07 M), 0 °C, 10 min. [b] Yields in % obtained by $^1$H-NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard. [c] Isolated yield.

r.t.) or concentration (0.033−0.20 M) only had minor effects on the overall outcome of the reaction (see ESI†). When scaling up the reaction to 1.0 mmol, we increased the oxidant loading to 2.5 equivalents to reach full conversion and thus were able to isolate the product **1b** in 63% yield (Table 1, entry 8). In summary, the transformation of indene **1a** into the corresponding isoquinoline **1b** was rapidly achieved open-flask in a variety of conditions including multiple solvents, oxidants, and ammonia sources, highlighting the robustness of our protocol.

With the optimised conditions in hand, we set out to examine the functional group tolerance and limitations of our method. For all reactions, we report the $^1$H-NMR yield on a 0.05-mmol scale and the isolated yield on a 1.00-mmol scale (Scheme 2). In the following sections, we discuss the substrate scope based on the NMR yields, to systematically compare substitution patterns and functional group effects.

Unsubstituted indene **2a** could successfully be converted into isoquinoline (**2b**), however, the lack of a phenyl ring at the 3-position led to a reduced, yet synthetically useful yield of 58%. This is an important feature, as recently reported one-step methods are not compatible with simple unsubstituted indene substrates.[25,26] We next systematically investigated the effect of substitutions at the double bond of the five-membered ring. Like the model system, 3-phenyl-1*H*-indene (**1a**), 3-methyl-1*H*-indene (**3a**) gave the product 1-methylisoquinoline (**3b**) in high yield (88%), possibly hinting at the beneficial effect of a substitution at the 3-position. A methyl group at the 2-position




Scheme 2 Substrate scope. For the scXRD structures, the ellipsoids are shown at 50% probability and hydrogen atoms are omitted for clarity.[a] $^1$H-NMR yield of 0.05-mmol scale crude reaction mixture using 1,1,2,2-tetrachloroethane as the internal standard.[b] Isolated yield of a 1.00-mmol scale reaction, conditions: indene (1.0 mmol), PIDA (2.5 mmol), ammonium carbamate (4.0 mmol), methanol (0.07 M), 0 °C for 20 min, then rt for 10 min.

of the indene (**4a**) gave 54% yield of 3-methylisoquinoline (**4b**), similar to the unsubstituted system. Next, we installed a phenyl at the 3-position and compared the results for a methyl group at either the 2- (**5a**), or 1-position (**6a**). Both reactions gave essentially identical yields (**5b:** 65% and **6b:** 68%), albeit higher than the previous substrates with no phenyl substitution at the 3-position. Additionally, as showcased by accessing isoquinoline **5b** from the tetrasubstituted indene precursor **5a,** steric

hindrance was well tolerated under the developed reaction conditions.

We next investigated the effect of polar groups at the 2- or 3-position on the reaction outcome. Indenes bearing a carboxylic acid on either 3- (**7a**) or 2-position (**8a**) gave the corresponding isoquinolines in comparable yields (**7b**: 58% and **8b**: 54%). Likewise, an amide on the double bond of the indene starting material was also tolerated under the reaction conditions (**9b**). Intriguingly, silyl-protected alcohol **10a** was converted into the lactam **10b**, with loss of the silyl group.

We next compared different substituents on the six-membered ring. Substrates bearing a bromine atom at any of the four possible positions on the benzene ring were tolerated in the reaction (**11a**, **12a**, **13a**, and **14a**). Similarly diminished yields were obtained when the bromide was either in the 4- (**11b**: 34%), 5- (**12b**: 31%), or 7-position (**13b**: 34%) of the starting indene, respectively. In contrast, 6-bromo-1*H*-indene **14a** gave a yield closer to that of the unsubstituted system (**14b**: 49% *vs.* **2b**: 58%). We observed a similar yield when subjecting 6-chloro-1*H*-indene **15a** to our reaction conditions, giving **15b** in 47% yield. To investigate a potential electronic effect at the 6-position of the indene, we exchanged the halides for an electron-donating methoxy group. The reaction afforded 6-methoxyisoquinoline **16b** in 50% yield, suggesting that electronic effects at this position do not influence the reaction's yield. In comparison, a methoxy group closer to the reaction centre resulted in an increase in yield to 67% of 8-methoxyisoquinoline **17b**.

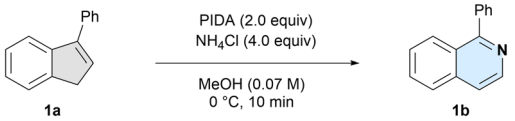
Having established that reactivity could be expected both with or without substitutions at any position on the indene core, we further explored the functional group tolerance of the reaction. A free phenol (**18a**) was well tolerated and gave phenol-containing isoquinoline **18b** in 50% yield. Protecting the phenol with a tri-isopropyl silyl group (**19a**) resulted in an even higher yield of product **19b** (87%). Other groups in *para* position on the phenyl group were well tolerated, such as a methoxy (**20b**: 67%) or a trifluoromethyl group (**21b**: 93%). Combining these results with that of our model system **1b**, it seems that the reaction yield is not influenced by the electronics of the pendant aryl substituents.

We further investigated other common functional groups, including a benzylic pyridine (**22a**) which was converted into the corresponding product **22b** in 83% yield, an internal alkyne (**23a**), which gave the product **23b** in 56% yield, and an indene bearing a ketone (**24a**) which afforded the desired product **24b** in 54% yield. As aldehydes are prone to oxidise to nitriles in the presence of ammonia and an oxidant,[32] we wondered whether we could achieve both the oxidation and the nitrogen insertion simultaneously. Indeed, aldehyde **25a** was converted to the nitrile product **25b** in 45% yield. Finally, we decided to expand our scope beyond indenes by testing two cyclopentadienes. We chose 1,2,3,4,5-pentamethyl cyclopentadiene and 1,3-di-*tert*-butylcyclopentadiene as our two substrates, due to their higher stability compared to the unsubstituted parent structure. To our delight, both 2,3,4,5,6-pentamethyl pyridine **26b** and 2,4-di-*tert*-butylpyridine **27b** were formed in high yields (**26b**: 95%, **27b**: 92%), clearly demonstrating the possibility to synthesise densely functionalised pyridine products from cyclopentadienes. Overall, commonly used functional groups were well tolerated in the reaction and synthetically useful yields were observed for non-, mono-, and di-substituted indene cores.

Apart from easily accessing isoquinolines, an intriguing application of our method would be the incorporation of the heavier $^{15}N$ isotope, which has a natural abundance of only around 0.3%. $^{15}N$ labelled molecules have been used in many different settings for their nuclear magnetic resonance (NMR)[33] and mass-related properties, such as in proteomics,[34] as sensitive protonation probes,[35,36] reaction-progress and complexation monitoring of COFs,[37,38] and more generally for studies on *N*-heterocycles.[39–41] $^{15}N$ NMR spectroscopy has some significant advantages compared to the method using the lighter isotope,[42] but suffers from high costs for the typically laborious syntheses of $^{15}N$ labelled precursors. Thus, an inexpensive protocol to incorporate the valuable $^{15}N$-label at a later stage in the synthesis could be attractive to access relevant labelled organic or organometallic structures.

We thus set out to evaluate whether our protocol could insert $^{15}N$ into indenes to form isotopically labelled isoquinolines. Due to the lack of commercially available $^{15}N$ ammonium carbamate, we changed our nitrogen source to $NH_4Cl$ and envisaged that adding a base could unlock the desired reactivity.[29,43] Surprisingly, when using four equivalents of $NH_4Cl$ as the ammonia source without any base, we could already see conversion of **1a** to the product **1b**, albeit in low quantities (Table 2, entry 1). By adding a base and changing the equivalents of the reagents, the reaction was optimised to afford the product **1b** in 80% yield on a 0.05-mmol scale and 49% NMR yield on a 1.0-mmol scale (Table 2, entries 2–7).

Table 2 Selected optimisation data for the nitrogen atom insertion into indenes using ammonium chloride[a]



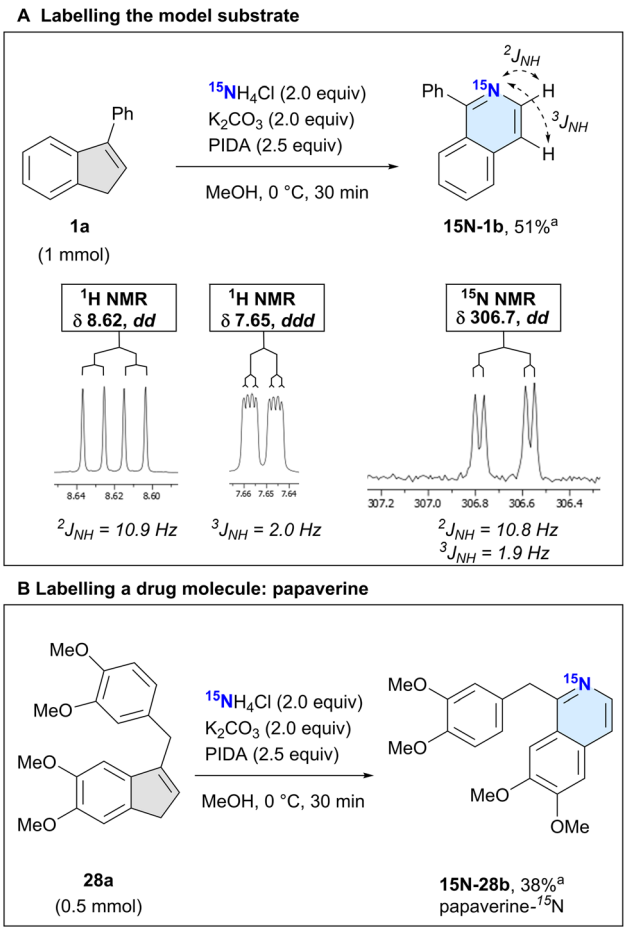

1a 1b

| Entry | Deviation from above | Yield[b] of **1b** [%] |
|---|---|---|
| **1** | None | 7 |
| **2** | With NaOAc (4.0 equiv.) | 27 |
| **3** | With $K_3PO_4$ (4.0 equiv.) | 48 |
| **4** | With $K_2CO_3$ (4.0 equiv.) | 69 |
| **5** | With $K_2CO_3$ (2.0 equiv.) | 71 |
| **6** | $NH_4Cl$ (2.0 equiv.), $K_2CO_3$ (2.0 equiv.) | 80 |
| **7** | 1-mmol scale, $NH_4Cl$ (2.0 equiv.), $K_2CO_3$ (2.0 equiv.), PIDA (2.5 equiv.) | 49 |

[a] Reaction conditions: indene (0.05 mmol), PIDA (0.10 mmol), ammonium chloride (0.20 mmol), methanol-$d_4$ (0.07 M), 0 °C, 10 min. [b] Yields in % obtained by $^1$H-NMR analysis of the crude reaction using 1,1,2,2-tetrachloroethane as the internal standard.

We next used the isotopically labelled salt, $^{15}NH_4Cl$, to convert 3-phenyl-1*H*-indene (**1a**) into 1-phenylisoquinoline-$^{15}N$ (**15N-1b**) in 51% isolated yield (Scheme 3A). We confirmed the incorporation of the heavier nitrogen isotope by high-resolution mass spectrometry (HRMS) and NMR analysis. The usual characteristic doublet in the $^1$H NMR spectrum of the H at the 3-position of **1b** was split into a doublet of doublets (dd, $J = 10.9$, 5.7 Hz), as was the signal corresponding to the H in the 4-position (ddd, $J$ = 5.7, 2.0, 0.9 Hz). We recorded a $^{15}$N NMR spectrum, noting a doublet of doublets at $\delta$ 306.7 (dd, $J = 10.8$, 1.9 Hz). This splitting is caused by the coupling of the nitrogen with the adjacent hydrogens at the 3- and 4-position of the isoquinoline, which was also confirmed by 2D $^1$H–$^{15}$N-HMBC experiments (see ESI†).

After this successful initial example, we next sought to demonstrate the utility of our labelling method by incorporating $^{15}$N into the isoquinoline-based drug papaverine, which is used to treat visceral spasms and vasospasms.[44] Having access to an isotopically labelled drug can greatly help identify metabolic pathways.[45,46] Subjecting **28a** to our reaction conditions, we obtained the product papaverine-$^{15}N$ (**15N-28b**) in 38% isolated yield (Scheme 3B). As with **15N-1b**, we confirmed the nitrogen isotope incorporation by HRMS and $^1$H/$^{15}$N NMR analyses.




Scheme 3 Isotopically labelled structures. [a]Isolated yields.

## Conclusions

In conclusion, we report a facile method to insert a nitrogen atom into indenes and cyclopentadienes, granting access to a wide variety of differently substituted and functionalised isoquinolines and two bulky pyridines. We could further expand our method to use $^{15}NH_4Cl$ as the nitrogen source, allowing for the convenient synthesis of $^{15}$N labelled isoquinolines.

## Data availability

All experimental and characterization data, as well as NMR spectra are available in the ESI.† Crystallographic data for compounds **14b** and **24b** have been deposited in the Cambridge Crystallographic Data Centre under accession number CCDC 2221959 (**14b**) and 2221960 (**24b**).

## Author contributions

P. F. conceived the project. P. F., J. C. R., B. B. B., O. G., and A. F. performed the experimental studies. B. M. supervised the research. P. F. wrote the original draft of the manuscript which was edited by all authors.

## Conflicts of interest

There are no conflicts to declare.

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