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A Metal-Free C–H Amination-Based Strategy for *N*-Amino Indole Synthesis

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An oxidative cyclization of electron-rich α-arylhydrazones promoted by phenyliodine bis(trifluoroacetate) (PIFA) has been accomplished. This metal-free, chemoselective transformation allows to obtain synthetically and medicinally important *N*-amino-1*H*-indoles, obviating the need for pre-functionalization of substrates.

Introduction

Over the last few decades, the need to find novel synthetic disconnections for the rapid assembly of organic molecules has prompted the scientific community to investigate unprecedented C–H activation processes. In comparison to the conventional cross-coupling reactions, oxidative C–H functionalization removes the requirement for pre-functionalization of both partners; as a consequence the high atom economy and bond-formation efficiencies are the major benefits of these transformations.[1] In this context, the direct amination[2] (C–H/N–H cross-coupling) offers a valuable platform for accessing interesting nitrogen-containing compounds, particularly heterocycles.

Indole derivatives are prominent motifs that are embedded in a large number of natural products, alkaloids, antibiotics, and polymers.[3] Among them, 1-aminoindoles exhibit promising pharmacological properties such as psychotropic, anticonvulsant, antidepressant, hypotensive, analgesic, serotonin 5-HT2 antagonists, antioxidant effects, and are potential therapeutic reagents for treatment of Alzheimer's disease.[4] Various 1-aminoindoles have been used as highly valuable intermediates for the construction of many nitrogen-containing cyclic frameworks.[5] Despite these applications, the limited presence of 1-aminoindoles in the literature can be ascribed to the few methods existing for their preparation. The most common are the syntheses based on intermolecular N–N coupling reaction of pre-synthetized indoles/indolines.[6] In addition, *N*–functionalized arenes such as nitrosoanilines, phenylhydrazines or diphenyldiazenes can be used as precursors containing the requisite N–N fragment for the assembly of 1-aminoindole framework. These approaches include Rh-catalyzed C–H activation and annulation of *N*–Boc(acetyl) arylhydrazines with diazo compounds,[7] alkenes/alkynes[8] or maleimides,[9] amine mediated [3 + 2] annulation of azonaphthalenes with aldehydes/ketones[10] and acid-assisted cascade ring-opening/ring-closure of 6,8-dioxabicyclo[3.2.1]octanes (6,8-DOBCOs) under the action of arylhydrazines.[11] Other methods have appeared on the intramolecular amination reaction by the electrolysis,[12] or Pd catalyzed cyclization of *N*,*N*-disubstituted *o*-chloroacetaldehyde hydrazones,[13] Cu-catalyzed intramolecular cyclization of Boc-protected ene-hydrazine,[14] the Pd-catalyzed intramolecular cyclization of 2-halo-phenylacetylenes and *N*,*N*-disubstituted hydrazines.[15] However, the presence of halogen substituent in the ortho position of the benzene nucleus is essential to ensure the success of these transformations. A survey of the literature reveals that only two examples of intramolecular C–H amination reaction of α-arylhydrazones have been reported (Figure 1).

In Xiao's and Xu's work, $Cu(OAc)_2$ was used as a catalyst for the construction of poly-substituted cinnolines via a six-membered ring annulation.[16] A complementary strategy to produce *N*-amino-3-nitrile-indoles was instead realized by Du, Zhang-Negrerie and co-workers using iron as a promoter.[17] However, a more than stoichiometric amount of metal catalyst ($FeBr_3$, 2.5 equiv.) is required for the reaction to proceed.

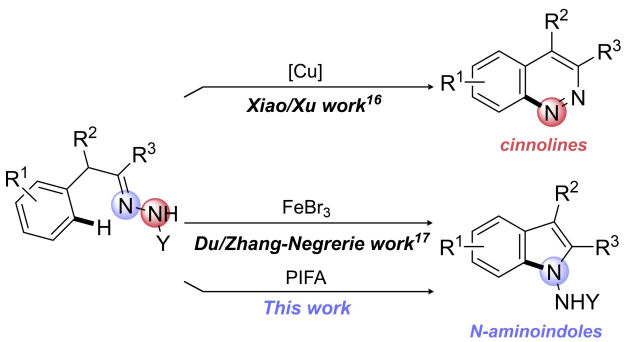

Figure 1. Intramolecular C–H aminations of α-arylhydrazones.

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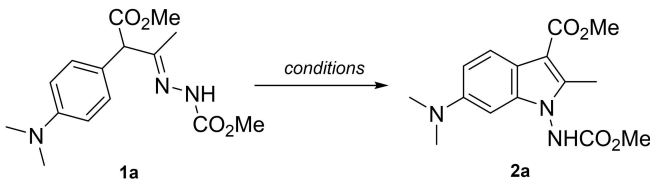
Therefore, the development of a greener and more sustainable protocols via direct N1–C1a bond formation to build *N*-aminoindoles, especially those functionalized in 3 with an ester group,[6a,b] from easily available precursors under transition metal-free conditions, is highly desirable.

With these remarks and our previous azacarboline synthesis[18] in mind, we speculated that α-indolylhydrazones could be exploited under oxidative conditions for a novel C–H amination strategy.

Herein we report a novel C–H amination of electron-rich α-aryl hydrazones using phenyliodine bis(trifluoroacetate) (PIFA), allowing for extremely high chemoselectivity toward 1-amino-pyrroles. The compatibility of the N–N single bond with inexpensive, non-toxic hypervalent iodine(III) reagent as an environmentally benign alternative to transition metals represents the main advantage of the present method. A range of α-arylhydrazones corresponding to general structure **1** were prepared via a Zn(II)-catalyzed Michael addition reaction of aromatic C(sp^2)–H nucleophiles with azoalkenes according to our previously reported method.[19]



Scheme 1. Representative model for the optimization of the synthesis of *N*-amino-1*H*-indole **2a**.

Results and Discussion

Our initial efforts started by using α-arylhydrazone (**1a**) as the model substrate for the optimization of the intramolecular C(sp^2)–H bond amination reaction (Scheme 1). After a preliminary screening of different transition metal-mediated reactions (Pd, Cu, and Fe; Table S1 in the Supporting Information), various forms of iodine reagents[20] have been explored (Table 1).

The combination of $PhIO_2$ with TFA in DCM [conditions applied by our group for the previously developed C(sp^2)–H bond amination reaction[18]] delivered the cyclized product **2a**, albeit in low yield (entry 1). To our delight, a satisfactory result was obtained in the absence of TFA and heating the reaction to 60 °C (entry 2). Further attempts to improve the yield by changing solvents and temperature (entries 3–5) as well the adding of base or acid promoters (entries 6–9) proved to be unfruitful. The treatment of the substrate **1a** with Koser's reagent (HTIB) as an oxidant led to the target *N*-amino-1*H*-indole **2a** in 45% yield (entry 10). Attempts to further improve the yield by lowering the temperature to 0 °C or adding K_2CO_3 and DIPEA as bases were not successful (entries 11–13). Then, the other two commonly used hypervalent iodine-(III) oxidants, PIDA and PIFA were tested. PIDA was found to be less effective than PIFA (entries 14–23). While the use of fluoroprotic solvents as TFE or HFIP was crucial to achieve high conversion of **1a**, the addition of PivOH or $BF_3{\cdot}Et_2O$[21] failed to improve the yield of **2a** (entries 24 and 25). Overall, the optimal conditions for the synthesis of *N*-amino indole were PIFA (1.3 equiv), DCM/TFE (1:1 mixture) as solvent at rt.

Table 1. Optimization studies for the cycloamination reaction of α-arylhydrazone **1a**.

Entry[a]	Oxidant [equiv.]	Additive [equiv.]	Solvent	Temp [°C]	Time [h]	Yield [%][b]
1	$PhIO_2$ (1.5)	TFA (1.0)	DCM	rt	12	18
2	$PhIO_2$ (2.3)	–	DCE	rt→60	>24	61[c]
3	$PhIO_2$ (2.3)	–	DMF	120	2	34
4	$PhIO_2$ (2.3)	–	CH_3NO_2	60	24	29
5	$PhIO_2$ (2.3)	–	HFIP	rt→60	9	9
6	$PhIO_2$ (2.3)	K_2CO_3 (2.0)	DCE	60	>24	<5
7	$PhIO_2$ (2.3)	*t*-BuOK (2.0)	DCE	50	12	13[c]
8	$PhIO_2$ (1.6)	PivOH (0.2)	DCE	rt	12	<5
9	$PhIO_2$ (1.6)	$FeCl_3$ (0.2)	DCM	rt	12	<5
10	HTIB (2.0)	–	DCM	rt	0.5	45
11	HTIB (2.0)	–	DCM	0	1	40
12	HTIB (2.0)	K_2CO_3 (2.0)	DCM	rt	12	27
13	HTIB (2.0)	DIPEA (1.0)	DCE	rt→60	12	14
14	PIDA (1.5)	TFA (0.3)	DCM	rt	12	<5
15	PIDA (1.5)	–	DCM	rt	12	<5
16	PIDA (1.5)	–	DCM/TFE (1:1)	0	>24	29
17	PIDA (1.5)	$CuBr_2$ (0.1)	DCM	rt	6	26
18	PIFA (1.3)	–	DCM	rt	16	46
19	PIFA (1.3)	–	TFE	rt	12	57
20	PIFA (1.3)	–	HFIP	rt	0.5	67
21	PIFA (1.3)	–	DCM/HFIP (1:1)	0	3	56
22	**PIFA (1.3)**	–	**DCM/TFE (1:1)**	**rt**	**3**	**76**
23	PIFA (1.3)	–	DCM/TFE (1:1)	0	12	66
24	PIFA (1.3)	PivOH (0.5)	DCM/TFE (1:1)	rt	12	54
25	PIFA (1.3)	BF_3 Et_2O (1.0)	DCM/TFE (1:1)	rt	1	73

[a] The reactions were conducted on 0.2 mmol scale using 2 mL of solvent. [b] Isolated yields after purification by column chromatography. [c] Traces of cinnoline [ref. 16] was also observed. Abbreviations used: PIDA = phenyliodine diacetate, PIFA = phenyliodine bis(trifluoroacetate), HTIB = hydroxy(tosyloxy)iodo]benzene, TFA = trifluoroacetic acid, PivOH = pivalic acid, DIPEA = *N*,*N*-diisopropylethylamine, DCM = dichloromethane, DCE = 1,2-dichloroethane, TFE = trifluoroethanol, HFIP = hexafluoroisopropanol.

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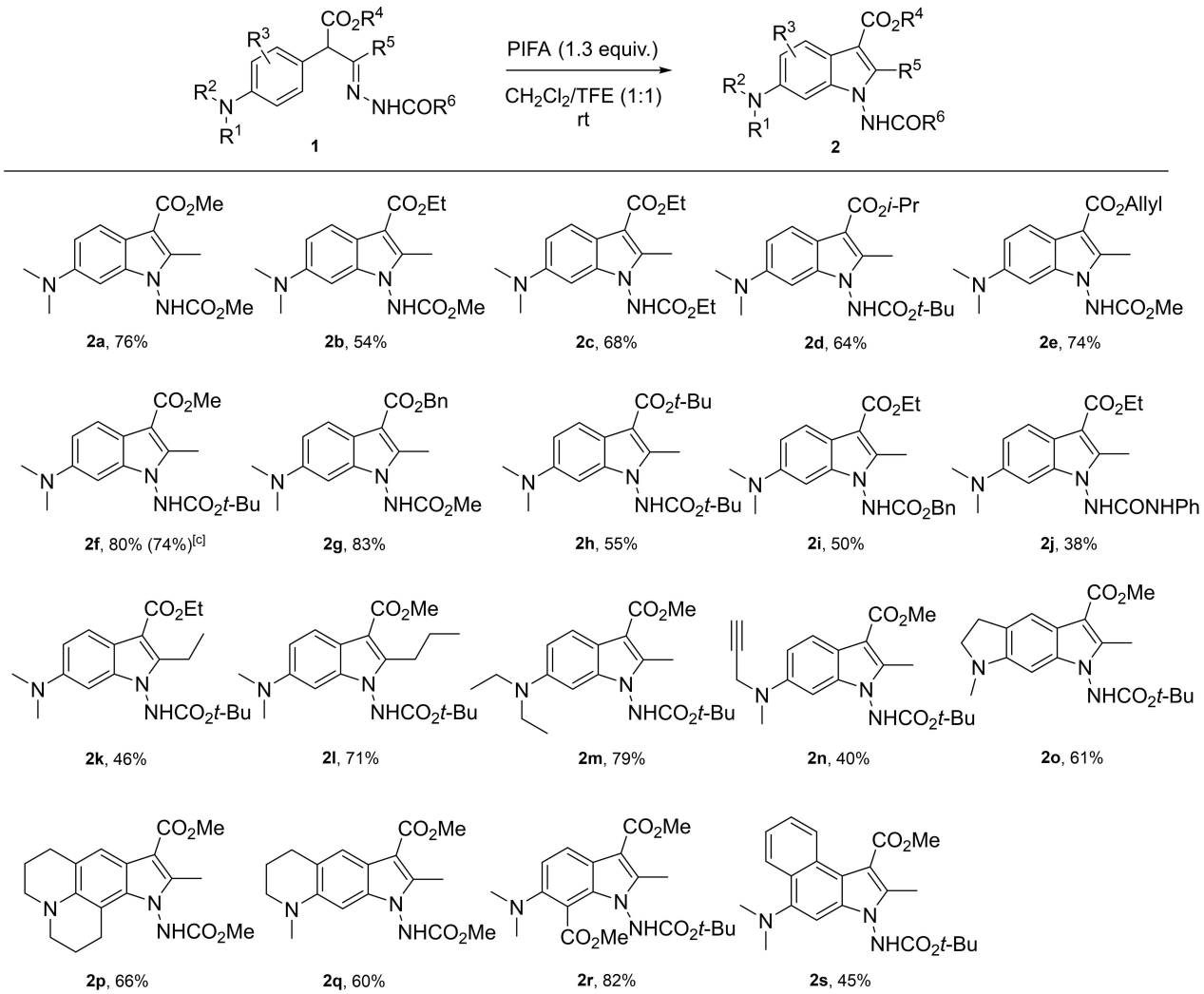
With the optimal conditions in hand, the scope of the intramolecular amination of C(sp^2)–H was explored. As shown in Table 2, different substituents were accommodated at the ester (R^4 = Me, Et, *i*-Pr, All, *t*-Bu, Bn) and carbamate (R^6 = OMe, OEt, O*t*-Bu) portion of α-aryl hydrazones delivering the corresponding *N*-amino-1*H*-indoles **2a**–**i** in moderate to good yields (54–83%). Importantly, the scalability of the method was verified by running the reaction of **1f** on 2.73 mmol scale (74% yield). α-Aryl semicarbazone **1j** (R^6 = NHPh) afforded product **2j** in only 38% yield. Incorporation of an ethyl and a propyl residue at the C-2 position of indole (**2k**, **2l**) was also tolerated. As regards the aniline portion, excellent yield (**2m**) was observed for the *N*,*N*-diethylaniline hydrazone substrate, whereas the *N*-methyl-*N*-propargyl residue offered the product **2n** with less yield. Pleasantly, *N*-amino-1*H*-indoles **2o**–**q** incorporating a five-, or six- ring system(s) between the N atom of anilino group and C5 or C5/C7 atoms of the benzene ring were also prepared in good yield. Notably, in the case of substrate **1r** which contains an ester group at the *ortho*-position of the anilino ring, the exclusive product **2r** was obtained in excellent yield. Similarly, *N*,*N*-dimethyl-1-naphtylamine hydrazone substrate **1s** underwent the cycloamination to generate the corresponding product **2s** in 45% yield. It is noteworthy that compounds **2o**, **2q** and **2r** were formed with complete control of regioselectivity, and no trace of isomer was detected for each of these products.

In order to understand the possible mechanism of the transformation, some control experiments were conducted (Scheme 2). First, the treatment of **1u** with PIFA in CH_2Cl_2 was found to give the hydrolyzed compound **3** as the main product (56% yield, Scheme 2a), and this result indicated that the cycloamination reaction in the absence of *N*,*N*-dialkyl moiety was completely inhibited. Second, when non-activated substrate **1u** was subjected to the optimized conditions, a mixture of ketone **3** and compound **4** was observed (Scheme 2b). The in situ formation of the azoalkene intermediate upon hyper-

Table 2. Scope for the PIFA-promoted intramolecular C–H bond amination of α-arylhydrazone **1**.[a,b]



[a] Reaction conditions: **1** (0.2 mmol) in CH_2Cl_2 (1 mL), then, PIFA (0.26 mmol) in TFE (1 mL), rt, 1–24 h. [b] Isolated yield after purification by column chromatography. [c] 2.73 mmol scale reaction (0.953 g).

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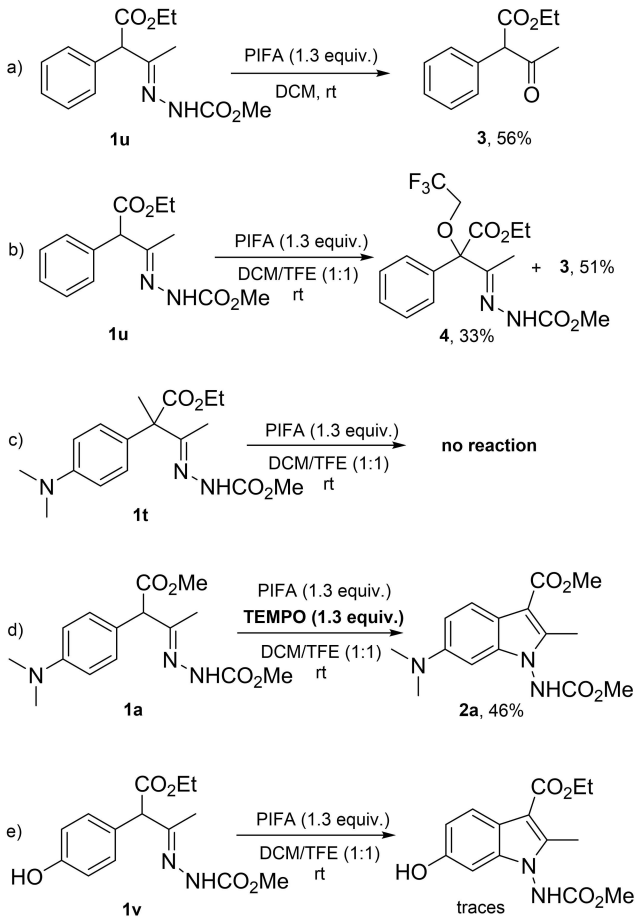
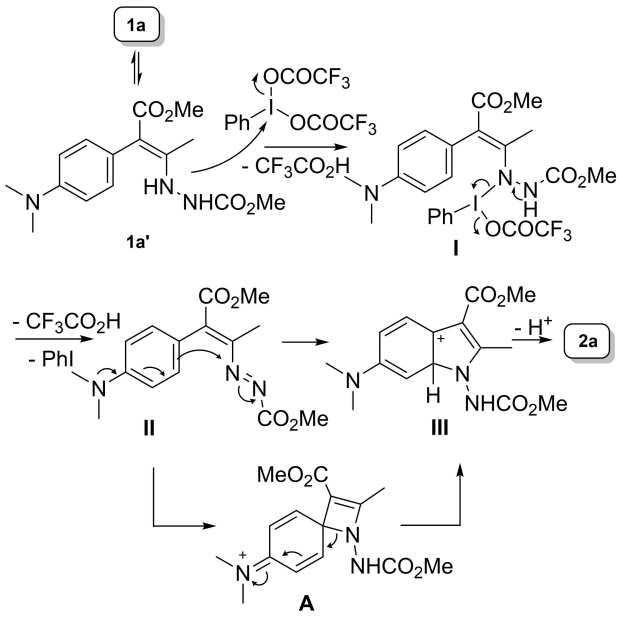


Scheme 2. Control experiments.



Scheme 3. Proposed mechanism for PIFA-mediated cycloamination.

valent iodine-promoted oxidation[14][22] followed by a nucleophilic attack of the trifluoroethoxy group on the α-position of **1u** could be responsible for the formation of this latter. The intense red color acquired by the solutions of **1a–s** under treatment with PIFA as well as the appearance of a less polar (not isolable) yellow/orange spot on TLC also support this. Third, when using **1t** as the substrate, no cycloamination reaction occurred (Scheme 2c). This fact suggests that the presence of a proton at the α-position of hydrazone is also fundamental for the proceeding of the reaction. Fourth, the application of TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) as a radical-trapping reagent did not significantly affect the transformation of **1a** to **2a**, thus indicating that radical species cannot play a role in the present C–H amination (Scheme 2d). Finally, the reaction of **1v** containing activating hydroxy group under the optimized reaction conditions furnished a complex mixture from which only trace amount of the cyclized product was observed (Scheme 2e).

Based on these observations and the literature reports,[14,18][20–24] a rational mechanistic sequence is proposed in Scheme 3. After a preliminary CH/NH tautomerization (1,3-H shift), the oxidation of ene-hydrazine **1a'** using PIFA may give the reactive azo compound **II**. It is plausible to assume that the reactions are initiated by attack of **1a'** on the electrophilic iodine center of PIFA to give intermediate **I** with loss of a CF_3CO_2H molecule. Then, a simultaneous release of PhI and CF_3CO_2H would occur from **I** to afford the transient azoalkene species **II**. Subsequently, a nucleophilic arene attack to the azo group followed by re-aromatization of the cation **III** may lead to the formation of the target *N*-amino-1*H*-indole **2a**. Likely, this intramolecular cyclization can occur via an ipso attack followed by rearrangement (via N-to-C bond migration) of the cationic spiro dieniminium salt **A** formed as an intermediate.[23][24] The involvement of species **A**[24] via oxidative dearomatizing cyclization pathway would support the key importance of a *N,N*-dialkyl group at the *para* position of the arylhydrazone substrate. Currently, direct attack of the phenyl group on the iodine-activated electrophilic nitrogen atom of **I** that leads to intermediate **III** with release of PhI and CF_3COO^- simultaneously, cannot be ruled out.

As a proof-of-concept demonstration of the synthetic utility of the reaction protocol developed herein, compound **2f** was subjected to further transformations (Scheme 4). Treated with $BF_3 \cdot OEt_2$ in DCM at rt,[25] the Boc group on the nitrogen atom was removed, affording **5** in nearly quantitative yield. Additionally, reductive cleavage of N–N bond to give **6** can be successfully realized by applying the Magnus' conditions.[26]

Conclusions

To conclude, we have developed a practical method for the synthesis of variously substituted 1-aminoindoles via an intramolecular oxidative C–N bond formation approach on electron-rich α-arylhydrazones. The synthetic value of this chemoselective protocol is demonstrated by the unique example of introducing the N–N single bond into the indole scaffold

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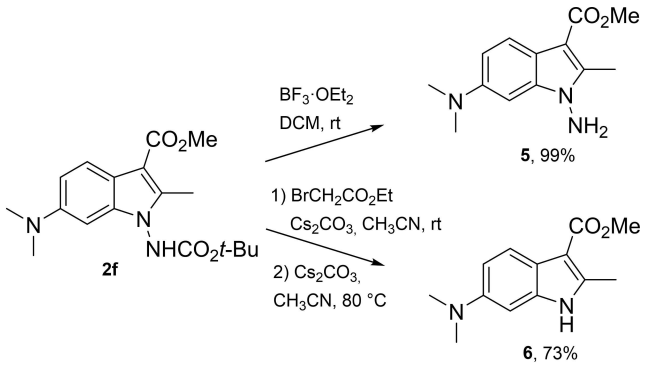

Scheme 4. Synthetic transformations of **2f**.

directly using hypervalent iodine(III) reagents promoting cycloamination[27] of hydrazones without the need of the expensive precious transition metal catalysts (rhodium or palladium).

Experimental Section

General information. All the commercially available reagents and solvents were used without further purification. α-Arylhydrazones **1a–t** were prepared according to our previously reported method with slight modifications.[19] Hydrazones **1u** and **1v** were prepared according to the modified known procedures.[28],[29] Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. NMR spectra (^1H, ^{13}C {decoupled} and ^{19}F) were recorded on a Bruker Ultrashield 400 spectrometer (400, 101 and 376 MHz, respectively) at 298 K using DMSO-d_6 or $CDCl_3$ as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in descending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, t = triplet q = quartet, qt = quintet, sept = septet, m = multiplet, and br = broad signal. All coupling constants (*J*) are given in Hz. High-resolution mass spectral (HRMS) analyses were performed using Orbitrap Exploris 240 Mass Spectrometers (Thermo Scientific) equipped with an ESI source. Melting points were determined in open capillary tubes and are uncorrected.

General procedure for PIFA-promoted intramolecular C(sp^2)–H amination

PIFA (0.26 mmol, 111.8 mg) in TFE (1 mL) was added dropwise via a syringe to a stirred solution of α-arylhydrazone **1** (0.2 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at room temperature until consumption of the starting material (TLC check). Then, saturated $NaHCO_3$ was added, and the mixture was extracted with ethyl acetate (3×10 mL). After the removal of the solvent, the crude mixture was purified by column chromatography on silica gel to afford, the *N*-amino indole **2**.

Procedure for the synthesis of 5

Compound **5** was prepared by applying the Taylor's conditions.[25] To a solution of **2f** (69.5 mg, 0.2 mmol) in CH_2Cl_2 (2 mL), $BF_3\cdot OEt_2$ (0.075 mL, 0.6 mmol) was added. The mixture was stirred at room temperature until the disappearance of the starting material (2.5 h). The solvent was removed under vacuum, ethyl acetate (5 mL) was added and the mixture was washed with saturated $NaHCO_3$ (3× 5 mL). The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under vacuum to afford compound **5** as a pale grey solid, which was washed with diethyl ether (49.3 mg, 99%).

Procedure for the synthesis of 6

Compound **6** was prepared by applying the modified Magnus' protocol.[26] To a solution of **2f** (69.5 mg, 0.2 mmol) in acetonitrile (2 mL), ethyl bromoacetate (0.033 mL, 0.3 mmol) and Cs_2CO_3 (162.9 mg, 0.5 mmol) were added. The mixture was stirred at room temperature until the disappearance of the starting material (3 h). The solvent was removed under vacuum, water (5 mL) was added, and the mixture was extracted with ethyl acetate (3×5 mL). The combined organic layer was dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was dissolved in acetonitrile (2 mL) and Cs_2CO_3 (162.9 mg, 0.5 mmol) was added. The mixture was stirred at 80 °C until TLC showed complete consumption of the intermediate (1 h). The solvent was removed under vacuum, water (5 mL) was added, and the mixture was extracted with ethyl acetate (3×5 mL). The collected organic phase was washed with brine, dried over Na_2SO_4 and the solvent was removed under vacuum, the residue was purified by column chromatography (ethyl acetate) to afford compound **6** as a brownish solid (33.8 mg, 73% yield).

Supporting Information

Additional references cited within the Supporting Information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: cyclization · C(sp^2)–H amination · indoles · hydrazones · hypervalent iodine(III) reagent

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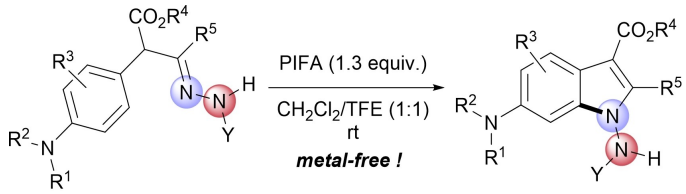

A metal-free chemoselective approach for the C–H amination of electron-rich α-aryl hydrazones is developed. This approach represents an easy transformation of readily available precursors into biological relevant *N*-based heterocycles in the absence of transition metal catalysts.

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A Metal-Free C–H Amination-Based Strategy for *N*-Amino Indole Synthesis