Article

Copper(II)-Photocatalyzed N-H Alkylation with Alkanes

Yiwen Zheng, Rok Narobe, Karsten Donabauer, Shahboz Yakubov, and Burkhard König

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.0c01924 • Publication Date (Web): 08 Jul 2020

Copper(II)-Photocatalyzed N–H Alkylation with Alkanes

Yi-Wen Zheng, Rok Narobe, Karsten Donabauer, Shahboz Yakubov and Burkhard König*

Institute of Organic Chemistry, Faculty of Chemistry and Pharmacy, University of Regensburg, 93040 Regensburg, Germany

KEYWORDS C–H activation, amination, alkylation, copper catalysis, photocatalysis

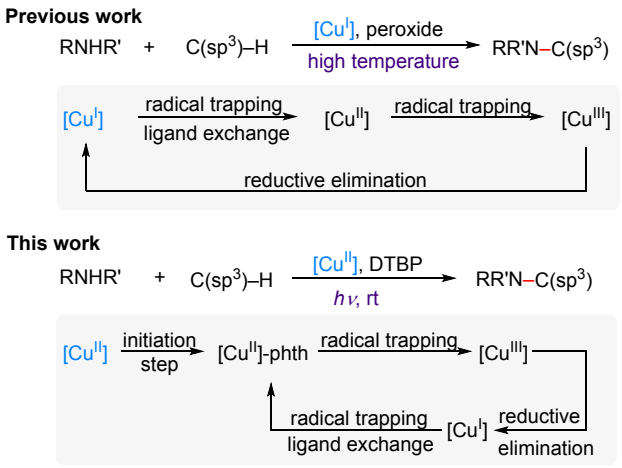
ABSTRACT: We report a practical method for the alkylation of N–H bonds with alkanes using a photoinduced copper(II)-peroxide catalytic system. Upon light irradiation, the peroxide serves as a hydrogen atom transfer (HAT) reagent to activate stable C(sp^3)–H bonds for the reaction with a broad range of nitrogen nucleophiles. The method enables the chemoselective alkylation of amides and was utilized for the late-stage functionalization of N–H bond containing pharmaceuticals with good to excellent yields. The mechanism of the reaction was preliminarily investigated by radical trapping experiments and spectroscopic methods.

The efficient synthesis of carbon-nitrogen bonds is important in organic synthesis as C–N bonds are a typical motif in natural products, pharmaceuticals and functional materials.[1] Accordingly, a variety of powerful approaches for C(sp^3)–N bond formations have been developed and advanced over the last decades. Examples include the coupling of nitrogen nucleophiles with alkyl halides,[2] reductive amination,[3] olefin hydroamination[4] and nitrene insertion.[5] Copper catalysis provides an alternative approach for the construction of C–N bonds. In recent years, Fu and coworkers have reported photoinduced copper-catalyzed alkylations of different nitrogen nucleophiles with alkyl halides[6] and a decarboxylation of *N*-hydroxyphthalimide (NHPI) esters[7] to afford *N*-alkylated products. The groups of Hu and MacMillan used dual copper and photoredox catalysis to achieve a decarboxylative alkylation of nitrogen nucleophiles with NHPI esters[8] or alkyl carboxylic acids.[9]

Compared to the use of alkyl halides, NHPI esters and alkyl carboxylic acids as alkylating reagents, copper-peroxide catalytic systems provide a straightforward approach for the N–H alkylation using unfunctionalized C(sp^3)–H bonds.[10] The proposed mechanism for these transformations usually starts with [Cu^I] and includes a sequence of *tert*-butoxy radical trapping, ligand exchange, alkyl radical trapping and reductive elimination to complete the copper-catalytic cycle (Scheme 1). However, the compatibility of a [Cu^{II}]-catalyst with these transformations is elusive.

The copper-peroxide system requires high temperatures in order to decompose the peroxide to produce alkoxy radicals, which abstract the hydrogen atom.[10g-j] The use of high temperatures imposes potential dangers[11] and substrate limitations, which may impede the synthetic use of this catalytic system, especially regarding late-stage functionalizations. Late-stage functionalization is a strategy to derive new bioactive molecules from natural products or drugs,[12] and to the best of our knowledge no copper-peroxide catalytic method was so far applied for the late-stage functionalization of N–H bond containing pharmaceuticals to demonstrate the utility of this approach. Furthermore, complex starting materials for late-stage functionalization may contain several N–H bonds with similar reactivities, requiring the use of a catalytic system that functions in a chemoselective manner.[13]

Scheme 1. Nitrogen nucleophile alkylation using copper-peroxide systems

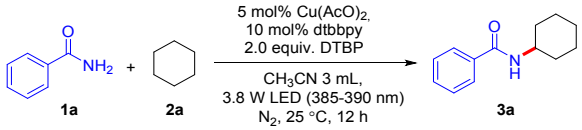


Herein, we report the use of peroxide as HAT reagent under light irradiation at room temperature, a [Cu^{II}] complex as metal catalyst and unactivated alkanes as

reaction partners to achieve alkylations of various nitrogen-containing compounds including amides, sulfonamides, phosphinic amides, aminophthalimide, indoles, azoles, purines, and imines (Scheme 1). We explored the chemoselectivity of the nitrogen nucleophiles and the late-stage functionalization of selected N–H bond containing pharmaceuticals. Further, mechanistic studies to arrive at a hypothesis for the copper(II)-peroxide reaction were conducted.

We began our investigation guided by the absorption spectra of $Cu(AcO)_2$ and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbbpy) in acetonitrile, which shows an absorption band at 360-450 nm (Figure S1). To our delight, irradiation of the acetonitrile solution containing benzamide, cyclohexane, $Cu(AcO)_2$, dtbbpy and di-*tert*-butyl peroxide (DTBP) at 25 ℃ using a 385 nm LED for 12 h gave 81% of *N*-cyclohexylbenzamide (**3a**) (Table 1, entry 1). No product was detected in the absence of either light, copper or DTBP, demonstrating the necessity of all components (entry 2-4). Without ligand, a low product yield was observed (entry 5, 12% yield). The reaction does not proceed without light even at 100 ℃ (entry 6). Intensity and wavelength of the irradiation were important for the reaction (entry 7-10), as a lower intensity LED led to a reduced reaction yield of 38% (entry 7) for the same reaction time, and the use of an LED with a slightly longer emission wavelength decreased the yield slightly to 63% (entry 8). The reaction was also feasible by irradiation with visible light (400 nm and 455 nm), albeit in low yields (entry 9-10). A comparable reaction outcome was observed using CuI instead of $Cu(AcO)_2$ (80%, Table S1, entry 2). Due to the intense absorption of the CuI/dtbbpy solution in the visible light region (Figure S2), we expected a higher product yield under irradiation of 455 nm LEDs using this copper complex, yet only 24% of the product was formed (Table S1, entry 3). A detailed screening of reaction conditions is given in the supporting information (Table S1) and the reaction conditions shown in entry 1 of Table 1 provided the best result.

Table 1. Reaction optimization for cyclohexane amidation

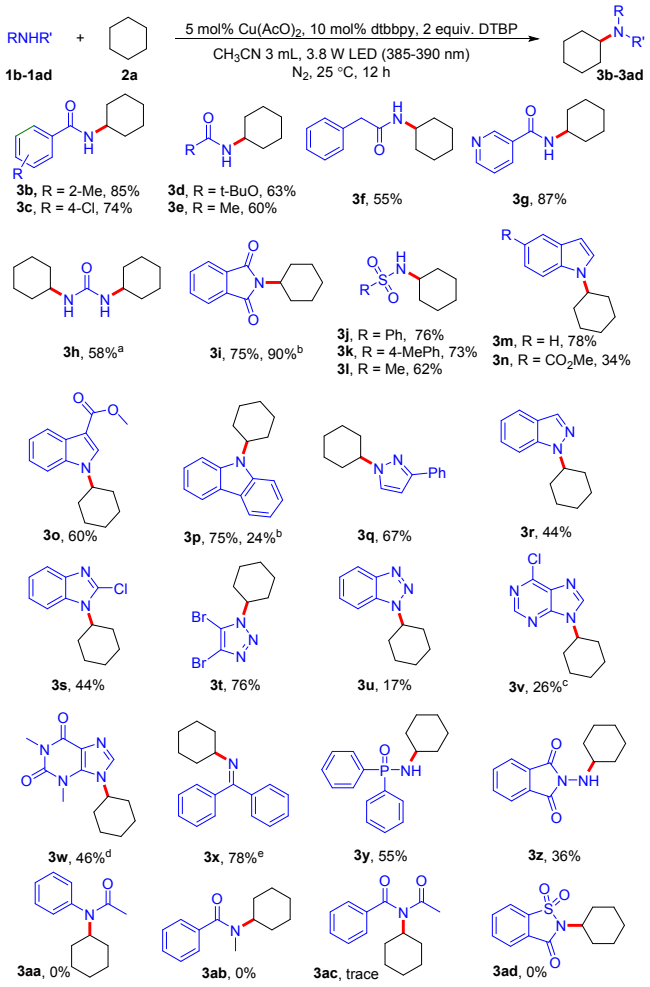


Entry	Deviations	Yield (%)[a]
1	none	81[b]
2	no light	0
3	no $Cu(AcO)_2$	0
4	no DTBP	0
5	no dtbbpy	12
6	no light at 100 ℃	0
7	1.0 W instead of 3.8 W	38
8	390-395 nm instead of 385-390 nm	63
9	0.35 W 400 nm instead of 385-390 nm	36[c]
10	5.0 W 455 nm instead of 385-390 nm	31[c]

Conditions: **1a** (0.2 mmol), **2a** (2 mmol). [a] NMR yield using 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yield. [c] 24 h.

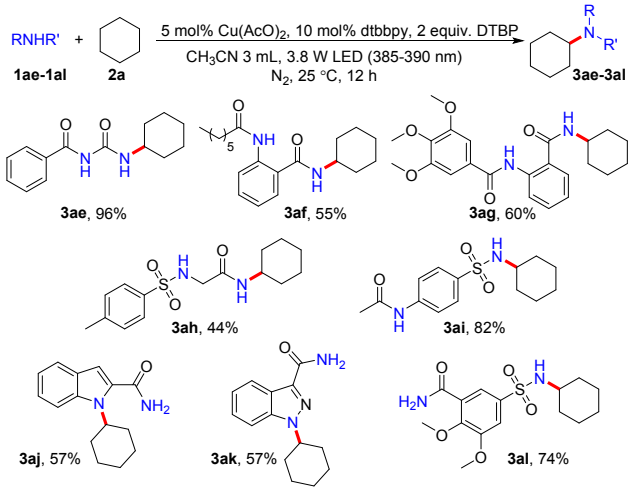
With the optimized catalytic system, different nitrogen atom containing substrates were explored (Scheme 2). Benzamides and alkyl amides provided the corresponding cyclohexylamides in good yields (**3b-3f**, 55-85% yield), and a heteroaromatic amide gave the coupling product in a high yield as well (**3g**, 87%). Both nitrogen atoms of urea were alkylated in a moderate yield (**3h**, 58% yield), and phthalimide was converted to its cyclohexyl congener in 75% yield (**3i**). Sulfonamides bearing aromatic and aliphatic substituents could both be employed in the C(sp^3)–H amidation (**3j-3l**, 62-80% yield). In addition to amides, nitrogen-containing heterocyclic compounds, such as indoles (**3m-3o**), azoles (**3p-3u**) and purines (**3v-3w**) gave the alkylation products in 17-78% yield. Imines, phosphinic amides and aminophthalimide were tolerated as well (**3x-3z**, 36-78% yield). However, no reaction was observed when aniline or ammonium carbamate was used. Further, secondary amides and sulfonamide (**1aa-1ad**) were also unsuitable substrates for this copper catalytic system, with the only exception being the planar phthalimide (**1i**), indicating the selectivity of the catalytic N–H bond alkylation for primary over secondary amides, likely due to steric effects.

Scheme 2. Scope of nitrogen nucleophiles for copper(II)-photocatalyzed N–H alkylation with cyclohexane



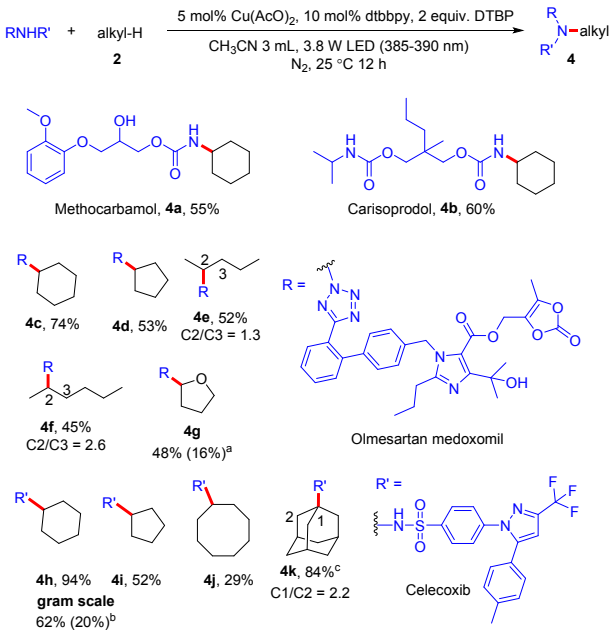
Conditions: **1** (0.2 mmol), **2a** (2 mmol). [a]4 equiv. DTBP was used. [b]CuI instead of $Cu(AcO)_2$ was used. [c]CH_3CN / H_2O = 10 / 1 (V / V). [d]CH_3CN / H_2O = 15 / 1 (V / V). [e]NMR yield.

Scheme 3. Chemoselective alkylation of amide and sulfonamide containing two N–H bonds



Conditions: **1** (0.2 mmol), **2a** (2 mmol).

Scheme 4. Late-stage functionalization of N–H bond containing pharmaceuticals via photoinduced copper(II)-peroxide catalysis



Conditions: Amide (0.2 mmol), **2** (2 mmol). [a]THF was used as solvent. [b]Reaction temperature is ca. 45 °C measured from the reaction solution; the yield in parentheses is *N*-methylated product. [c]Acetone was used as solvent.

Amides and sulfonamides possessing primary and secondary amide N–H bonds were exclusively alkylated on the primary amide or sulfonamide (**3ae-3ai**; 44-96%, Scheme 3). Besides the preference for primary positions, chemoselectivity was also observed in the presence of two different N–H functional groups. We employed compound **1aj** having one indole N–H bond and one primary amide. To our delight, the alkylation proceeded only at the indole N–H in 57% yield (**3aj**). When the amide contains an indazole N–H bond (**1ak**), the alkylation occurred preferentially on the N–H bond of the indazole (**3ak**, 57% yield). In competition with a primary amide, a primary sulfonamide moiety gave the alkylation product in 74% yield (**3al**). The p*K*a values of indole, indazole and sulfonamide N–H are lower than that of benzamide (Scheme S1). Combined with the results of **3aj-3al**, the alkylation of the more acid N–H seems to be preferred using this approach.

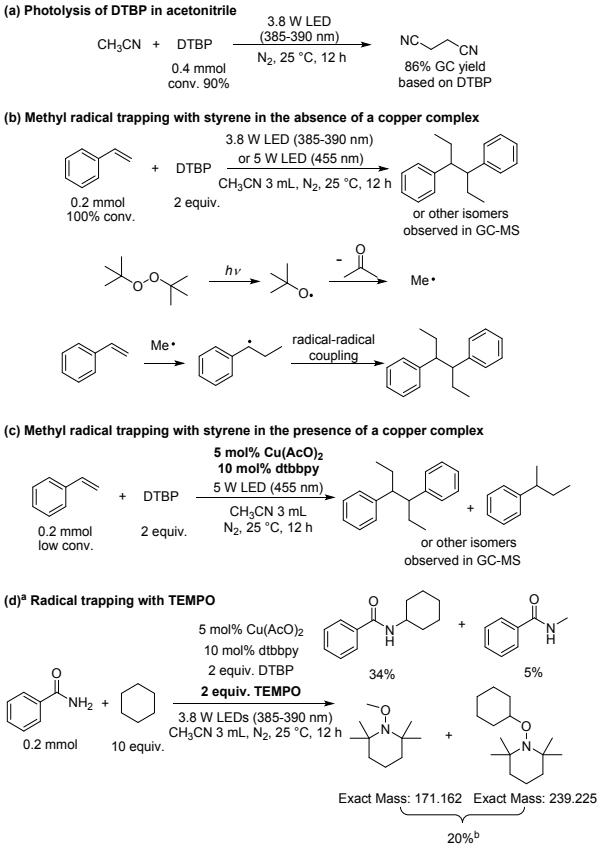
To illustrate the applicability of this N–H alkylation strategy further, late-stage alkylations of N–H containing pharmaceuticals were examined (Scheme 4). Methocarbamol and Carisoprodol were alkylated at the primary nitrogen atoms in good yields (**4a** and **4b**, 55% and 60% yield, respectively). Next, we examined the alkylation of Olmesartan medoxomil and Celecoxib using different alkanes. Olmesartan medoxomil reacted with different alkanes and both cycloalkanes and open chain alkanes gave good yields of the coupling products (**4c-4f**, 45-74% yield). Only the secondary C–H bond amination

products of *n*-pentane and *n*-hexane were isolated and separated. Ethers such as THF are also compatible substrates (**4g**, 48% yield). Celecoxib was functionalized with cyclohexane, cyclopentane and cyclooctane in moderate to excellent yields (**4h-4j**, 29-94% yield). When adamantane was employed as alkylating reagent, acetone instead of acetonitrile was used as solvent to increase the solubility, which gave the alkylated product in a good yield (**4k**, 84% yield). A gram scale late-stage functionalization of Celecoxib was carried out and gave 62% yield of **4h** with 20% of the *N*-methylated byproduct.[14] In most of the above N–H alkylations, the *N*-methylated byproduct was detected as well. A likely origin of the methyl radical is through β-methyl scission of the *tert*-butoxy radical.[15]

Concerning the reaction mechanism, a previous report proposed that Cu(II) is oxidized to Cu(III) by DTBP at 115 °C.[10h] Further, the bond dissociation enthalpy (BDE) of the O–O bond in DTBP is 37.5±2.4 kcal/mol,[16] and the energy of 385 nm light (74.3 kcal/mol) and 455 nm light (62.9 kcal/mol) are sufficient to photolyze DTBP to form *tert*-butoxy radicals. Therefore, there are two possible ways the transformation is initiated under our catalytic conditions: reduction of DTBP by the excited state of the copper complex or photolysis of DTBP to generate *tert*-butoxy radicals. Emission quenching experiments with the copper complexes ([Cu^{I}] and [Cu^{II}]) and DTBP showed no quenching of the emission of the copper complexes (Figure S4 and S5). This indicates that DTBP is not reduced by electron transfer from the excited state of the copper complexes. Thus, the *tert*-butoxy radical may be produced by the photolysis of DTBP under irradiation. A solution of DTBP in acetonitrile was irradiated by a 385-390 nm LED under N_2 for 12 h (Scheme 5a) resulting in 90% conversion of DTBP and 86% of acetonitrile homo-coupling product (Figure S6). According to the BDEs of acetonitrile (97 kcal/mol) and *tert*-butanol (106 kcal/mol),[17] the *tert*-butoxy radical can abstract a hydrogen atom from acetonitrile giving an acetonitrile radical, which produces succinonitrile *via* radical-radical coupling. In addition, an acetonitrile solution of DTBP and styrene was irradiated by a 385-390 nm LED or 455 nm LED under N_2 for 12 h (Scheme 5b). After the reaction, 3,4-diphenylhexane was detected by GC-MS in both cases (Figure S8 and S9), indicating the formation of methyl radicals from DTBP. When DTBP and styrene were irradiated by a 455 nm LED in the presence of the copper complex, traces of 3,4-diphenylhexane were produced as well with a low conversion of styrene (Scheme 5c and Figure S10).[18] The photolysis could be further supported by assessing the conversion of DTBP under different reaction conditions (Table S2). A lower light intensity (Table S2, entry 6) and higher wavelength (455 nm, Table S2, entry 9) decreased the DTBP conversion. Further, DTBP is converted also in the absence of $Cu(AcO)_2$ without the formation of product (Table S2, entry 3). The DTBP conversion is even higher in this case, likely due to the absence of the competing light absorption of the copper complex. Overall, the experimental results sugest that *tert*-butoxy radicals are produced by the photolysis of DTBP.

As next step, the *tert*-butoxy radical is proposed to abstract a hydrogen atom from an alkane, yielding an alkyl radical. Therefore, a radical trapping experiment with TEMPO was performed (Scheme 5d).

Scheme 5. Photolysis of DTBP and radical trapping experiment with TEMPO



(a) Photolysis of DTBP in acetonitrile. (b) Methyl radical trapping with styrene in the absence of a copper complex. (c) Methyl radical trapping with styrene in the presence of a copper complex. (d) Radical trapping with TEMPO. [a]Products observed by GC-MS and ^{1}H-NMR; NMR yields were derived using 1,3,5-trimethoxybenzene as internal standard. [b]Yield is based on the initial amount of TEMPO.

When 2 equiv. of TEMPO were added to the model reaction, the yield of the alkylated benzamide decreased from 81% to 34% and both the methyl radical and the cyclohexyl radical were captured by TEMPO and detected by GC-MS and ^{1}H-NMR (Figure S11 and S12). This result indicates that the *tert*-butoxy radical acts as a HAT reagent. Further it supports that it is the source of methyl radicals giving rise to the observed *N*-methylated reaction by-products.

As [Cu^{II}] is, in contrast to [Cu^{I}] and [Cu^{III}], paramagnetic, electron paramagnetic resonance (EPR) spectroscopy was used to investigate the mechanism of this [Cu^{II}]-peroxide system. The EPR spectrum of $Cu(AcO)_2$ and dtbbpy in acetonitrile shows the characteristic four-line signal (Figure 1a).[19] The spectrum does not change upon addition of DTBP (Figure S14), but the resonance signals vanished after 10 h of irradiation (Figure 1b), indicating the formation of putative [Cu^{III}] species by radical addition. As a second step, after the irradiation of this solution, phthalimide was added in the dark and a new [Cu^{II}] signal

appeared with a hyperfine splitting (Figure 1c), which was similar to the [Cu^{II}]-NHAd hyperfine splitting in a previous report.[20] Therefore, this hyperfine splitting is likely to originate from a [Cu^{II}]-phth complex (compound **A** in Figure 2). To support this, the EPR spectrum of $Cu(AcO)_2$, dtbbpy and phthalimide in the presence of KO^{t}Bu in acetonitrile was measured after 6 h of stirring. The identical hyperfine splitting as depicted in Figure 1c was obtained (Figure 1d and Figure S21) suggesting that [Cu^{II}]-phth was formed. Upon irradiation of a solution of $Cu(AcO)_2$, dtbbpy, DTBP and phthalimide, a similar resonance signal of [Cu^{II}]-phth was detected as well (Figure S16). In order to investigate if a [Cu^{II}]-phth complex is the catalytically active species, *in situ* generated [Cu^{II}]-phth was subjected to the model reaction conditions instead of the combination of $Cu(AcO)_2$ as catalyst and phthalimide as substrate (Scheme 6). Indeed, **3i** was obtained in 22% yield under these conditions (Figure S23), and no product was observed when the reaction was carried out in dark, indicating that [Cu^{II}]-phth is likely to be a key intermediate for this transformation.

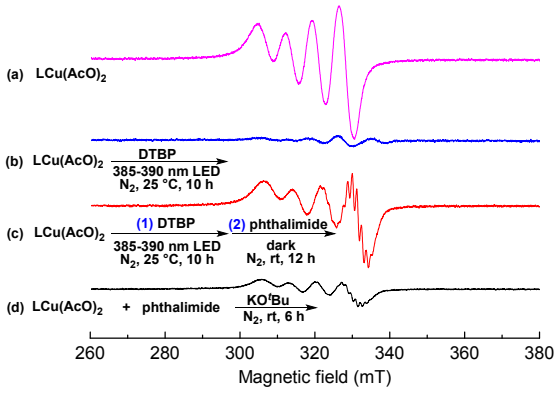
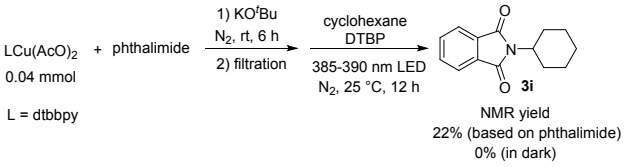


Figure 1. X-band EPR spectra (9.45 G, 293 K) of Cu complexes under different conditions [0.04 mmol $Cu(AcO)_2$, 0.04 mmol L, 0.4 mmol DTBP, 0.08 mmol phthalimide, 0.08 mmol KO^{t}Bu, 3 mL CH_3CN]. L = dtbbpy. EPR spectra were measured at 20 °C under N_2. Previously irradiated samples were measured at least one hour after irradiation (3.8 W 385-390 nm LED) to avoid interference caused by transient radicals.

Scheme 6. Reaction from *in situ* generated [Cu^{II}]-phth



Based on the above experimental results and mechanistic studies, we propose a mechanism for the alkylation of nitrogen nucleophiles *via* a photoinduced copper(II)-peroxide catalytic system as shown in Figure 2 for the example of phthalimide. During an initiation step a [Cu^{II}]-phth complex (**A**) is formed from a copper source and the amide under the influence of peroxide and light. The catalytic cycle begins with photolysis of DTBP. The generated *tert*-butoxy radical abstracts a hydrogen atom from cyclohexane to generate a cyclohexyl radical, which is trapped by **A** producing a [Cu^{III}] complex (**B**). The coupling product **3i** is then generated via reductive elimination from **B**, simultaneously forming a [Cu^{I}] complex (**C**). According to previous reports[10], *tert*-butoxy radicals are able to add to [Cu^{I}] complexes to form a [Cu^{II}]O^{t}Bu species (**D**). The [Cu^{II}] species **A** is then regenerated by ligand exchange of the [Cu^{II}]O^{t}Bu complex **D** with phthalimide, accompanied by the formation of ^{t}BuOH. This step is supported by the formation of **A** by the irradiation of a solution containing CuI, dtbbpy, DTBP and phthalimide (Figure S16).

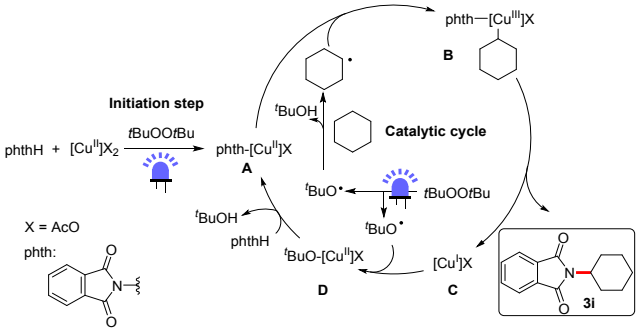


Figure 2. Proposed reaction mechanism.

In conclusion, a mild photoinduced copper(II)-peroxide strategy was developed for the alkylation of amides and other nitrogen nucleophiles with unactivated alkanes. The reaction is applicable to the late-stage *N*-alkylation of N–H bond containing drugs. In amides containing more than one N–H bond a chemoselective reaction of primary amides, sulfonamides and N–H bonds in heterocycles was observed. The preliminary mechanistic studies for this transformation reveal a photoinduced initiation step for the copper(II)-peroxide system in comparison to the copper(I)-peroxide system, and the key component for this reaction might be a [Cu^{II}]-phth complex.

ASSOCIATED CONTENT

Supporting Information.
This material is available free of charge via the Internet at http://pubs.acs.org.
Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: burkhard.koenig@ur.de

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the German Science Foundation (DFG, KO 1537/18-1). Y.-W-Z. thanks for the support of Sino-German (CSC-DAAD) Postdoc Scholarship Program. R.N. thanks DAAD for One-Year Research Grant scholarship.

ABBREVIATIONS

HAT, hydrogen atom transfer; NHPI, *N*-hydroxyphthalimide; dtbbpy, 4,4'-di-*tert*-butyl-2,2'-bipyridine; DTBP, di-*tert*-butyl peroxide; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy free radical; EPR, electron paramagnetic resonance.

REFERENCES

(1) (a) Mann, A., Amino-Based Building Blocks for the Construction of Biomolecules. In *Amino Group Chemistry*, Ricci, A., Ed. WILEY-VCH: Weinheim, 2008; pp 207-256; (b) Ćirić-Marjanović, G., Recent Advances in Polyaniline Research: Polymerization Mechanisms, Structural Aspects, Properties and Applications. *Synth. Met.* **2013,** *177*, 1-47; (c) Vitaku, E.; Smith, D. T.; Njardarson, J. T., Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014,** *57*, 10257-10274.

(2) (a) Lawrence, S. A., Substitution on the Amine Nitrogen (Replacement of Halogen Functionalities). In *Science of Synthesis*, Enders, D.; Schaumann, E., Eds. Thieme: Stuttgart, 2009; Vol. 40, pp 523-547; (b) Peacock, D. M.; Roos, C. B.; Hartwig, J. F., Palladium-Catalyzed Cross Coupling of Secondary and Tertiary Alkyl Bromides with a Nitrogen Nucleophile. *ACS Cent. Sci.* **2016,** *2*, 647-652.

(3) (a) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J., Borrowing Hydrogen in the Activation of Alcohols. *Adv. Synth. Catal.* **2007,** *349*, 1555-1575; (b) Yang, Q.; Wang, Q.; Yu, Z., Substitution of Alcohols by N-Nucleophiles via Transition Metal-Catalyzed Dehydrogenation. *Chem. Soc. Rev.* **2015,** *44*, 2305-2329; (c) Hoshimoto, Y.; Ogoshi, S., Triarylborane-Catalyzed Reductive *N*-Alkylation of Amines: A Perspective. *ACS Catal.* **2019,** *9*, 5439-5444; (d) Irrgang, T.; Kempe, R., 3d-Metal Catalyzed N- and C-Alkylation Reactions via Borrowing Hydrogen or Hydrogen Autotransfer. *Chem. Rev.* **2019,** *119*, 2524-2549.

(4) (a) Reznichenko, A. L.; Hultzsch, K. C., Early Transition Metal (Group 3–5, Lanthanides and Actinides) and Main Group Metal (Group 1, 2, and 13) Catalyzed Hydroamination. *Top. Organomet. Chem.* **2013,** *43*, 51-114; (b) Nishina, N.; Yamamoto, Y., Late Transition Metal-Catalyzed Hydroamination. *Top. Organomet. Chem.* **2013,** *43*, 115-143.

(5) (a) Díaz-Requejo, M. M.; Pérez, P. J., Coinage Metal Catalyzed C–H Bond Functionalization of Hydrocarbons. *Chem. Rev.* **2008,** *108*, 3379-3394; (b) Collet, F.; Lescot, C.; Dauban, P., Catalytic C–H Amination: the Stereoselectivity Issue. *Chem. Soc. Rev.* **2011,** *40*, 1926-1936; (c) Singh, R.; Mukherjee, A., Metalloporphyrin Catalyzed C–H Amination. *ACS Catal.* **2019,** *9*, 3604-3617; (d) Bakhoda, A.; Jiang, Q.; Badiei, Y. M.; Bertke, J. A.; Cundari, T. R.; Warren, T. H., Copper-Catalyzed C(sp^3)–H Amidation: Sterically Driven Primary and Secondary C–H Site-Selectivity. *Angew. Chem. Int. Ed.* **2019,** *58*, 3421-3425.

(6) (a) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C., Transition-Metal-Catalyzed Alkylations of Amines with Alkyl Halides: Photoinduced, Copper-Catalyzed Couplings of Carbazoles. *Angew. Chem. Int. Ed.* **2013,** *52*, 5129-5133; (b) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C., Photoinduced, Copper-Catalyzed Alkylation of Amides with Unactivated Secondary Alkyl Halides at Room Temperature. *J. Am. Chem. Soc.* **2014,** *136*, 2162-2167; (c) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C., Asymmetric Copper-Catalyzed C-N Cross-Couplings Induced by Visible Light. *Science* **2016,** *351*, 681-684; (d) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C., Photoinduced, Copper-Catalyzed Alkylation of Amines: A Mechanistic Study of the Cross-Coupling of Carbazole with Alkyl Bromides. *J. Am. Chem. Soc.* **2017,** *139*, 12716-12723; (e) Ahn, J. M.; Peters, J. C.; Fu, G. C., Design of a Photoredox Catalyst that Enables the Direct Synthesis of Carbamate-Protected Primary Amines via Photoinduced, Copper-Catalyzed *N*-Alkylation Reactions of Unactivated Secondary Halides. *J. Am. Chem. Soc.* **2017,** *139*, 18101-18106; (f) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C., Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light. *J. Am. Chem. Soc.* **2017,** *139*, 17707-17710.

(7) Zhao, W.; Wurz, R. P.; Peters, J. C.; Fu, G. C., Photoinduced, Copper-Catalyzed Decarboxylative C–N Coupling to Generate Protected Amines: An Alternative to the Curtius Rearrangement. *J. Am. Chem. Soc.* **2017,** *139*, 12153-12156.

(8) Mao, R.; Frey, A.; Balon, J.; Hu, X., Decarboxylative C(sp^3)–N Cross-Coupling via Synergetic Photoredox and Copper Catalysis. *Nat. Catal.* **2018,** *1*, 120-126.

(9) (a) Liang, Y.; Zhang, X.; MacMillan, D. W. C., Decarboxylative sp^3 C–N Coupling via Dual Copper and Photoredox Catalysis. *Nature* **2018,** *559*, 83-88; (b) Nguyen, V. T.; Nguyen, V. D.; Haug, G. C.; Vuong, N. T. H.; Dang, H. T.; Arman, H. D.; Larionov, O., Visible Light-Enabled Direct Decarboxylative N-Alkylation. *Angew. Chem. Int. Ed.* **2020**, *59*, 7921-7927.

(10) (a) Kharasch, M.; Fono, A., Communications - Radical Substitution Reactions. *J. Org. Chem.* **1958**, *23*, 325-326; (b) Pelletier, G.; Powell, D. A., Copper-Catalyzed Amidation of Allylic and Benzylic C–H Bonds. *Org. Lett.* **2006,** *8*, 6031-6034; (c) Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y., Copper-Catalyzed Amidation of sp^3 C–H Bonds Adjacent to a Nitrogen Atom. *Org. Lett.* **2007,** *9*, 3813-3816; (d) Wiese, S.; Badiei, Y. M.; Gephart, R. T.; Mossin, S.; Varonka, M. S.; Melzer, M. M.; Meyer, K.; Cundari, T. R.; Warren, T. H., Catalytic C–H Amination with Unactivated Amines through Copper(II) Amides. *Angew. Chem. Int. Ed.* **2010,** *49*, 8850-8855. (e) Gephart, R. T.; Warren, T. H., Copper-Catalyzed sp^3 C–H Amination. *Organometallics* **2012,** *31*, 7728-7752; (f) Ramirez, T. A.; Zhao, B.; Shi, Y., Recent Advances in Transition Metal-Catalyzed sp^3 C–H Amination Adjacent to Double Bonds and Carbonyl Groups. *Chem. Soc. Rev.* **2012,** *41*, 931-942; (g) Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F., Copper-Catalyzed Intermolecular Amidation and Imidation of Unactivated Alkanes. *J. Am. Chem. Soc.* **2014,** *136*, 2555-2563; (h) Teng, F.; Sun, S.; Jiang, Y.; Yu, J.-T.; Cheng, J., Copper-Catalyzed Oxidative C(sp^3)–H/N–H Coupling of Sulfoximines and Amides with Simple Alkanes via a Radical Process. *Chem. Commun.* **2015,** *51*, 5902-5905; (i) Xiao, J.; Su, Q.; Dong, W.; Peng, Z.; Zhang, Y.; An, D., Copper-Catalyzed Oxidative Alkylation (Methylation) of Phosphonamides and Phosphinamides Using Dicumyl Peroxide. *J. Org. Chem.* **2017,** *82*, 9497-9504; (j) Wang, C.-S.; Wu, X.-F.; Dixneuf, P. H.; Soulé, J.-F., Copper-Catalyzed Oxidative Dehydrogenative C(sp^3)–H Bond Amination of (Cyclo)Alkanes using NH-Heterocycles as Amine Sources. *ChemSusChem* **2017,** *10*, 3075-3082.

(11) Duh, Y.-S.; Hui wu, X.; Kao, C.-S., Hazard Ratings for Organic Peroxides. *Process Saf. Prog.* **2008,** *27*, 89-99.

(12) (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K., C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2012,** *51*, 8960-9009; (b) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W., The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-Like Molecules. *Chem. Soc. Rev.* **2016,** *45*, 546-576.

(13) Take aim. *Nat. Chem.* **2012,** *4*, 955.

(14) The decreased yield of the scale up reaction is presumably due to the lower cooling capacity of the lager scale up reactor (see Scheme S2).

(15) (a) Kochi, J. K., Chemistry of Alkoxy Radicals: Cleavage Reactions. *J. Am. Chem. Soc.* **1962,** *84*, 1193-1197; (b) Walling, C.; Padwa, A., Positive Halogen Compounds. VI. Effects of Structure and Medium on the β-Scission of Alkoxy Radicals. *J. Am. Chem. Soc.* **1963,** *85*, 1593-1597; (c) Bacha, J. D.; Kochi, J. K., Polar and Solvent Effects in the Cleavage of *t*-Alkoxy Radicals. *J. Org. Chem.* **1965,** *30*, 3272-3278.

(16) Borges dos Santos, R. M.; Muralha, V. S. F.; Correia, C. F.; Simões, J. A. M., Solvation Enthalpies of Free Radicals: O–O Bond Strength in Di-*tert*-butylperoxide. *J. Am. Chem. Soc.* **2001,** *123*, 12670-12674.

(17) Luo, Y.-R., *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, USA (FL), **2007**.

(18) The small amounts of 3,4-diphenylhexane with low conversion of styrene may result from the lower DTBP photolysis efficiency using 455 nm LED (Table S2, entry 9). Small amounts of

sec-butylbenzene were also detected. This may be due to the stabilization of the methyl radical by a copper complex.

(19) Vantourout, J. C.; Miras, H. N.; Isidro-Llobet, A.; Sproules, S.; Watson, A. J. B., Spectroscopic Studies of the Chan–Lam Amination: A Mechanism-Inspired Solution to Boronic Ester Reactivity. *J. Am. Chem. Soc.* **2017,** *139*, 4769-4779.

(20) Wiese, S.; Badiei, Y. M.; Gephart, R. T.; Mossin, S.; Varonka, M. S.; Melzer, M. M.; Meyer, K.; Cundari, T. R.; Warren, T. H., Catalytic C-H Amination with Unactivated Amines through Copper(II) Amides. *Angew. Chem. Int. Ed.* **2010,** *49*, 8850-8855.

Table of Contents (TOC)