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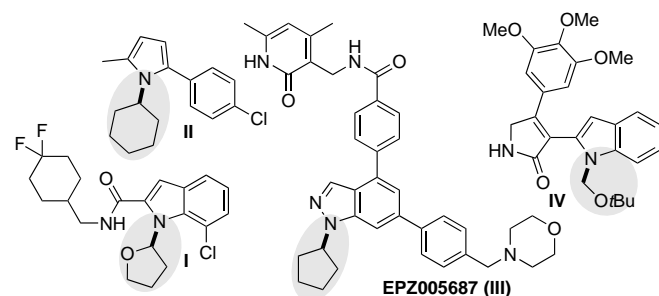
# Copper-Catalyzed Oxidative Dehydrogenative C(sp<sup>3</sup>)-H Bond Amination of (Cyclo)Alkanes using *NH*-Free Heterocycles as Amine Sources

Chang-Sheng Wang,<sup>[a]</sup> Xiao-Feng Wu,<sup>[b]</sup> Pierre H. Dixneuf<sup>[a]</sup> and Jean-François Soulé<sup>\*[a]</sup>

**Abstract:** A copper-catalyzed oxidative C(sp<sup>3</sup>)-H/N-H coupling of *NH*-heterocycles with affordable (cyclo)alkanes was developed. This protocol involved C(sp<sup>3</sup>)-N bond formation *via* a radical pathway generated by a homolytic cleavage of di-*tert*-butyl peroxide and trapping of the radical(s) by copper catalysts. The reaction tolerated a series of functional groups, such as bromo, fluoro, ester, ketone, nitrile, methyl and methoxy. *NH*-free indoles, pyrroles, pyrazoles, indazoles and benzotriazoles have been successfully *N*-alkylated.

## Introduction

*N*-alkyl heterocycle derivatives constitute an important class of organic compounds, which have been widely used in biology, synthetic and polymer chemistry.<sup>[1]</sup> As example, The *N*-alkyl indole **I** displays biological activity for the treatment of neurodegenerative diseases.<sup>[2]</sup> The *N*-cycloalkyl pyrrole **II** is an analogue of BN1212 exhibiting antitubercular properties.<sup>[3]</sup> The *N*-cyclopentylindazole **III** was used as a selective inhibitor of EZH2.<sup>[4]</sup> The *N*-(*tert*-butoxymethyl)indole **IV** has shown inhibition properties on vascular endothelial growth factors, which are important signaling proteins involved in both vasculogenesis and angiogenesis (Figure 1).<sup>[5]</sup>



**Figure 1.** Examples of *N*-Alkyl heterocycles Displaying Biological Activities.

Despite this wide applicability, ecofriendly routes for the synthesis of *N*-alkyl heterocycles are limited. One of the most common synthetic pathway involves S<sub>N</sub>2 reaction using a stoichiometric amount of a strong base and an appropriate alkylating agent (e.g., alkyl halide, alkyl triflate, *etc.*) generation a lot of waste (Figure 2a).<sup>[6]</sup> Since the discovery of transition-metal catalyzed C-H bond functionalizations,<sup>[7]</sup> catalytic C-H amination provides an appealing method for the straightforward construction of C-N bonds.<sup>[8]</sup> General protocols for the transition-metal catalyzed C-H amination required electrophilic amines, *via* an internal oxidant strategy (e.g., azides,<sup>[9]</sup> *N*-haloamines<sup>[10]</sup> or oximes<sup>[11]</sup>). However, such protocols could not be employed for the *N*-functionalization of *NH*-heterocycles. Amines can be directly used, although an external oxidant is required.<sup>[12]</sup> However, only rare examples of C-H amination with *NH*-heterocycles have been reported.<sup>[13]</sup> This lack of exploitation is probably due to the presence of competitive C(sp<sup>2</sup>)-H bonds on *NH*-heterocycles, which are generally more reactive.<sup>[14]</sup> Although synthetic tools enabling C(sp<sup>2</sup>)-N bond formation have been well established,<sup>[15]</sup> facile intermolecular amination of C(sp<sup>3</sup>)-H bonds under mild conditions still remains a challenge in synthetic chemistry.<sup>[4, 11d, 16]</sup>

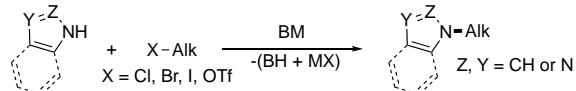
Recently, cross-dehydrogenative coupling reactions have attracted increasing attention owing to the use of abundant hydrocarbons (i.e., arenes, olefins, or cycloalkanes) as unreactive coupling partners for the C-C, C-O, and C-N bond formation.<sup>[17]</sup> Warren and co-workers reported the oxidative dehydrogenative amination of alkanes with unactivated amines using copper(II) as catalyst associated to di-*tert*-butyl peroxide (DTBP) (Figure 2b).<sup>[18]</sup> Outstanding achievements are emerging in this area<sup>[19]</sup> although only amines with low nucleophilicity were successfully alkylated. For example, Hartwig and co-workers reported C(sp<sup>3</sup>)-H amination of cyclohexane with phthalimide and sulfonamides.<sup>[19c]</sup> Cai and co-workers have reported that with *NH*-indoles, using nickel catalyst, regioselective C2- or C3-products were obtained without the formation of *N*-alkylated indole (Figure 2c).<sup>[20]</sup> In addition, Yi and co-workers have reported that under metal-free conditions in the presence of DTBP, the cross-dehydrogenative coupling between *NH*-indoles and (cyclo)alkanes took place at the C7 position of the indole unit, and in some cases C2 or C4 regioselectivity was overserved (Figure 2d).<sup>[21]</sup> To the best of our knowledge, oxidative dehydrogenative amination of (cyclo)alkanes using electron-rich *NH*-heteroarenes as amine sources has not been reported yet owing to the chemoselectivity issue between C-H or N-H reactivity.<sup>[22]</sup> Inspired by previous works on the generation of alkyl radical in the presence of coordinated amines,<sup>[18, 19c]</sup> we herein report a general method for the C-N bond formation *via* C-H/N-H cross-coupling of *NH*-free

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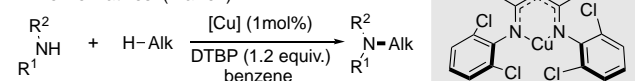
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indoles, pyrroles, benzotriazoles, indazoles, and pyrazoles with (cyclo)alkanes to afford the corresponding *N*-alkylated heterocycles in good yields with a high chemoselectivity (Figure 2e).

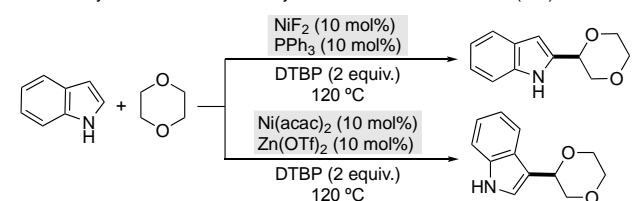
**a. Synthesis of *N*-Alkylheterocycles via  $S_N2$  reaction.<sup>[6]</sup>**



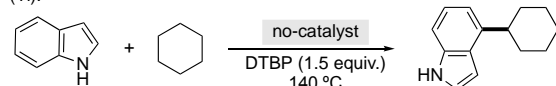
**b. Copper-Catalyzed Oxidative Dehydrogenative Amination of Electron-Deficient Amine Derivatives (Warren).<sup>[18]</sup>**



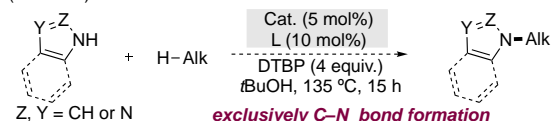
**c. Ni-Catalyzed CDC C2 or C3 Alkylations of Indole Derivatives (Cai).<sup>[19]</sup>**



**d. Metal-Free C7 Alkylation of Indole Derivatives with Cyclohexanes via CDC (Yi).<sup>[21]</sup>**



**e. Copper-Catalyzed Oxidative Dehydrogenative Amination with *NH*-Heterocycles (this work)**



**Figure 2.** *N*-Alkylation of amines and *NH*-Heterocycles

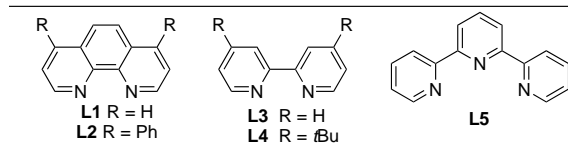
## Results and Discussion

We started our investigation using *NH*-free indole and cyclohexane as model substrates. The reaction was initially studied with DTBP as an oxidant, in *t*BuOH without catalyst. As reported by Yi,<sup>[21]</sup> we have not observed the formation of the amination product **1** after heating at 135 °C over 15 h, but we did observe the formation of C-alkylated products (Table 1, entry 1). When FeCl<sub>3</sub> (5 mol%) in the presence of phenanthroline (**L1**) (10 mol%) was used as the catalytic system, the amination product **1** was obtained in low yield with predominant formation of other C2, C3 and C7-alkylated products (Table 1, entry 2). FeCl<sub>2</sub>, in concert with **L1**, gave a similar result (Table 1, entry 3). In contrast, when copper (II or I) oxides, combined with **L1**, were used as catalysts, **1** was selectively obtained in 41% and 50% yield, respectively without the formation of other C2, C3 and C7-alkylated products (Table 1, entries 4 and 5). Encouraged by these results, a number of other copper sources, including CuBr, CuI, [MeCN]<sub>4</sub>Cu(I)PF<sub>6</sub>, Cu(I)Br(Me<sub>2</sub>S), and Cu(OAc)<sub>2</sub>·*n*-H<sub>2</sub>O were evaluated in the presence of **L1** (Table 1, entries 6–10). The results showed that Cu(I)Br(Me<sub>2</sub>S) displayed the highest catalytic

activity for this reaction and *N*-cyclohexylindole (**1**) was isolated in 67% yield (Table 1, entry 10). Next, we evaluated without success the influence of other *N,N*-bidentate ligands, such as 4,7-diphenyl-1,10-phenanthroline (**L2**), 2,2'-bipyridine (**L3**), 4,4'-di-*tert*-butyl-2,2'-bipyridine (**L4**) and 2,2':6',2''-terpyridine (**L5**) (Table 1, entries 11–14). When the reaction is performed in absence of phenanthroline (**L1**), the yield in **1** dropped to 10% concurrent with the formation of other C2, C3 and C7-alkylated products (Table 1, entry 15). Other oxidants such as TBHP, BPO were inefficient for the coupling of cyclohexane bonds with *NH*-indole; whereas, DCP give a lower yield of 32% in the desired product **1** (Table 1, entries 16–18). It is important to note that using a lower amount of cyclohexane the yield of **1** decreased (Table 1, entry 19). The reaction is less efficient in other solvents such as benzene, trifluorotoluene, or 1,2-dichloroethane (Table 1, entries 20–22).

**Table 1** Optimization of Oxidative Dehydrogenative Amination of Cyclohexane with *NH*-free Indole.

Entry	Cat.	L	oxidant	solvent	Yield in <b>1</b> (%) <sup>[a]</sup>
1	–	–	DTBP	–	0 <sup>[b]</sup>
2	FeCl <sub>3</sub>	<b>L1</b>	DTBP	<i>t</i> BuOH	5 <sup>[b]</sup>
3	FeCl <sub>2</sub>	<b>L1</b>	DTBP	<i>t</i> BuOH	8 <sup>[b]</sup>
4	CuO (II)	<b>L1</b>	DTBP	<i>t</i> BuOH	41
5	Cu <sub>2</sub> O (I)	<b>L1</b>	DTBP	<i>t</i> BuOH	50
6	CuBr	<b>L1</b>	DTBP	<i>t</i> BuOH	77
7	CuI	<b>L1</b>	DTBP	<i>t</i> BuOH	62
8	Cu(OAc) <sub>2</sub> · <i>n</i> -H <sub>2</sub> O	<b>L1</b>	DTBP	<i>t</i> BuOH	65
9	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	<b>L1</b>	DTBP	<i>t</i> BuOH	52
10	CuBr(Me <sub>2</sub> S)	<b>L1</b>	DTBP	<i>t</i> BuOH	87 (67)
11	CuBr(Me <sub>2</sub> S)	<b>L2</b>	DTBP	<i>t</i> BuOH	55
12	CuBr(Me <sub>2</sub> S)	<b>L3</b>	DTBP	<i>t</i> BuOH	22
13	CuBr(Me <sub>2</sub> S)	<b>L4</b>	DTBP	<i>t</i> BuOH	39
14	CuBr(Me <sub>2</sub> S)	<b>L5</b>	DTBP	<i>t</i> BuOH	13
15	CuBr(Me <sub>2</sub> S)	–	DTBP	<i>t</i> BuOH	10 <sup>[b]</sup>
16	CuBr(Me <sub>2</sub> S)	<b>L1</b>	TBHP	<i>t</i> BuOH	NR
17	CuBr(Me <sub>2</sub> S)	<b>L1</b>	BPO	<i>t</i> BuOH	NR
18	CuBr(Me <sub>2</sub> S)	<b>L1</b>	DCP	<i>t</i> BuOH	32
19 <sup>[c]</sup>	CuBr(Me <sub>2</sub> S)	<b>L1</b>	DTBP	<i>t</i> BuOH	46
20	CuBr(Me <sub>2</sub> S)	<b>L1</b>	DTBP	C <sub>6</sub> H <sub>6</sub>	28
21	CuBr(Me <sub>2</sub> S)	<b>L1</b>	DTBP	CF <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	35
22	CuBr(Me <sub>2</sub> S)	<b>L1</b>	DTBP	DCE	45

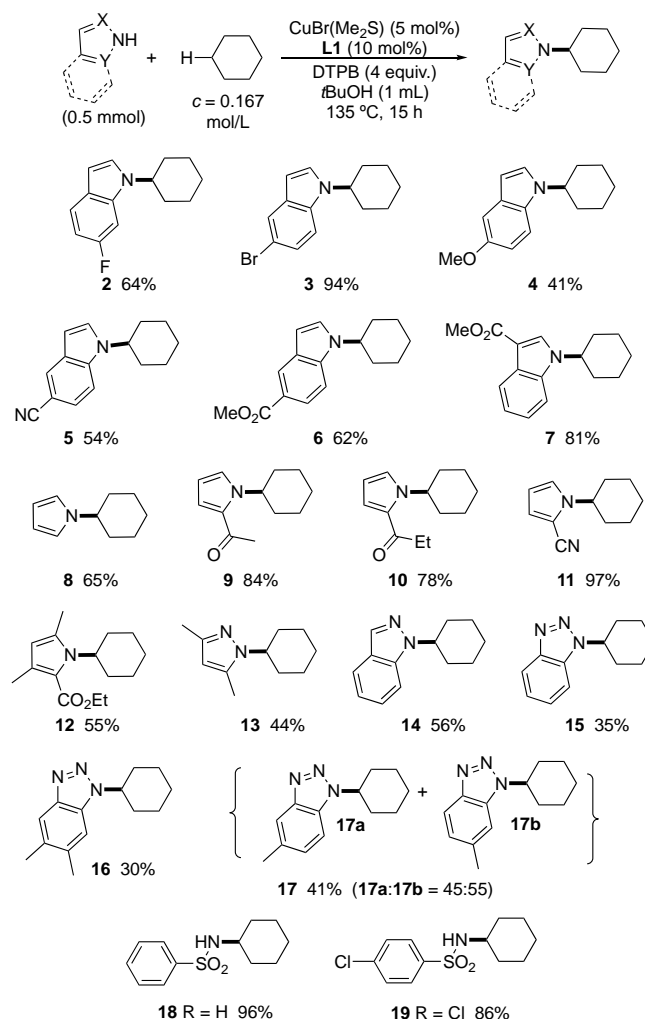


[a] Determined by GC-analysis using *n*-dodecane as internal standard, isolated yield is shown in parentheses. [b] Formation of other C2, C3 and C7-alkylated products. [c] Reaction performed at 0.5 mol/L of cyclohexane.

With the optimized reaction conditions in hands, we then explored the substrate scope. Firstly, we investigated the reactivity of *NH*-heterocycles with cyclohexane using Cu/**L1**/DTBP system (Scheme 1). *NH*-6-Fluoroindole and *NH*-5-bromoindole were successfully *N*-alkylated to deliver the corresponding *N*-cyclohexylindoles **2** and **3** in 64% and 94% yield, respectively. It should be mentioned that for these reactions, no cleavage of the C–halogen bonds were observed, allowing further transformations. An electron-donating group on the indole moiety,

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such as 5-methoxyl, slightly affected the yield in the coupling product **4**; while an electron-withdrawing group such as nitrile or methyl ester allowed the formation of the desired *N*-alkylindoles **5** and **6** in 54% and 62% yields, respectively. The reaction conditions tolerate a C3 substituent on the indole moiety such as ester. Indeed, from methyl *NH*-indole-3-carboxylate the optimized reaction conditions gave exclusively the *N*-alkylation product **7** in 81%. Whereas, indole bearing a C2-substituent such as methyl or phenyl did not allow the formation of the corresponding *N*-alkylation product. Under these reaction conditions, *NH*-pyrrole was also alkylated affording *N*-cyclohexylpyrrole **8** in 65% yield, without the formation of C2 or C3 alkylation products. Cu/L1/DTBP-catalyzed oxidative dehydrogenative amination tolerated functional groups such as ketone and nitrile. Indeed, 2-acetyl, 2-propionyl, and 2-nitrile pyrroles successfully reacted with cyclohexane to afford the *N*-cyclohexylpyrroles **9–11** in 84–97% yields. A trisubstituted pyrrole including ethyl ester group was also *N*-alkylated to afford **12** in 55% yield. Poly-nitrogen heterocyclic compounds are ubiquitous structural elements important to a wide range of fine and bulk chemical fields.<sup>[23]</sup> Therefore, we investigated their reactivity in oxidative dehydrogenative amination. *NH*-3,5-Dimethylpyrazole and *NH*-indazole smoothly reacted in the presence of cyclohexane to give the corresponding *N*-alkylated products **13** and **14** in moderate yields, but without the formation of C-alkylation products. *NH*-Benzotriazole displayed poor reactivity, as the *N*-alkylated products **15–17** were isolated in moderate to low yields. In the case of 5-methylbenzo[1,2,3]triazole, the product was isolated as mixture of two regioisomers **17a** and **17b** in 55:45 ratio. Finally, our catalytic system displayed similar performance than other protocols<sup>[19a]</sup> for the *N*-alkylation of sulfonamides, as **18** and **19** were obtained in 96% and 86% yields. It is important to note that some functional groups on the heterocycle moiety such as nitro, amino, or hydroxyl are not compatible with the reaction conditions.

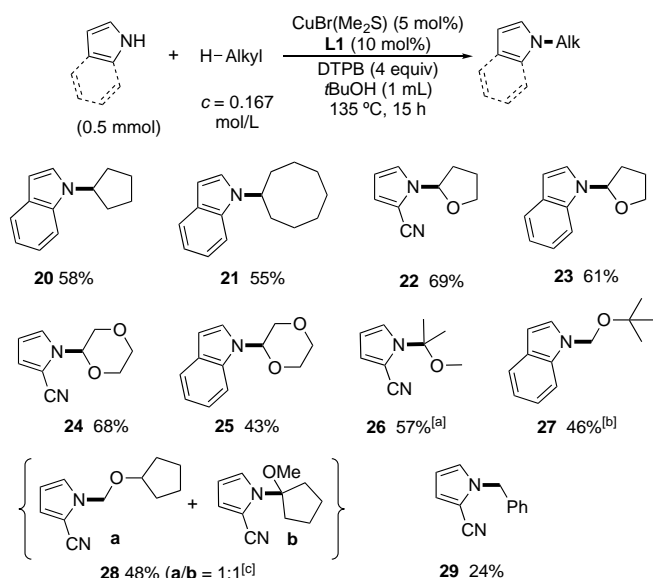


**Scheme 1.** Scope of *NH*-Heterocycle in Cu-catalyzed C(sp<sup>3</sup>)-H Amination of Cyclohexane.

Substrate scope studies were also carried out on other hydrocarbons using *NH*-pyrrole or *NH*-indole as amine sources (Scheme 2). As expected, the reaction between *NH*-indole with linear alkanes (e.g., pentane or hexane) leads to a variety of *N*-alkylated product at C1, C2, C3 carbons. The direct amination of other cycloalkanes (e.g., cyclopentane and cyclooctane) with *NH*-indole allowed the formation of **20** and **21** in 58% and 55% yields, respectively. Tetrahydrofuran can be also used as suitable alkylating agent through the regioselective C(sp<sup>3</sup>)-H bond activation.<sup>[24]</sup> The amination occurred at the  $\alpha$ -position of the oxygen atom to afford **22** and **23** in 69% and 61% yields from *NH*-2-cyanopyrrole and *NH*-indole. Similarly, 1,4-dioxane was successfully coupled with 2-cyanopyrrole and indole giving the *N*-alkylated products **24** and **25** in 68% and 43% yield, respectively. Interestingly, the reaction of 2-cyanopyrrole with 2,2-dimethoxypropane led selectively to the formation of *N*-(2-methoxypropan-2-yl)-2-cyanopyrrole (**26**) in 57% yield. This product results from the substitution of one methoxy group. Methyl *tert*-butyl ether reacted at the methoxy position to afford

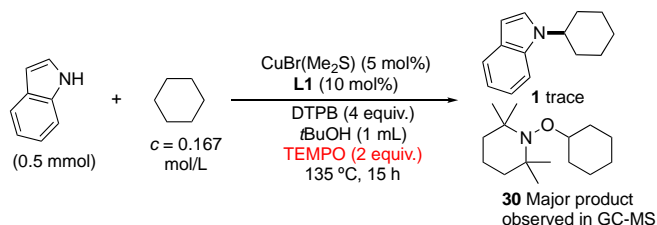
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regioselectively the *N*-alkylated heterocycle **27** in 46% yield. In contrast, cyclopentyl methyl ether provided a mixture of two regioisomers **28a** and **28b** in 1:1 ratio. These regioselectivities are in line with a radical pathway, in which the radical is stabilized by the oxygen atom. Finally, from toluene, pyrrole was *N*-benzylated in moderate yield.



**Scheme 2.** Scope of (Cyclo)Alkanes in Cu-catalyzed C(sp<sup>3</sup>)-H Amination with *NH*-Heterocycle. [a] Using 2,2-dimethoxypropane as alkane source; [b] Using methyl *tert*-butyl ether as alkane source; [c] Using methyl cyclopentyl ether as alkane source

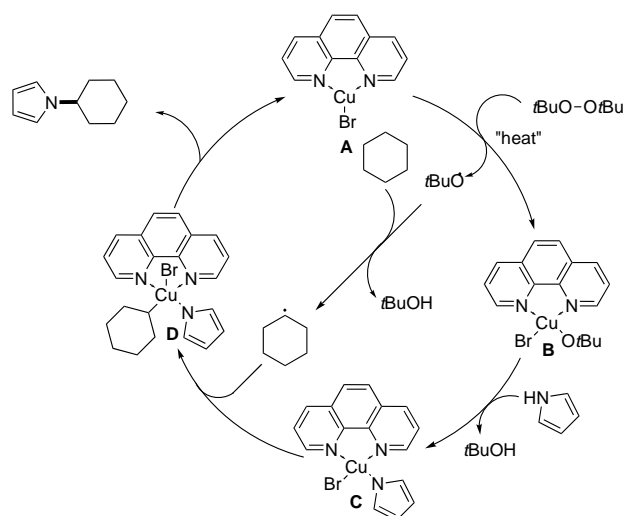
To obtain a better understanding of the mechanism, a radical control experiment was carried out in the presence of a radical scavenger (Scheme 3). When 2 equivalents of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction under the standard conditions, no desired product **1** was detected. However, we have observed the formation of the adduct cyclohexane-TEMPO **30** (determined by GC-MS), which implied that a radical process is involved in the oxidative dehydrogenative amination of (cyclo)alkanes with *NH*-heterocycles.



**Scheme 3.** Radical Trapping Experiment with TEMPO.

Based on our experimental results and previous reports,<sup>[19]</sup> a possible mechanism is described in Scheme 4. First, homolytic

cleavage of the DTBP peroxide under heating allowed the formation of *tert*-butoxyl radical (*t*BuO<sup>•</sup>) which is trapped by the copper(I) **A** to generate the copper(II) alkoxide **B**.  $\sigma$ -Bond metathesis of **B** with an *NH*-heterocycle regenerates intermediate **C**. The coordination of the *N*-heterocycle to the copper centre renders the N atom particularly reactive toward reaction with C-based radicals (R<sup>•</sup>), which are generated by abstracting a hydrogen atom from (cyclo)alkane by *tert*-butoxyl radical (*t*BuO<sup>•</sup>). Reaction of the alkyl radical (R<sup>•</sup>) with Cu(II) **C** should allow the formation of the Cu(III) intermediate **D**, which undergoes a reductive elimination to release the desired *N*-alkylated heterocycle and reduce the Cu center to regenerate active copper(I) **A**.



**Scheme 4.** Proposed Mechanism.

## Conclusions

In summary, we have described a copper-catalyzed oxidative dehydrogenative amination of unactivated alkanes with *NH*-heterocycles to produce exclusively the corresponding *N*-alkylated products without formation of a C-C bond. Choice of copper source as well as the phenanthroline ligand were found to be critical to suppress the formation of C-alkylated heterocycles. A wide variety of *NH*-heterocycles including poly-nitrogen heterocyclic compounds were successfully *N*-alkylated. Moreover, the reaction conditions tolerate a broad variety of substituents of the heterocycles such as methyl, methoxy, fluoro, bromo, ketone, ester, and nitrile. This method employs abundant and cheap feedstock under oxidative conditions, without any pre-functionalization or the production of stoichiometric metal salt waste, making it very attractive for practical use in the preparation of useful *N*-alkylated heterocyclic derivatives.

## Experimental Section



**General Remarks:** All reactions were run in Schlenk tubes without the use of an inert atmosphere. Commercial *NH*-free heterocycles and (cyclo)alkanes were used without purification. The reactions were followed by GC and NMR.  $^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded with a Bruker 400 MHz spectrometer in  $\text{CDCl}_3$  solutions. Chemical shifts are reported in ppm relative to  $\text{CDCl}_3$  (7.26 for  $^1\text{H}$  NMR and 77.0 for  $^{13}\text{C}$  NMR). Flash chromatography was performed on silica gel (230–400 mesh).

**General Procedure for Copper-Catalyzed Oxidative Dehydrogenative C(sp<sup>3</sup>)-H Bond Amination of (Cyclo)Alkanes with *NH*-free Heterocycles:** In a dried 25 mL Schlenk tube equipped with a magnetic stirrer,  $\text{CuBr}(\text{Me}_2\text{S})$  (5.0 mg, 0.025 mmol, 5 mol%) and 1,10-phenanthroline (9.0 mg, 0.05 mmol, 10 mol%) were dissolved in *t*-BuOH (1 mL) and (cyclo)alkane (1 mL). Then, *NH*-free heterocycles (0.5 mmol) and additional (cyclo)alkane (2 mL) were successfully added before addition of DTBP (292 mg, 2.0 mmol, 4 equiv.). The resulting solution mixture was stirred at 135 °C over 15 h. After evaporation of solvent, the product was purified using flash column chromatography on silica gel.

***N*-Cyclohexylindole (1):** Following the general procedure using *NH*-indole (58 mg, 0.5 mmol) and cyclohexane (3 mL), **1** was isolated in 67% yield (66 mg) as a colorless oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.70 (d,  $J$  = 7.8 Hz, 1H), 7.45 (d,  $J$  = 8.2 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.16 (d,  $J$  = 7.2 Hz, 1H), 4.28 (tt,  $J$  = 3.7, 11.8 Hz, 1H), 2.28 – 2.12 (m, 2H), 2.08 – 1.92 (m, 3H), 1.74 (td,  $J$  = 3.1, 12.3 Hz, 2H), 1.56 (tdd,  $J$  = 3.3, 8.1, 12.9 Hz, 3H), 1.44 – 1.25 (m, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 135.6, 128.5, 124.1, 121.1, 121.0, 119.3, 109.5, 101.0, 55.1, 33.6, 26.1, 25.8. MS(EI)  $m/z$ (%) = 199 ([M]<sup>+</sup>, 49), 156 (30), 130 (10), 117 (100), 90 (14), 55 (13).

***N*-Cyclohexyl-6-fluoroindole (2):** Following the general procedure using 6-Fluoro-*NH*-indole (68 mg, 0.5 mmol) and cyclohexane (3 mL), **2** was isolated in 64% yield (69 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.55 (dd,  $J$  = 8.6, 5.5 Hz, 1H), 7.22 (d,  $J$  = 3.2 Hz, 1H), 7.08 (dd,  $J$  = 10.2, 1.7 Hz, 1H), 6.89 (dd,  $J$  = 9.4, 2.2 Hz, 1H), 6.51 (d,  $J$  = 3.1 Hz, 1H), 4.12 (tt,  $J$  = 11.8, 3.6 Hz, 1H), 2.23 – 2.06 (m, 2H), 2.04 – 1.90 (m, 2H), 1.76 – 1.64 (m, 2H), 1.60 – 1.44 (m, 2H), 1.40 – 1.24 (m, 2H).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) -121.6.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 159.6 (d,  $J$  = 236.6 Hz), 135.5 (d,  $J$  = 12.0 Hz), 124.9, 124.5 (d,  $J$  = 3.6 Hz), 121.5 (d,  $J$  = 10.2 Hz), 108.0 (d,  $J$  = 24.6 Hz), 101.2, 95.9 (d,  $J$  = 26.3 Hz), 55.4, 33.4, 25.9, 25.6. MS(EI)  $m/z$ (%) = 217 ([M]<sup>+</sup>, 36), 174 (11), 135 (100), 108 (14), 55 (19).

**5-Bromo-*N*-cyclohexylindole (3):** Following the general procedure using 5-bromo-*NH*-indole (97 mg, 0.5 mmol) and cyclohexane (3 mL), **3** was isolated in 94% yield (130 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.75 (dd,  $J$  = 1.4, 1.0 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.22 (d,  $J$  = 3.2 Hz, 1H), 6.45 (d,  $J$  = 3.2 Hz, 1H), 4.17 (tt,  $J$  = 11.8, 3.7 Hz, 1H), 2.19 – 2.03 (m, 2H), 2.01 – 1.86 (m, 2H), 1.87 – 1.75 (m, 1H), 1.75 – 1.62 (m, 2H), 1.61 – 1.40 (m, 2H), 1.40 – 1.21 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 134.2, 130.1, 125.2, 123.9, 123.4, 112.4, 110.9, 100.6, 55.4, 33.5, 25.9, 25.6. MS(EI)  $m/z$  (%) = 277 ([M]<sup>+</sup>, 100), 236 (20), 197 (82), 168 (8), 155 (37), 116 (62), 89 (35), 55 (73).

***N*-Cyclohexyl-5-methoxyindole (4):** Following the general procedure using 5-methoxy-*NH*-indole (74 mg, 0.5 mmol) and cyclohexane (3 mL), **4** was isolated in 41% yield (46 mg) as a light yellow oil after purification using flash column chromatography with

pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.29 (d,  $J$  = 8.9 Hz, 1H), 7.21 (d,  $J$  = 3.2 Hz, 1H), 7.12 (d,  $J$  = 2.4 Hz, 1H), 6.91 – 6.85 (m, 1H), 6.44 (d,  $J$  = 3.1 Hz, 1H), 4.17 (tt,  $J$  = 11.7, 3.6 Hz, 1H), 3.87 (s, 3H), 2.23 – 2.10 (m, 2H), 2.01 – 1.87 (m, 2H), 1.85 – 1.75 (m, 1H), 1.75 – 1.65 (m, 2H), 1.54 – 1.43 (m, 2H), 1.38 – 1.23 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 153.9, 130.9, 128.7, 124.6, 111.5, 110.1, 102.6, 100.5, 55.9, 55.3, 33.6, 26.0, 25.7. MS(EI)  $m/z$ (%) = 229 ([M]<sup>+</sup>, 100), 214 (8), 186 (26), 147 (57), 132 (63), 104 (14), 55 (18).

***N*-Cyclohexylindole-5-carbonitrile (5):** Following the general procedure **A**, using *NH*-indole-5-carbonitrile (71 mg, 0.5 mmol) and cyclohexane 3 mL, **5** was isolated in 54 % yield (60 mg) as a light yellow oil, after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.96 (s, 1H), 7.43 – 7.39 (m, 2H), 7.34 (d,  $J$  = 3.3 Hz, 1H), 6.58 (d,  $J$  = 3.3 Hz, 1H), 4.23 (tt,  $J$  = 3.7, 11.9 Hz, 1H), 2.16 – 2.08 (m, 2H), 2.01 – 1.92 (m, 2H), 1.86 – 1.78 (m, 1H), 1.72 (ddd,  $J$  = 3.2, 12.5, 24.7 Hz, 2H), 1.57 – 1.44 (m, 2H), 1.36 – 1.23 (m, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 137.0, 128.2, 126.6, 126.5, 124.1, 120.9, 110.3, 102.3, 102.2, 55.6, 33.5, 25.8, 25.5. MS(EI)  $m/z$ (%) = 224 ([M]<sup>+</sup>, 41), 181 (18), 142 (100), 115 (9), 83 (10), 55 (26).

**Methyl *N*-cyclohexylindole-5-carboxylate (6):** Following the general procedure **A**, using methyl *NH*-indole-5-carboxylate (88 mg, 0.5 mmol) and cyclohexane 3 mL, **6** was isolated in 62 % yield (80 mg) as a light yellow oil, after purification using flash column chromatography with pentane : ethyl acetate = 30 : 1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 8.40 (d,  $J$  = 1.3 Hz, 1H), 7.91 (dd,  $J$  = 1.6, 8.7 Hz, 1H), 7.38 (d,  $J$  = 8.7 Hz, 1H), 7.28 (d,  $J$  = 3.3 Hz, 1H), 6.60 (d,  $J$  = 3.2 Hz, 1H), 4.24 (tt,  $J$  = 3.7, 11.9 Hz, 1H), 3.93 (s, 3H), 2.13 (d,  $J$  = 11.3 Hz, 2H), 1.95 (d,  $J$  = 13.5 Hz, 2H), 1.81 (d,  $J$  = 13.1 Hz, 1H), 1.71 (qd,  $J$  = 3.2, 12.5 Hz, 2H), 1.58 – 1.44 (m, 2H), 1.36 – 1.22 (m, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 168.3, 138.0, 128.0, 125.5, 124.0, 122.5, 121.3, 109.0, 102.8, 55.4, 51.8, 33.5, 25.9, 25.6. MS(EI)  $m/z$ (%) = 257 ([M]<sup>+</sup>, 100), 226 (14), 214 (19), 175 (45), 144 (97), 116 (31), 89 (11), 55 (31).

**Methyl 1-cyclohexyl-1*H*-indole-3-carboxylate (7):** Following the general procedure **A**, using methyl 1*H*-indole-3-carboxylate (88 mg, 0.5 mmol) and cyclohexane 3 mL, **7** was isolated in 81% yield (104 mg) as a light yellow oil, after purification using flash column chromatography with pentane : ethyl acetate = 30 : 1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 8.24 – 8.19 (m, 1H), 7.97 (s, 1H), 7.45 – 7.38 (m, 1H), 7.31 – 7.25 (m, 2H), 4.23 (tt,  $J$  = 3.6, 11.8 Hz, 1H), 3.93 (s, 3H), 2.16 (d,  $J$  = 11.5 Hz, 2H), 2.00 – 1.91 (m, 2H), 1.81 (d,  $J$  = 13.1 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.58 – 1.43 (m, 2H), 1.36 – 1.23 (m, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 165.6, 136.2, 131.0, 126.7, 122.4, 121.8, 121.8, 110.0, 106.9, 55.6, 50.9, 33.4, 25.8, 25.5. MS(EI)  $m/z$ (%) = 257 ([M]<sup>+</sup>, 88), 226 (14), 175 (43), 144 (100), 116 (12), 55 (23).

***N*-Cyclohexylpyrrole (8):** Following the general procedure using *NH*-pyrrole (34 mg, 0.5 mmol) and cyclohexane (3 mL), **8** was isolated in 65% yield (48 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 6.79 – 6.74 (m, 2H), 6.20 – 6.15 (m, 2H), 3.83 (tt,  $J$  = 11.6, 3.6 Hz, 1H), 2.20 – 2.06 (m, 2H), 1.97 – 1.87 (m, 2H), 1.81 – 1.70 (m, 1H), 1.70 – 1.57 (m, 2H), 1.52 – 1.37 (m, 2H), 1.33 – 1.19 (m, 1H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 118.4, 107.4, 58.7, 34.7, 25.8, 25.5. MS(EI)  $m/z$ (%) = 149 ([M]<sup>+</sup>, 67), 106 (19), 94 (23), 67 (100), 55 (23).

**2-Acetyl-*N*-Cyclohexylpyrrole (9):** Following the general procedure using 2-acetyl-*NH*-pyrrole (55 mg, 0.5 mmol) and cyclohexane (3

mL), **9** was isolated in 84% yield (80 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 7.11 – 7.07 (m, 1H), 6.96 (dd, *J* = 4.0, 1.6 Hz, 1H), 6.14 (dd, *J* = 4.0, 2.7 Hz, 1H), 5.17 – 5.06 (m, 1H), 2.43 (s, 3H), 2.17 – 1.95 (m, 2H), 1.92 – 1.81 (m, 2H), 1.77 – 1.68 (m, 1H), 1.54 – 1.42 (m, 4H), 1.27 – 1.12 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ (ppm) 188.4, 130.0, 125.5, 120.4, 108.1, 56.6, 34.6, 27.8, 25.9, 25.7. MS(EI) *m/z*(%) = 191 ([M]<sup>+</sup>, 38), 176 (62), 148 (10), 120 (7), 109 (46), 94 (100) 55 (25).

***N*-Cyclohexyl-2-propionylpyrrole (10).** Following the general procedure using 2-propionyl-*NH*-pyrrole (62 mg, 0.5 mmol) and cyclohexane (3 mL), **10** was isolated in 78% yield (80 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.10 – 7.07 (m, 1H), 6.98 (dd, *J* = 1.6, 4.0 Hz, 1H), 6.14 (dd, *J* = 2.7, 4.0 Hz, 1H), 5.22 – 5.05 (m, 1H), 2.82 (q, *J* = 7.4 Hz, 2H), 2.14 – 2.00 (m, 2H), 1.92 – 1.78 (m, 2H), 1.79 – 1.67 (m, 1H), 1.54 – 1.44 (m, 4H), 1.20 – 1.17 (m, 1H), 1.17 (t, *J* = 7.4 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 191.9, 129.7, 125.2, 119.3, 108.0, 56.7, 34.6, 32.7, 25.9, 25.7, 9.0. MS(EI) *m/z*(%) = 205 ([M]<sup>+</sup>, 24), 176 (42), 162 (3), 148 (8), 123 (14), 94(100), 81 (5), 55(16).

***N*-Cyclohexylpyrrole-2-carbonitrile (11).** Following the general procedure using *NH*-pyrrole-2-carbonitrile (46 mg, 0.5 mmol) and cyclohexane (3 mL), **11** was isolated in 97% yield (84 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 6.91 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.74 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.15 (dd, *J* = 3.9, 2.8 Hz, 1H), 4.08 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.14 – 2.03 (m, 2H), 1.96 – 1.84 (m, 2H), 1.80 – 1.69 (m, 1H), 1.69 – 1.57 (m, 2H), 1.52 – 1.35 (m, 2H), 1.30 – 1.18 (m, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 123.1, 119.6, 114.1, 109.2, 102.8, 58.4, 34.2, 25.6, 25.2. MS(EI) *m/z*(%) = 174 ([M]<sup>+</sup>, 59), 93 (84), 83 (38), 67 (52), 55 (100).

**Ethyl-*N*-cyclohexyl-3,5-dimethylpyrrole-2-carboxylate (12).** Following the general procedure using ethyl 3,5-dimethyl-*NH*-pyrrole-2-carboxylate (84 mg, 0.5 mmol) and cyclohexane (3 mL), **12** was isolated in 55% yield (68 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 5.73 (s, 1H), 5.08 – 4.77 (m, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 2.25 (s, 3H), 2.14 – 1.96 (m, 2H), 1.91 – 1.80 (m, 4H), 1.76 – 1.62 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.30 – 1.16 (m, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 162.3, 135.4, 129.6, 119.5, 112.5, 59.4, 57.1, 31.9, 26.6, 25.5, 15.2, 14.7, 14.5. MS(EI) *m/z*(%) = 249 ([M]<sup>+</sup>, 96), 204 (23), 176 (68), 167 (72), 138 (82), 121 (100), 95 (76), 55 (36).

***N*-Cyclohexyl-3,5-dimethylpyrazole (13).** Following the general procedure using 3,5-dimethyl-1*H*-pyrazole (48 mg, 0.5 mmol) and cyclohexane (3 mL), **13** was isolated in 44% yield (39 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 5.75 (s, 1H), 3.96 – 3.74 (m, 1H), 2.23 (s, 3H), 2.22 (s, 3H), 1.93 – 1.81 (m, 6H), 1.74 – 1.64 (m, 1H), 1.43 – 1.27 (m, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 146.8, 137.6, 104.5 (d, *J* = 11.9 Hz), 57.2 (d, *J* = 10.7 Hz), 32.9, 25.9, 25.2, 13.6 (d, *J* = 8.9 Hz), 11.0 (d, *J* = 9.1 Hz). MS(EI) *m/z*(%) = 178 ([M]<sup>+</sup>, 30), 163 (9), 135 (9), 123 (14), 109 (63), 97 (100), 81 (9).

***N*-Cyclohexylindazole (14).** Following the general procedure using *NH*-indazole (59 mg, 0.5 mmol) and cyclohexane (3 mL), **14** was isolated in 56% yield (56 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 8.02 (s, 1H), 7.73 (d, *J* = 8.1

Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 4.60 – 4.26 (m, 1H), 2.11 – 1.99 (m, 2H), 1.99 – 1.92 (m, 2H), 1.84 – 1.74 (m, 1H), 1.63 – 1.59 (m, 1H), 1.54 – 1.41 (m, 2H), 1.41 – 1.30 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ (ppm) 138.6, 132.5, 125.8, 124.0, 121.2, 120.4, 109.2, 58.2, 32.5, 25.9, 25.5. MS(EI) *m/z*(%) = 200 ([M]<sup>+</sup>, 37), 171 (13), 157 (37), 131(59), 118 (100), 91 (23), 77 (13).

***N*-Cyclohexylbenzo[d][1,2,3]triazole (15).** Following the general procedure using *NH*-benzo[d][1,2,3]triazole (60 mg, 0.5 mmol) and cyclohexane (3 mL), **15** was isolated in 35% yield (35 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 8.06 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.45 (t, *J* = 6.6 Hz, 1H), 7.34 (d, *J* = 6.9 Hz, 1H), 4.72 – 4.59 (m, 1H), 2.23 – 2.15 (m, 2H), 2.06 – 1.94 (m, 2H), 1.87 – 1.77 (m, 1H), 1.62 – 1.34 (m, 5H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ (ppm) 146.1, 132.2, 126.7, 123.7, 120.1, 109.8, 59.1, 32.6, 25.6, 25.3. MS(EI) *m/z*(%) = 201 ([M]<sup>+</sup>, 26), 147 (12), 133 (27), 120 (100), 91 (57), 64(29), 55(25). mp 102–104 °C.

***N*-Cyclohexyl-5,6-dimethylbenzo[d][1,2,3]triazole (16).** Following the general procedure using 5,6-dimethyl-*NH*-benzo[d][1,2,3]triazole (74 mg, 0.5 mmol) and cyclohexane (3 mL), **16** was isolated in 30% yield (35 mg) as a light yellow solid after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.79 (s, 1H), 7.33 (s, 1H), 4.68 – 4.52 (m, 1H), 2.44 (s, 3H), 2.41 (s, 3H), 2.21 – 2.14 (m, 4H), 2.07 – 1.96 (m, 2H), 1.86 – 1.77 (m, 1H), 1.61 – 1.34 (m, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 145.4, 136.9, 133.4, 131.2, 119.1, 109.3, 58.9, 32.5, 25.6, 25.3, 20.9, 20.4. MS (EI) *m/z*(%) = 229 ([M]<sup>+</sup>, 26), 158 (9), 119(100), 91 (13), 55 (36). mp 122–124 °C.

***N*-Cyclohexyl-5-methylbenzo[d][1,2,3]triazole (17a) and *N*-cyclohexyl-6-methylbenzo[d][1,2,3]triazole (17b).** Following the general procedure using 5-methyl-*NH*-benzo[d][1,2,3]triazole (74 mg, 0.5 mmol) and cyclohexane (3 mL), **17a** and **17b** was isolated in 41% yield (44 mg) in 45:55 ratio as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.92 (d, *J* = 8.5 Hz, 1H, **17b**), 7.81 (s, 1H, **17a**), 7.46 (d, *J* = 8.5 Hz, 1H, **17a**), 7.34 (s, 1H, **17b**), 7.31 – 7.26 (m, 1H, **17a**), 7.17 (dd, *J* = 1.4, 8.5 Hz, 1H, **17b**), 4.76 – 4.47 (m, 1H, **17a+17b**), 2.54 (s, 3H, **17b**), 2.51 (s, 3H, **17a**), 2.23 – 2.09 (m, 4H, **17a+17b**), 2.08 – 1.92 (m, 2H, **17a+17b**), 1.87 – 1.75 (m, 1H, **17a+17b**), 1.61 – 1.46 (m, 2H, **17a+17b**), 1.45 – 1.33 (m, 1H, **17a+17b**). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 146.7 (**17a**), 144.7 (**17b**), 137.2 (**17b**), 133.7 (**17a**), 132.7 (**17a**), 130.7 (**17b**), 129.1 (**17a**), 126.0 (**17b**), 119.4 (**17b**), 118.9 (**17a**), 109.3 (**17b**), 109.0 (**17a**), 59.0 (**17a**), 58.8 (**17b**), 32.5 (**17a**), 32.5 (**17b**), 25.6 (**17a** and **17b**), 25.3 (**17a** and **17b**), 22.0 (**17a** or **17b**), 21.4 (**17a** or **17b**). MS (EI) *m/z*(%) = 215 ([M]<sup>+</sup>, 74), 186 (15), 172(28), 158 (75), 144 (53), 105 (100), 91 (38), 55 (76).

***N*-Cyclohexylbenzenesulfonamide (18).** Following the general procedure using benzenesulfonamide (79 mg, 0.5 mmol) and cyclohexane (3 mL), **18** was isolated in 96 % yield (114 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 10 : 1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 7.93 – 7.86 (m, 2H), 7.57 – 7.51 (m, 1H), 7.51 – 7.43 (m, 2H), 5.14 (d, *J* = 7.5 Hz, 1H), 3.18 – 3.03 (m, 1H), 1.74 – 1.66 (m, 2H), 1.64 – 1.56 (m, 2H), 1.51 – 1.41 (m, 1H), 1.27 – 1.19 (m, 1H), 1.19 – 1.12 (m, 3H), 1.12 – 1.00 (m, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ (ppm) 141.5, 132.4, 129.0, 126.9, 52.7, 33.8, 25.1, 24.6. MS (EI) *m/z*(%) = 239 ([M]<sup>+</sup>, 32), 210 (7), 196 (87), 158 (9), 141(72), 98 (46), 77 (100), 51 (23).

**4-Chloro-N-Cyclohexylbenzenesulfonamide (19).** Following the general procedure using 4-chlorobenzenesulfonamide (95 mg, 0.5 mmol) and cyclohexane (3 mL), **19** was isolated in 86% yield (117 mg) as a light yellow solid after purification using flash column chromatography with pentane : ethyl acetate = 10 : 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.83 (d,  $J$  = 8.4 Hz, 1H), 7.45 (d,  $J$  = 8.4 Hz, 1H), 5.15 (d,  $J$  = 7.6 Hz, 1H), 3.12 (tt,  $J$  = 6.8, 13.5 Hz, 1H), 1.76 – 1.67 (m, 2H), 1.64 – 1.56 (m, 2H), 1.53 – 1.42 (m, 1H), 1.26 – 1.05 (m, 5H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 140.1, 138.8, 129.3, 128.4, 52.8, 33.8, 25.1, 24.6. MS (EI)  $m/z$ (%) = 273 ( $[\text{M}]^+$ , 34), 244 (7), 230 (100), 175 (70), 153 (8), 111(84), 75 (33), 55(21).

**N-Cyclopentylindole (20).** Following the general procedure using *NH*-indole (58 mg, 0.5 mmol) and cyclopentane (3 mL), **20** was isolated in 58 % yield (54 mg) as a light orange oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.69 (d,  $J$  = 7.8 Hz, 1H), 7.46 (d,  $J$  = 8.2 Hz, 1H), 7.30–7.23 (m, 2H), 7.20–7.12 (m, 1H), 6.56 (d,  $J$  = 3.2 Hz, 1H), 4.91–4.79 (m, 1H), 2.32 – 2.21 (m, 2H), 2.06–1.90 (m, 4H), 1.86–1.77 (m, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 136.2, 128.6, 124.5 (d,  $J$  = 6.9 Hz), 121.2 (d,  $J$  = 1.8 Hz), 120.9 (d,  $J$  = 4.2 Hz), 119.3, 109.9, 101.0, 57.0, 32.6, 24.1. MS (EI)  $m/z$ (%) = 185 ( $[\text{M}]^+$ , 40), 156 (24), 117 (100), 90 (16).

**N-Cyclooctylindole (21).** Following the general procedure using *NH*-indole (58 mg, 0.5 mmol) and cyclooctane (3 mL), **21** was isolated in 55% yield (62 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.69 (d,  $J$  = 7.9 Hz, 1H), 7.43 (d,  $J$  = 8.2 Hz, 1H), 7.28 (d,  $J$  = 3.3 Hz, 1H), 7.24 (d,  $J$  = 7.5 Hz, 1H), 7.15 (t,  $J$  = 7.5 Hz, 1H), 6.55 (d,  $J$  = 3.1 Hz, 1H), 4.63 – 4.53 (m, 1H), 2.21 – 1.99 (m, 2H), 1.94 – 1.83 (m, 2H), 1.82 – 1.65 (m, 10H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 135.3, 128.5, 124.7, 121.1, 121.0, 119.2, 109.6, 101.0, 56.0, 33.4, 26.9, 26.1, 24.9. MS (EI)  $m/z$ (%) = 227 ( $[\text{M}]^+$ , 67), 156 (54), 143 (37), 130 (23), 117 (100), 90 (14), 69 (15), 14 (55).

**N-(Tetrahydrofuran-2-yl)pyrrole-2-carbonitrile (22).** Following the general procedure using *NH*-pyrrole-2-carbonitrile (46 mg, 0.5 mmol) and tetrahydrofuran (3 mL), **22** was isolated in 69% yield (56 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 6.97 (dd,  $J$  = 1.7, 2.5 Hz, 1H), 6.83 (dd,  $J$  = 1.5, 3.8 Hz, 1H), 6.17 (t,  $J$  = 3.4 Hz, 1H), 6.00 (dd,  $J$  = 3.7, 6.5 Hz, 1H), 4.21 (dd,  $J$  = 7.4, 14.1 Hz, 1H), 3.99 (dd,  $J$  = 7.2, 15.3 Hz, 1H), 2.54 – 2.35 (m, 1H), 2.28 – 2.17 (m, 1H), 2.16 – 2.00 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 123.6, 121.4, 113.7, 109.6, 101.6, 88.3, 69.5, 33.6, 24.5. MS(EI)  $m/z$ (%) = 162 ( $[\text{M}]^+$ , 12), 131 (5), 92 (10), 71 (100).

**N-(Tetrahydrofuran-2-yl)indole (23).** Following the general procedure using *NH*-indole (58 mg, 0.5 mmol) and tetrahydrofuran (3 mL), **23** was isolated in 61% yield (57 mg) as a colorless yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.69 (d,  $J$  = 7.8 Hz, 1H), 7.53 (d,  $J$  = 8.3 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.20 (t,  $J$  = 7.5 Hz, 1H), 6.60 (d,  $J$  = 3.1 Hz, 1H), 6.60 (d,  $J$  = 3.1 Hz, 1H), 6.29 (dd,  $J$  = 6.1, 4.3 Hz, 1H), 4.18 (td,  $J$  = 7.9, 6.0 Hz, 1H), 4.05 (dd,  $J$  = 15.3, 7.3 Hz, 1H), 2.47 – 2.39 (m, 2H), 2.26 – 2.11 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 135.7, 129.2, 124.0, 121.8, 121.0, 120.0, 110.0, 102.3, 85.8, 68.4, 31.6, 24.8. MS(EI)  $m/z$ (%) = 187 ( $[\text{M}]^+$ , 21), 117 (100), 89 (10), 71 (22).

**N-(1,4-Dioxan-2-yl)pyrrole-2-carbonitrile (24).** Following the general procedure using *NH*-pyrrole-2-carbonitrile (46 mg, 0.5 mmol) and 1,4-dioxane (3 mL), **24** was isolated in 68% yield (60 mg) as a

light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.20 (dd,  $J$  = 2.7, 1.5 Hz, 1H), 6.85 (dd,  $J$  = 3.9, 1.4 Hz, 1H), 6.23 (t,  $J$  = 3.6 Hz, 1H), 5.55 (dd,  $J$  = 6.7, 3.0 Hz, 1H), 4.01 (dd,  $J$  = 11.8, 3.0 Hz, 1H), 3.93 – 3.71 (m, 5H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 125.1, 121.2, 113.2, 110.1, 103.6, 80.6, 68.7, 66.0, 64.9. MS(EI)  $m/z$ (%) = 178 ( $[\text{M}]^+$ , 20), 118 (7), 86 (100), 59 (12).

**N-(1,4-Dioxan-2-yl)indole (25).** Following the general procedure **A** using *NH*-indole (58 mg, 0.5 mmol) and 1,4-dioxane (3 mL), **25** was isolated in 43% yield (44 mg) as a white solid after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.68 (d,  $J$  = 7.8 Hz, 1H), 7.52 (d,  $J$  = 8.2 Hz, 1H), 7.47 (d,  $J$  = 3.4 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.23 – 7.16 (m, 1H), 6.61 (d,  $J$  = 3.2 Hz, 1H), 5.80 – 5.74 (m, 1H), 4.14 – 4.10 (m, 2H), 3.97 – 3.81 (m, 4H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 136.1, 128.8, 125.5, 122.2, 121.1, 120.4, 110.1, 103.0, 79.2, 68.7, 66.4, 64.6. MS (EI)  $m/z$ (%) = 203( $[\text{M}]^+$ , 18), 117(100), 90 (12). mp 76–78 °C.

**N-(2-Methoxypropan-2-yl)pyrrole-2-carbonitrile (26).** Following the general procedure using *NH*-pyrrole-2-carbonitrile (46 mg, 0.5 mmol) and 2,2-dimethoxypropane (3 mL), **26** was isolated in 57% yield (47 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 6.93 (dd,  $J$  = 2.8, 1.7 Hz, 1H), 6.91 (dd,  $J$  = 3.8, 1.6 Hz, 1H), 6.15 (dd,  $J$  = 3.7, 3.0 Hz, 1H), 3.12 (s, 3H), 1.81 (s, 6H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 124.3, 123.4, 114.7, 108.7, 101.4, 89.8, 50.1, 27.0. MS(EI)  $m/z$ (%) = 164 ( $[\text{M}]^+$ , 4), 133 (11), 92(11), 73 (100).

**N-(Tert-butoxymethyl)indole (27).** Following the general procedure using *NH*-indole (58 mg, 0.5 mmol) and 2-methoxy-2-methylpropane (3 mL), **27** was isolated in 46% yield (47 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.66 (d,  $J$  = 7.9 Hz, 1H), 7.53 (d,  $J$  = 8.2 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.22 (d,  $J$  = 3.2 Hz, 1H), 7.20 – 7.14 (m, 1H), 6.56 (d,  $J$  = 3.2 Hz, 1H), 5.56 (s, 2H), 1.29 (s, 9H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 136.1, 129.1, 127.5, 121.9, 120.9, 119.9, 110.1, 102.4, 74.2, 70.3, 28.0. MS(EI)  $m/z$ (%) = 203 ( $[\text{M}]^+$ , 20), 130 (35), 117(100), 57 (22).

**N-((Cyclopentyl)oxy)methylpyrrole-2-carbonitrile (28a) and 1-(1-methoxycyclopentyl)pyrrole-2-carbonitrile (28b).** Following the general procedure using *NH*-pyrrole-2-carbonitrile (46 mg, 0.5 mmol) and methoxycyclopentane (3 mL), **28a** was isolated in 24% yield (23 mg) as pure form as a light yellow oil, and **28b** was isolated in 24% yield (23 mg) as pure form as a light yellow oil after purified using flash column chromatography with pentane : ethyl acetate = 40 : 1. **28a**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 7.00 (dd,  $J$  = 2.6, 1.6 Hz, 1H), 6.83 (dd,  $J$  = 3.9, 1.5 Hz, 1H), 6.24 (dd,  $J$  = 3.8, 2.9 Hz, 1H), 5.35 (s, 2H), 4.01 – 3.91 (m, 1H), 1.68 (ddd,  $J$  = 6.9, 4.2, 1.7 Hz, 4H), 1.63 – 1.44 (m, 4H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 126.7, 120.9, 113.4, 110.4, 104.0, 80.2, 76.1, 32.3, 23.5. MS(EI)  $m/z$ (%) = 190 ( $[\text{M}]^+$ , 51), 159 (43), 145 (15), 132 (25), 106 (100), 97 (25), 71 (48), 67 (52).

**28 b**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 6.97 (dd,  $J$  = 2.8, 1.7 Hz, 1H), 6.90 (dd,  $J$  = 3.8, 1.6 Hz, 1H), 6.13 (dd,  $J$  = 3.8, 2.9 Hz, 1H), 2.96 (s, 3H), 2.59 – 2.47 (m, 2H), 2.20 – 2.06 (m, 2H), 1.92 – 1.73 (m, 4H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 125.3, 123.2, 114.7, 108.4, 102.5, 99.1, 50.0, 35.9, 22.2. MS(EI)  $m/z$ (%) = 190 ( $[\text{M}]^+$ , 4), 119 (3), 106 (4), 92 (100), 78 (77), 69(44), 51(12).



**N-Benzylpyrrole-2-carbonitrile (29).** Following the general procedure using *NH*-pyrrole-2-carbonitrile (46 mg, 0.5 mmol) and toluene (3 mL), **29** was isolated in 24% yield (22 mg) as a light yellow oil after purification using flash column chromatography with pentane : ethyl acetate = 40 : 1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (m) 7.41 – 7.31 (m, 3H), 7.22 – 7.16 (m, 2H), 6.87 – 6.81 (m, 2H), 6.21 (dd, *J* = 3.9, 2.8 Hz, 1H), 5.21 (s, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm) 136.0, 129.0, 128.4, 127.4, 126.6, 120.3, 113.8, 109.9, 104.2, 52.4. MS(EI) *m/z*(%) = 182 ([M]<sup>+</sup>, 18), 91 (100), 65 (14).

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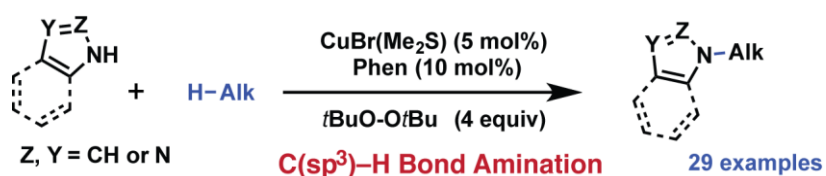
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Layout 2:

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A variety of *N*-alkylated heterocycles is readily synthesized by direct C–H bond amination of low cost (cyclo)alkanes catalyzed by inexpensive copper salts. A broad *NH*-free heterocycles scope has been used as amine sources and the reaction displayed a good functional group compatibility.

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J.-F. Soulé\*

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**Copper-Catalyzed Oxidative  
Dehydrogenative C(sp<sup>3</sup>)-H Bond  
Amination of (Cyclo)Alkanes using  
*NH*-Free Heterocycles as Amine  
Sources**