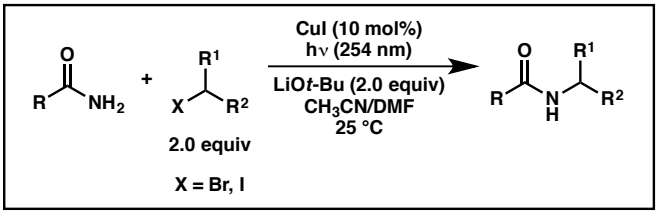
CHAPTER 1

Photoinduced, Copper-Catalyzed Alkylation of Amides with Unactivated Secondary Alkyl Halides at Room Temperature[†]



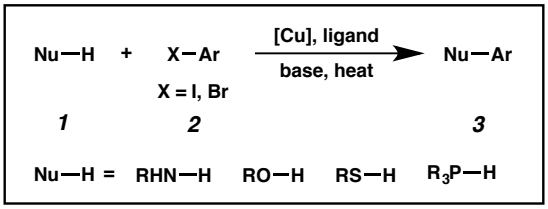
[†] This work was performed in collaboration with Dr. Hien-Quang Do and Dr. Alex C. Bissember, and was partially adapted from the publication: Do, H.-Q.; Bachman, S.; Bissember, A. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162–2167. Copyright 2014 American Chemical Society.

1.1 Introduction

The copper-mediated formation of C−C and C−heteroatom bonds, or the Ullman-type reaction, is a well-established process in organic chemistry.[1] The "classic" Ullman reaction, developed in 1901, used a stoichiometric amount of copper to couple two aryl halides, generating symmetrical biaryl products.[2] By 1929, the reaction scope was expanded to the cross coupling of aryl halides with anilines,[3] phenols,[4] amides,[5] and β-dicarbonyls.[6] Limitations of these pioneering studies include the requirement for high temperatures (170–210 °C)[2–6] and often stoichiometric amounts of copper.[2,3,6]

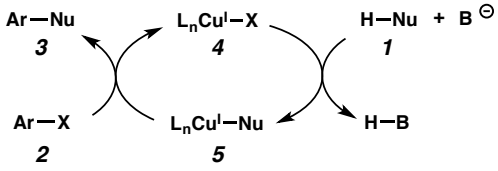
Milder conditions (80–100 °C) and catalytic amounts of copper are sufficient for a variety of Ullman-type reactions in which an organic additive is used (Scheme 1.1).[1] Proposed rationalizations for the rate-accelerating effect of an added ligand include improved solubility of copper–nucleophile intermediates,[7] prevention of copper aggregation in solution or disproportionation of the presumed copper(I) catalyst,[7b] increasing the copper species' propensity to undergo oxidative addition and/or reductive elimination,[8] and preventing multiple ligations of nucleophile to generate an inactive copper–nucleophile species.[7b,9]

Scheme 1.1 Scope of the Ullman-type reaction



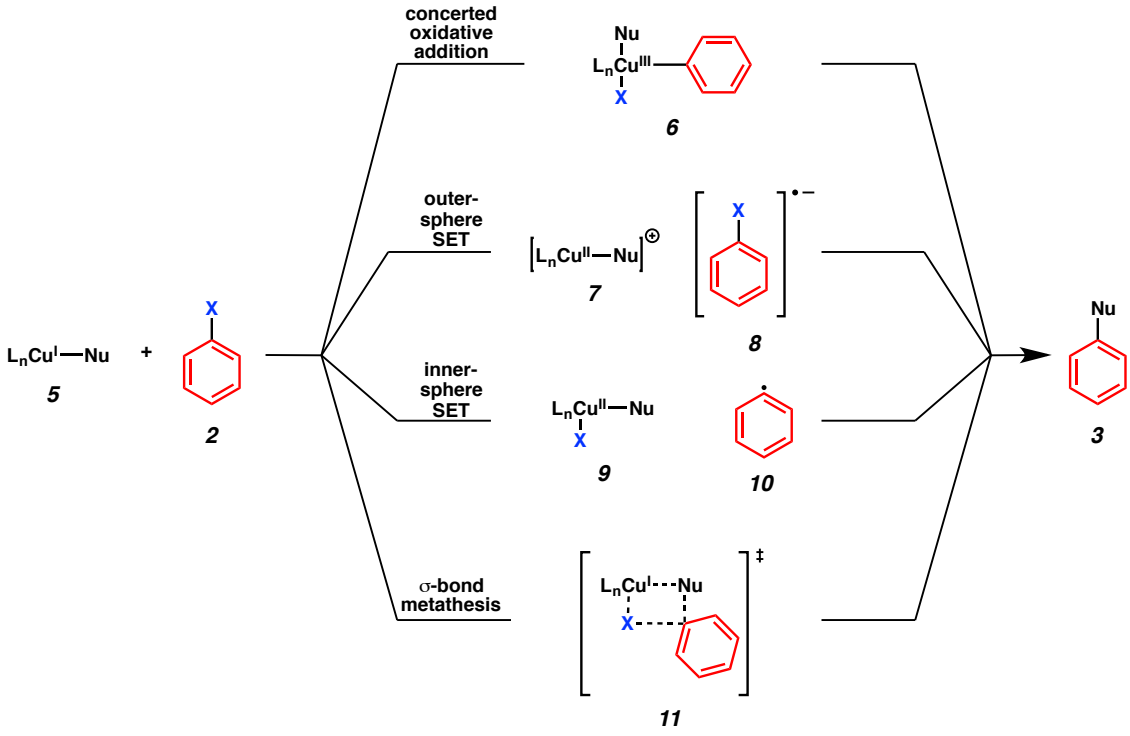
In efforts toward understanding the role of ancillary ligands in Ullman-type reactions, well-defined, ligated copper(I)–nucleophile complexes have been synthesized and shown to be kinetically and chemically competent intermediates.[9, 10] These experiments, as well as computational studies,[11] support the generally accepted proposal that Ullman-type reactions proceed by coordination of the deprotonated nucleophile (**1**) to a copper(I) species (**4**), followed by rate-determining activation of the aryl halide (Figure 1.1).[1] The mechanism of the aryl halide activation step remains under investigation.

Figure 1.1 Proposed intermediacy of a copper–nucleophile species in Ullman-type reactions



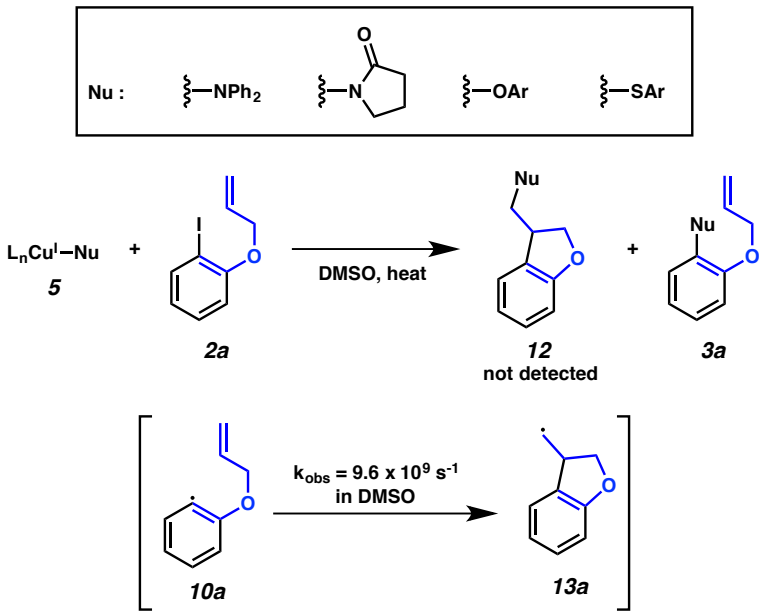
Proposed mechanisms for aryl halide activation include concerted oxidative addition, inner sphere or outer sphere single electron transfer (SET), and σ-bond metathesis (Figure 1.2).[1] SET pathways have been supported by computational studies,[11c,d,12] but little experimental evidence for such pathways existed until recently.[13]

Figure 1.2 Proposed mechanisms for aryl halide activation



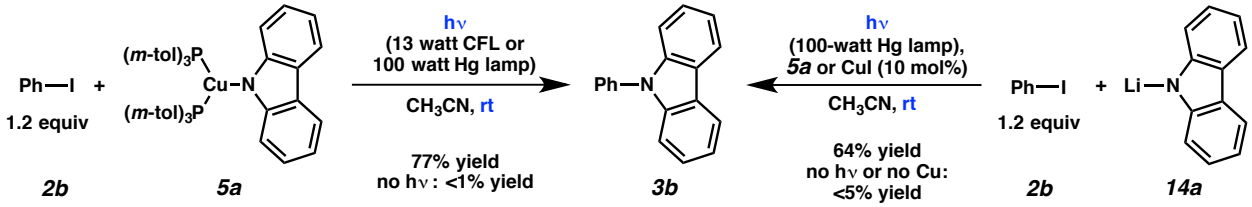
In several systems, experimental evidence has been considered inconsistent with the formation of aryl radical intermediates.[10a–d] For example, various copper–nucleophile complexes (**5**) were reported to couple with aryl iodide **2a** to generate exclusively the uncyclized products (**3a**, Scheme 1.2).[10a–d] Because aryl radical **10a** rearranges with a unimolecular rate constant of ~10^{10} s^{-1} in DMSO,[14] the absence of cyclized products (**12**) has been cited as evidence against SET to the aryl iodide.[10a–d]

Scheme 1.2 Coupling of various copper–nucleophile complexes with an aryl radical probe



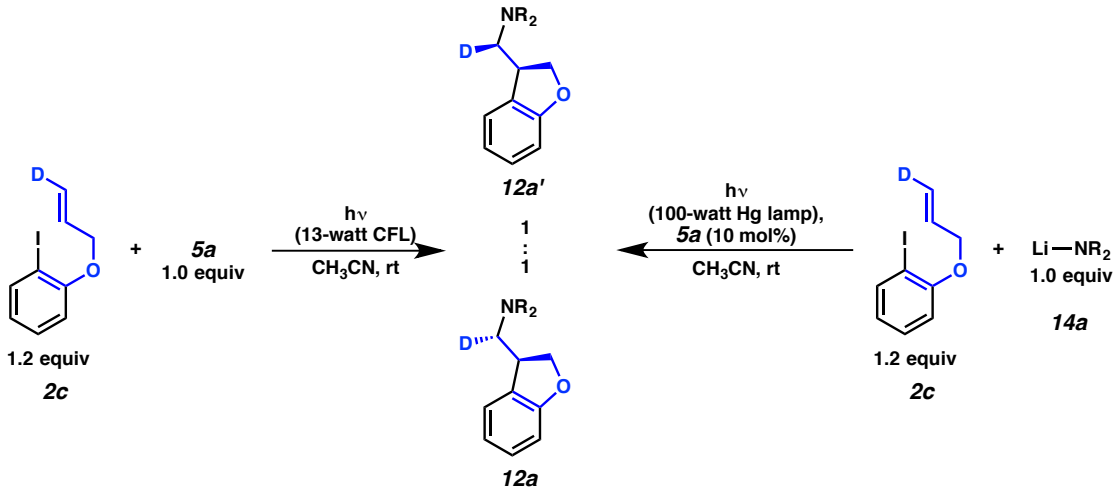
In 2012, Fu and Peters reported the light-mediated, room temperature C–N coupling of copper–carbazolide complex **5a** with aryl halides (Scheme 1.3).[15] *N*-arylation of lithium carbazolide (**14a**) with iodobenzene (**2b**) can also be achieved using a catalytic amount of either complex **5a** or CuI. For both stoichiometric and catalytic C–N bond forming processes, little to no reaction is observed in the dark.

Scheme 1.3 Light- and copper-mediated C–N bond formation at room temperature



A variety of data are consistent with an SET pathway for this photoinduced, copper-mediated C–N coupling. For example, in contrast to previous mechanistic studies of thermal copper-mediated *N*-arylation,[10a,b] radical probe **2a** generates exclusively the cyclized coupling product (**12**). Under both stoichiometric and catalytic conditions, deuterium-labeled aryl iodide **2c** yields a 1:1 mixture of diastereomeric cyclized C–N coupled products **12a** and **12a'** (Scheme 1.4). This is inconsistent with aryl halide cyclization via concerted oxidative addition/syn-insertion/reductive-elimination, which would be expected to give a single diastereomer.

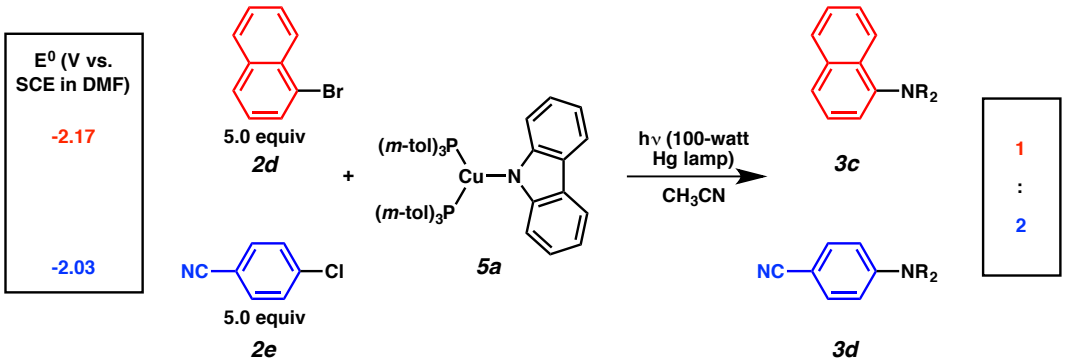
Scheme 1.4 Cyclization and coupling of a deuterium-labeled radical probe



Again contrasting previous studies of thermal copper-mediated C–N coupling,[10a,b] a competition experiment between 1-bromonapthalene (**2d**) and 4-chlorobenzonitrile (**2e**) results in predominant cross-coupling of the aryl chloride (Scheme 1.5). Because aryl chloride **2e** is easier to reduce than aryl bromide **2d**, and both substrates have similar

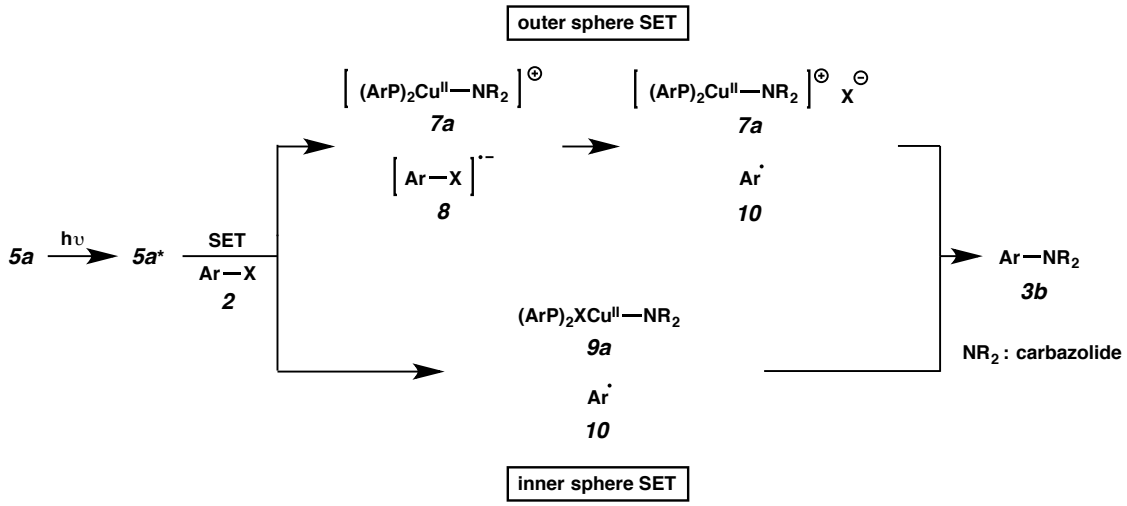
rates of dissociation of the halide from the radical anion, this result is consistent with an SET pathway.[10a]

Scheme 1.5 Competition experiment between aryl halides with different standard reduction potentials



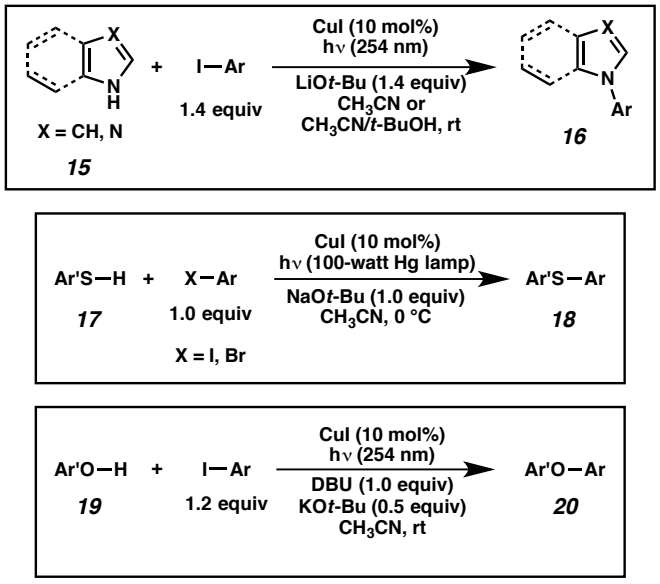
Additional evidence for an SET pathway includes EPR data consistent with the formation of a copper-containing radical when copper−carbazolide complex **5a** is irradiated in the presence of iodobenzene (**2b**). Thus, one possible mechanism for the aryl halide activation step could be SET from photoexcited species **5a*** to the aryl halide (**2**), thereby generating a copper(II) species and ultimately an aryl radical (**10**, Figure 1.3).

Figure 1.3 One possible mechanism for photoinduced aryl halide activation by a copper–carbazolide complex



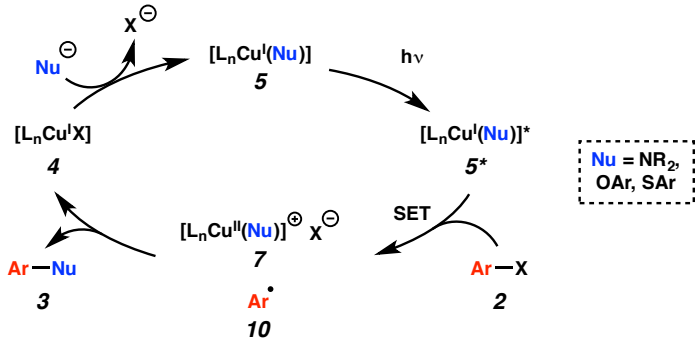
This initial discovery prompted the development of several general methods for copper-catalyzed arylation of heteroatom nucleophiles under mild conditions (Scheme 1.6).[16]

Scheme 1.6 Photoinduced, copper-catalyzed arylation of nitrogen heterocycles, thiols, and phenols



These copper-catalyzed, photoinduced C(aryl)−heteroatom bond formations do not necessarily proceed by a common mechanism; however, we hypothesize that in each case, photoexcitation of a copper−nucleophile complex (**5**) and single electron transfer to the aryl halide are involved in the catalytic cycle (Figure 1.4).

Figure 1.4 One possible catalytic cycle for photoinduced, copper-catalyzed arylation

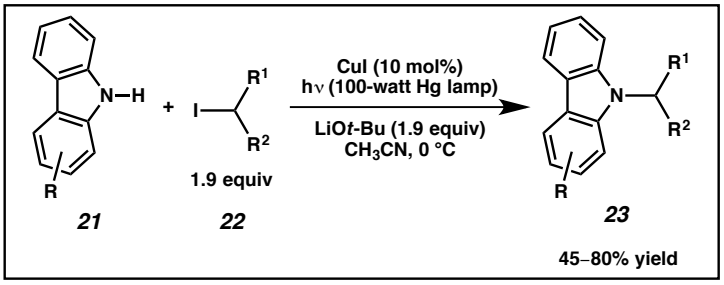


The cross-coupling of radical probe **2a** to generate *N*-alkylated carbazole (**12a** and **12a'**, Scheme 1.4) suggested that photoinduced, copper-catalyzed C(sp^3)−N bond forming reactions are also possible.[15] Traditional Ullman-type,[1] Buchwald-Hartwig,[17] and Chan-Lam reactions [18] are well-established strategies for C(sp^2)−N coupling, and reductive amination[19] and olefin hydroamination[20] are effective for the formation of C(sp^3)−N bonds, but there are few examples of transition metal-catalyzed functionalization of amines with alkyl halides.[21]

Fu and Peters reported that catalytic copper and light indeed effect *N*-alkylation of carbazoles (**21**) with unactivated secondary alkyl halides (**22**, Scheme 1.7).[22] This photoinduced, copper-catalyzed C(sp^3)−N coupling contrasts direct nucleophilic substitution of alkyl halides by amines, as it occurs under very mild conditions (0 °C) and is compatible with sterically hindered substrates. In addition, this represents one of the

few examples of transition metal-catalyzed couplings of amines with alkyl halides.[20] This work provided a proof-of-principle for C(sp^3)−N bond formations; however we were interested in expanding this strategy to a more general and ubiquitous class of nitrogen nucleophiles, such as amides.

Scheme 1.7 Photoinduced, copper-catalyzed N-alkylation of carbazole



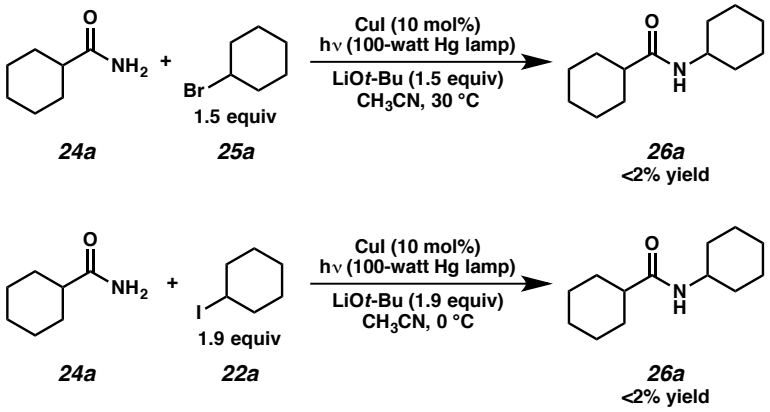
`

N-alkylated amides are an important motif in pharmaceuticals,[23] natural products,[24] and polymers.[25] Existing strategies for alkylation of primary amides include direct nucleophilic substitution of alkyl halides, transamidation of amides with alkyl amines,[26] hydroamidation of alkenes,[27] and amidation of unactivated alkanes.[28] Despite the efficacy of these reactions, there is a lack of a general and mild strategy for *N*-alkylation to generate α-branched *N*-alkyl amides.

1.2 Results and Discussion

The optimal conditions for coupling carbazoles with unactivated secondary alkyl bromides and iodides were ineffective when carbazole was replaced by cyclohexanecarboxamide (**24a**) (Scheme 1.8);[22] however the use of 254 nm light instead of a Hg lamp provided efficient coupling with bromocyclohexane at room temperature. The finalized conditions resulting from optimization of various reaction parameters are shown in Table 1, Entry 1.

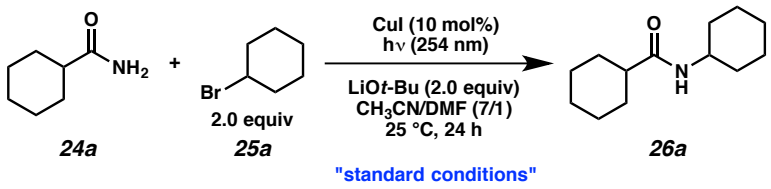
Scheme 1.8 Attempted amide alkylation under conditions previously described for carbazole alkylation



Control reactions in the absence of copper(I) iodide, light, or lithium *tert*-butoxide resulted in little to no C−N bond formation (Table 1.1, entries 2−3). Using copper(I) bromide or copper(I) chloride instead of copper(I) iodide as the precatalyst was only slightly detrimental to yield (entries 5, 6), whereas use of bases other than lithium *tert*-butoxide caused a significant decrease in yield (entries 7−10). While only a minor decrease in yield was observed in the absence of *N,N*-dimethylformamide (entry 11), the co-solvent was particularly helpful when aryl amides were used as coupling partners.[29]

Using a smaller excess of base and electrophile was significantly detrimental to yield (entry 12), whereas decreasing the catalyst loading to as low as 2.5 mol% had little effect on yield (entries 13−16). Irradiation of the reaction mixture with longer-wavelength light resulted in little to no cross-coupling (entries 17, 18), but a household Honeywell 36 W UVC air-treatment lamp was a highly effective light source (entry 19). Irradiation of the reaction mixture with the Honeywell UVC lamp at 0 °C instead of room temperature resulted in a decrease in yield (entry 20). Addition of 1.0 equivalent of water to the reaction mixture did not significantly affect the reaction efficiency (entry 21).

Table 1.1 Effect of reaction parameters on photoinduced, copper-catalyzed N-alkylation



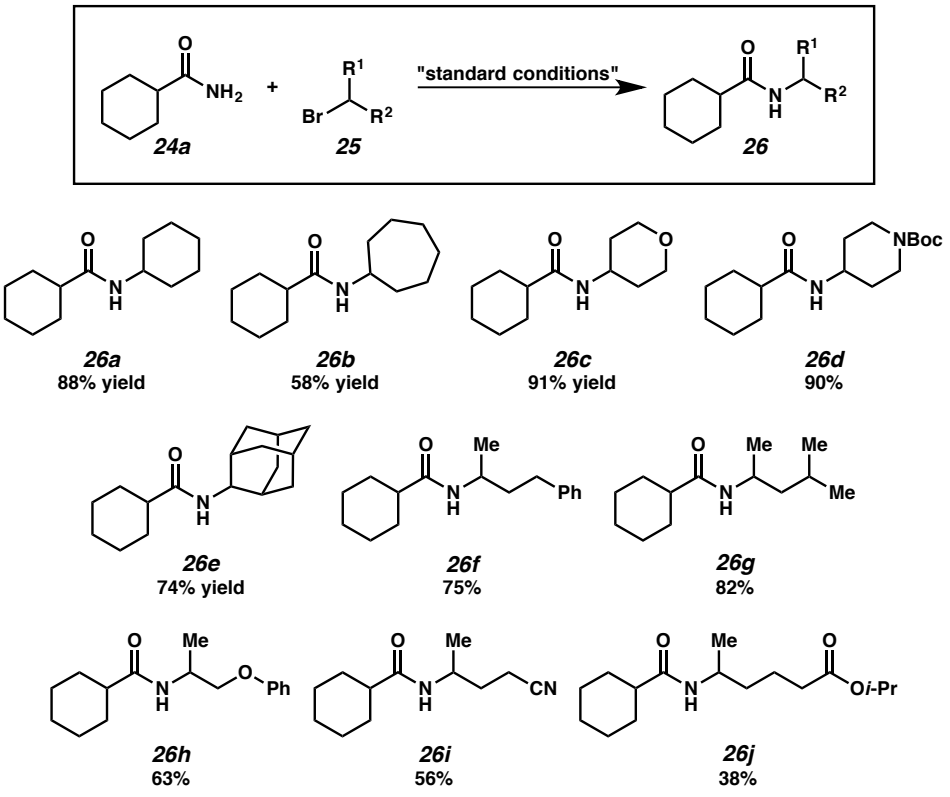
24a ***25a*** **"standard conditions"** ***26a***

entry	change from the "standard conditions"	yield (%)[a]
1	none	90
2	no CuI	<2
3	no hν	<2
4	no LiO*t*-Bu	<2
5	CuBr, instead of CuI	82
6	CuCl, instead of CuI	78
7	NaO*t*-Bu instead of LiO*t*-Bu	38
8	KO*t*-Bu instead of LiO*t*-Bu	10
9	Cs_2CO_3 instead of LiO*t*-Bu	9
10	K_3PO_4 instead of LiO*t*-Bu	4
11	no DMF	83
12	1.2 equiv CyBr and 1.2 equiv LiO*t*-Bu	40
13	CuI (5.0 mol%)	87
14	CuI (2.5 mol%)	83
15	CuI (1.0 mol%)	69
16	CuI (0.5 mol%)	30
17	hν (300 nm)	10
18	hν (100 W Hg lamp)	<2
19	Honeywell 36 W UVC air-treatment lamp	90
20	Honeywell 36 W UVC air-treatment lamp, 0 °C	33
21	1.0 equiv H_2O	85

[a]Determined through GC analysis (average of two experiments).

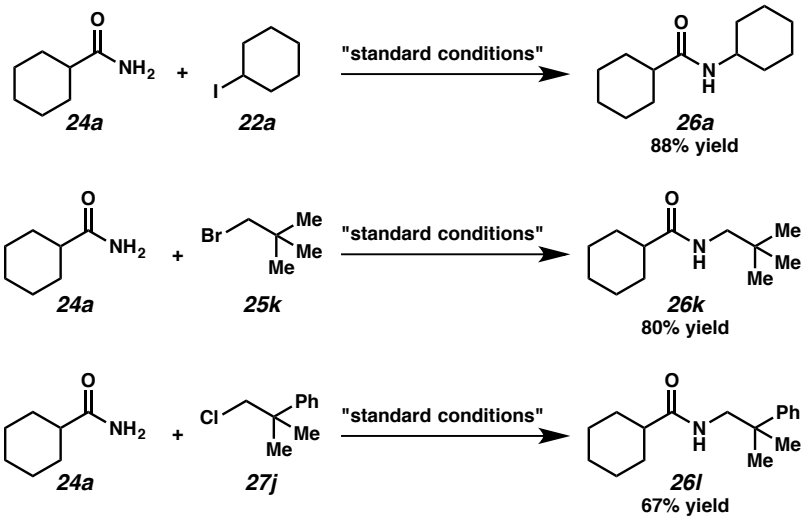
This photoinduced, copper-catalyzed C–N coupling reaction is compatible with a variety of both cyclic and acyclic alkyl bromides (Scheme 1.9). Functional groups including a cyclic ether (**26c**), an acyclic ether (**26h**), a carbamate (**26d**), and a nitrile (**26i**) are tolerated. A moderate yield was obtained for an alkyl bromide containing a pendant ester (**26j**), possibly due to transesterification with the *tert*-butoxide base.

Scheme 1.9 Scope with respect to unactivated secondary alkyl bromides



In addition to unactivated secondary alkyl bromides, an unactivated secondary alkyl iodide (**22a**), neopentyl bromide (**25k**) and neophyl chloride (**27j**) are suitable coupling partners (Scheme 1.10). The coupling of particularly poor S_N2 substrates **25k** and **27j** demonstrates this strategy's complementarity to direct nucleophilic substitution.

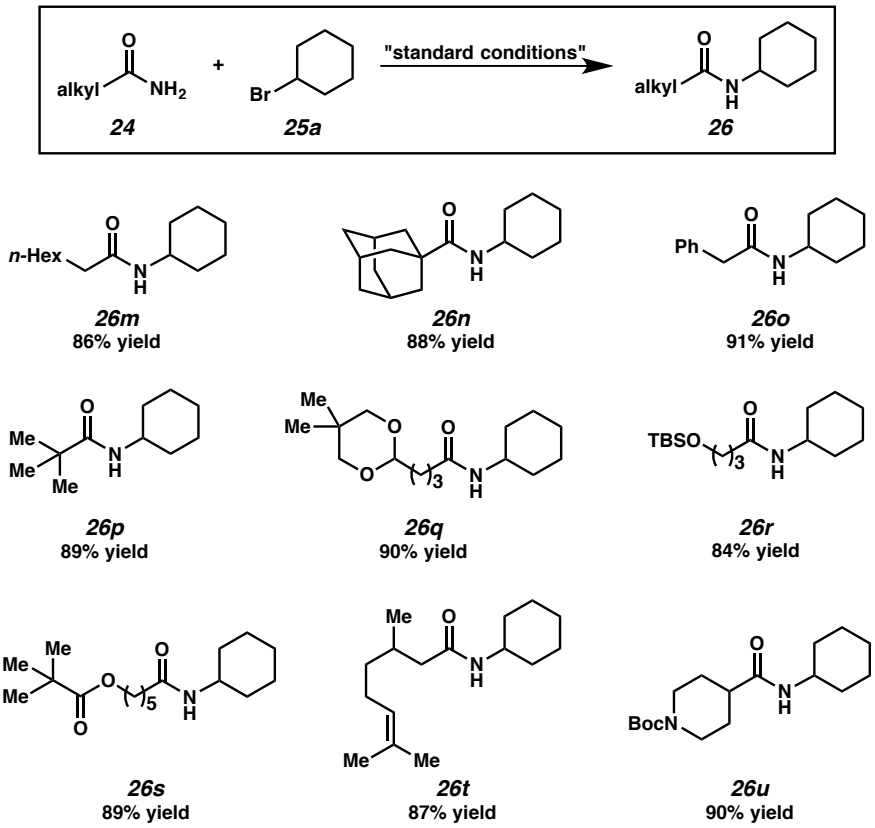
Scheme 1.10 Coupling of an unactivated secondary alkyl iodide and neopentyl halides



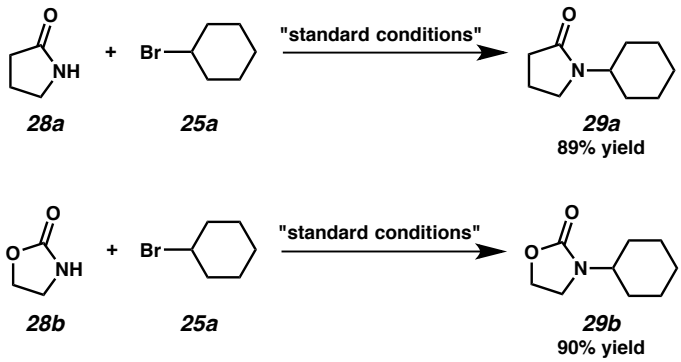
The scope of this *N*-alkylation reaction is broad with respect to the amide; an array of aliphatic primary amides can be coupled with unactivated secondary alkyl bromides in good yield (Scheme 1.11). The standard reaction conditions are effective for amides functionalized with a pendant acetal (**26q**), a TBS-protected alcohol (**26r**), an ester (**26s**), a trisubstituted olefin (**26t**), and a carbamate (**26u**).

Although we have not developed general conditions for the coupling of secondary amides, a lactam (**28a**) and an oxazolidinone (**28b**) furnish the corresponding tertiary amides **29a** and **29b**, respectively, in good yield (Scheme 1.12).

Scheme 1.11 Scope with respect to aliphatic amides



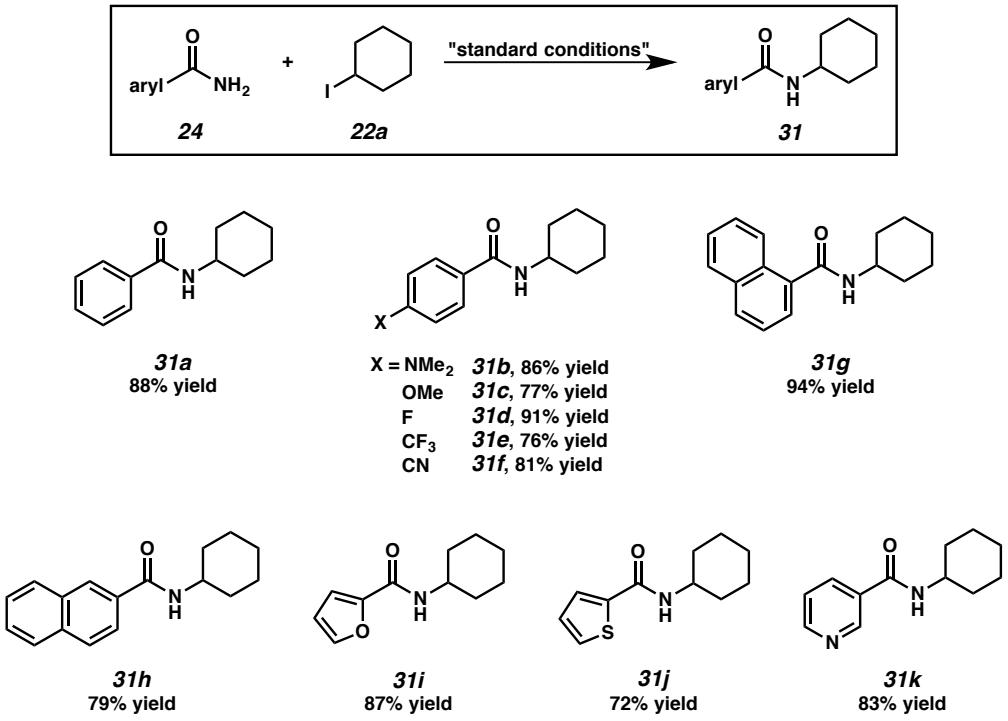
Scheme 1.12 C–N coupling of cyclic secondary amides



Primary aryl amides are also good substrates in this photoinduced, Cu-catalyzed C–N coupling; in this case unactivated secondary alkyl bromides are inferior to the corresponding alkyl iodides (Scheme 1.13). Aryl amides with substitution at the *para*

position are well-tolerated, including dimethylamino, methoxy, fluoro, trifluoromethyl, and cyano functional groups (**31b**–**f**). The aryl substituent can be a naphthyl-, furyl- , thiophenyl-, or pyridyl-derivative (**31g**–**k)**.

Scheme 1.13 Scope with respect to aryl amides



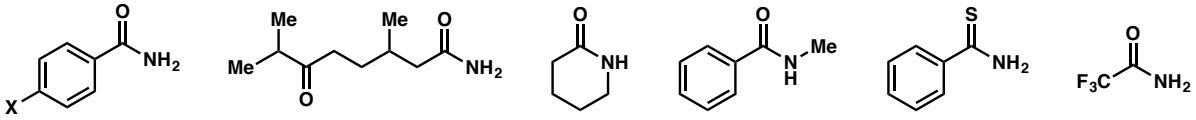
Despite the broad scope of this reaction with respect to both the amide and alkyl halide coupling partners, we are aware of several limitations. Under the standard conditions (Table 1.1, entry 1), an unactivated secondary alkyl chloride (**27m**), a tertiary alkyl bromide (**32a**), and an aryl bromide (**2f**) result in low yields (<50%) of C–N coupling (Figure 1.5), while an aryl iodide (**2g**) effects *N*-arylation in moderate yield (~50%).

Figure 1.5 Examples of electrophiles resulting in low to moderate yields

27m ***32a*** ***2f*** ***2g***

With respect to the nucleophile, aryl amides with a *para*-chloro or -bromo substituent (**30h** and **30i**) undergo transhalogenation and hydrodehalogenation, thus low yields of the desired alkylation are observed (Figure 1.6). An aliphatic amide containing a pendant ketone (**24v**), a δ-lactam (**28c**), *N*-methyl benzamide (**33**), and a thioamide (**34**) are poor substrates (<50% yield), while trifluoroacetamide (**35**) can be coupled with a secondary alkyl iodide in moderate (~50%) yield.

Figure 1.6 Examples of nucleophiles resulting in low to moderate yields



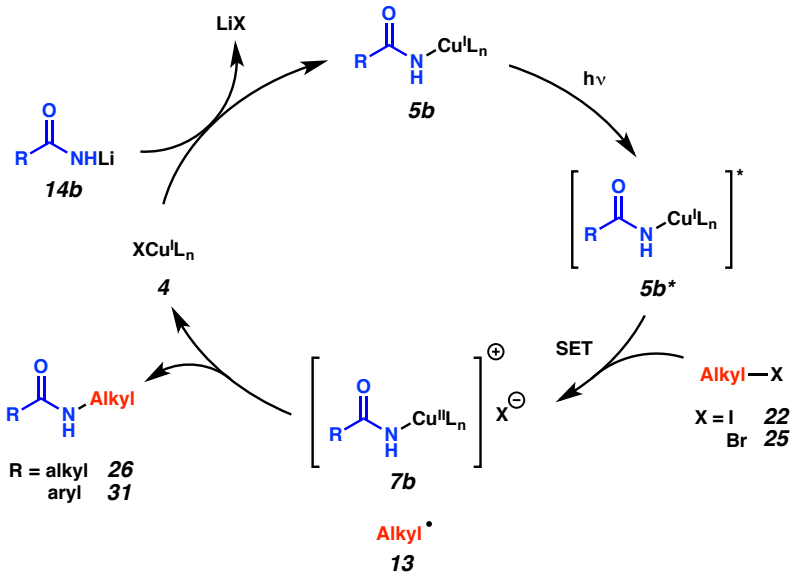
X = Cl ***30h***
Br ***30i***

24v ***28c*** ***33*** ***34*** ***35***

1.3 Mechanistic studies

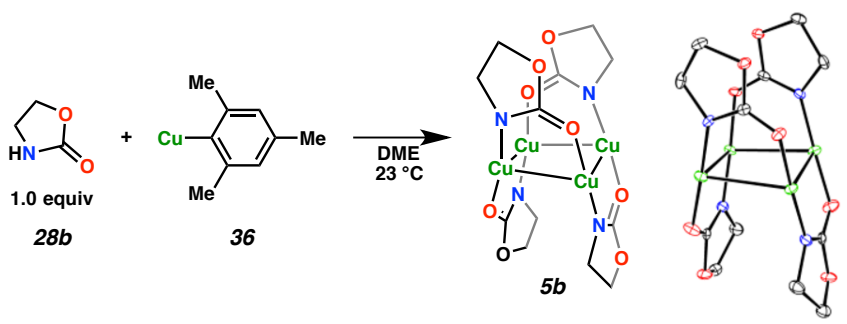
A possible mechanism for this photoinduced, copper-catalyzed *N*-alkylation reaction is shown in Figure 1.7. We hypothesize that irradiation of a copper(I)−amidate complex (**5b**) generates photoexcited species **5b***, which then reduces the alkyl halide by one electron, resulting in an alkyl radical intermediate (**13**).

Figure 1.7 One possible mechanism for photoinduced, Cu-catalyzed amide alkylation



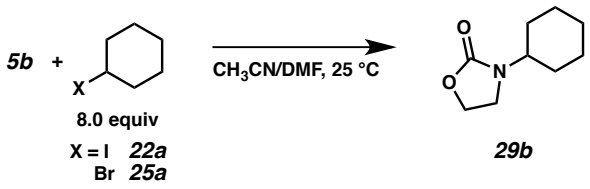
In order to test our hypothesis that a copper(I)−amidate complex (e.g., **5b**) is an intermediate in this photoinduced, copper-catalyzed C−N coupling, we hoped to obtain X-ray quality crystals of a copper complex containing a primary amide. Although these attempts were unsuccessful, we synthesized and crystallographically characterized copper−oxazolidinyl complex **5c** (Scheme 1.14).

Scheme 1.14 Synthesis of X-ray quality crystals of a copper–oxazolidinyl complex



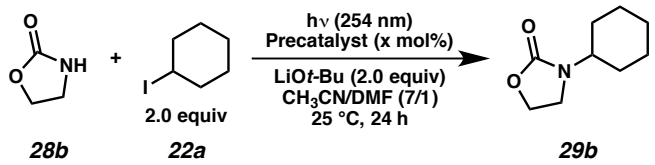
Complex **5b** reacts with an alkyl iodide (**22a**) and an alkyl bromide (**25a**) to furnish the corresponding *N*-alkylated oxazolidinone **29b** in good yield (Table 1.2). Either complex **5b** or CuI can be used as a precatalyst for C–N coupling between oxazolidinone **28b** and alkyl iodide **22a** (Table 1.3).

Table 1.2 Chemical competence of a copper–oxazolidinyl complex



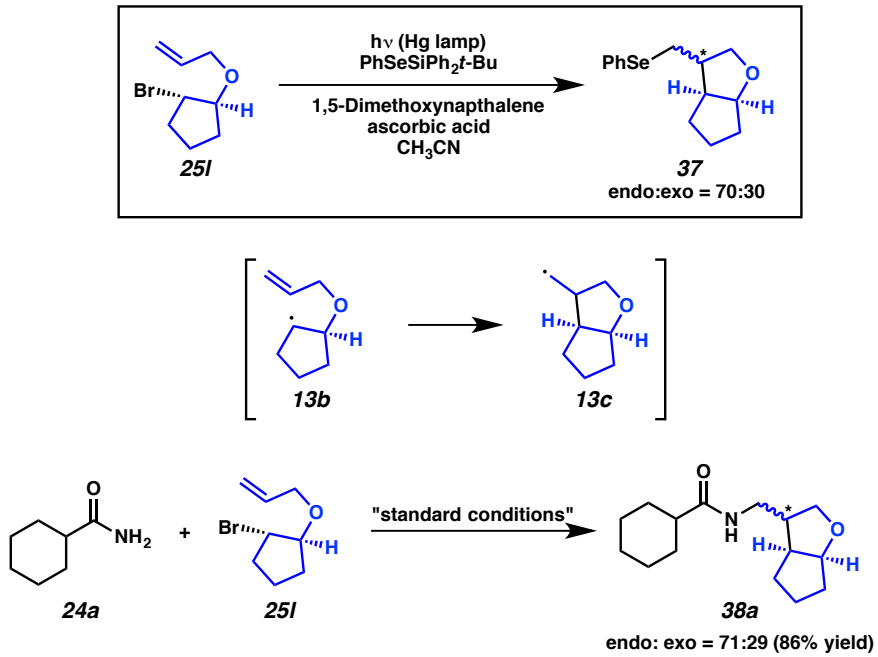
Conditions	Yield (%)
no hν, *22a* or *25a*	<2
hν (254 nm), *22a*	73
hν (254 nm), *25a*	80

Table 1.3 Use of a copper–oxazolidinyl complex or CuI as a precatalyst



Precatalyst	Yield (%)
CuI (10 mol%)	85
5b (2.5 mol%)	83

Scheme 1.15 Cyclization of an alkyl bromide under previously reported conditions and under N-alkylation conditions

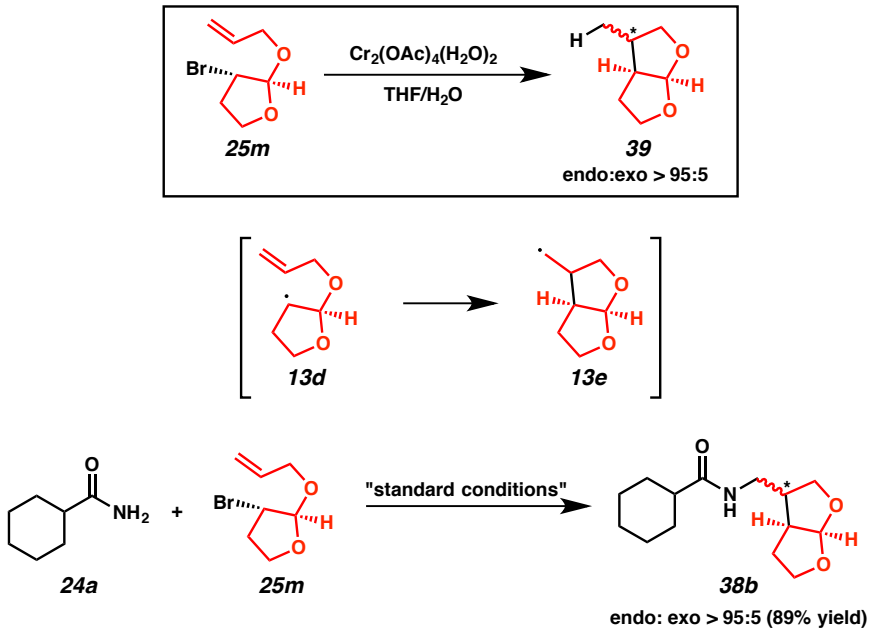


To explore the possibility of alkyl radical formation throughout the course of the reaction, alkyl bromides **25l** (Scheme 1.15) and **25m** (Scheme 1.16) were subjected to the standard conditions. **25l** has been reported in the literature to undergo photosensitized electron transfer (PET) cyclization and termination with *in situ*-generated PhSeSePh to generate **37** as a 70:30 mixture of diastereomers (Figure 1.24).[30] When **25l** is subjected

to our photoinduced, copper-catalyzed *N*-alkylation conditions, the C−N coupled/cyclized product **38a** is obtained in good yield, with similar diastereoselectivity. The analogous product distributions observed in these two reactions suggest the possibility of a common intermediate, such as alkyl radical **13b**.

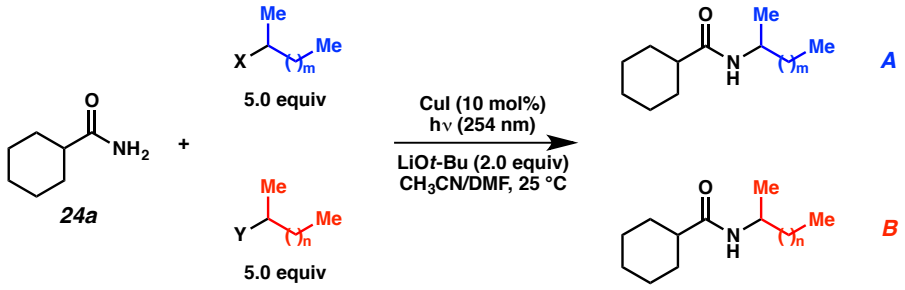
Similarly, the free-radical cyclization of alkyl bromide **25m** induced by chromium(II)-acetate has been reported to generate a >95:5 mixture of diastereomers (**39**),[31] and the same ratio of *N*-alkylated products (**38b**) is observed when **25m** is coupled under our standard conditions (Scheme 1.18). Overall, these data are consistent with the intermediacy of alkyl radicals in this photoinduced, copper-catalyzed C−N bond forming reaction.

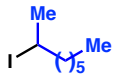
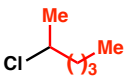
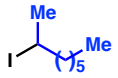
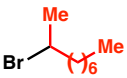
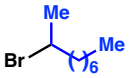
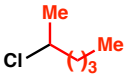
Scheme 1.16 Cyclization of an alkyl bromide under previously reported conditions and under N-alkylation conditions



An electrophile competition experiment demonstrates that a secondary alkyl iodide (**22b**) can be selectively coupled in the presence of a secondary alkyl chloride or bromide (**27o** and **25n**, respectively, Table 1.4). Secondary alkyl bromide **25n** also reacts preferentially in a competition experiment with alkyl chloride **27o**. This trend in reactivity is consistent with the alkyl halides' relative propensity to undergo one-electron reduction;[32] however these observations could also be accommodated by the alkyl halides' relative reactivity toward two-electron oxidative addition.

Table 1.4 Electrophile competition experiments



Substrates		A:B
		>50:1
22b	**27o**	
		10:1
22b	**25n**	
		>50:1
25n	**27o**	

1.4 Conclusion

We have developed, to the best of our knowledge, the first general method for transition metal-catalyzed *N*-alkylation of amides with unactivated secondary alkyl halides. Within our current program of study of photoinduced, copper-catalyzed cross-coupling reactions, this is the first reported class of nucleophiles that does not contain an aromatic ring on the heteroatom. This coupling reaction is effective for the synthesis of a variety of both aliphatic and aromatic *N*-alkyl amides under a single set of reaction conditions. The standard reaction conditions are operationally simple; no ligand is required, the reaction is run at room temperature, an inexpensive precatalyst (CuI) is used, and a commercial and readily available UVC lamp is an effective source of irradiation.

Under the standard reaction conditions, the stereochemical outcome of cyclization and cross-coupling of secondary alkyl bromides bearing pendant olefins are consistent with a possible SET/radical pathway. We have shown that a crystallographically characterized copper(I)−amidate undergoes C−N coupling when subjected to the reaction conditions and is a competent precatalyst for the cross-coupling of an amide with an alkyl iodide. These data are consistent with the photoexcitation of a copper−nucleophile complex and generation of an alkyl radical under the reaction conditions.

1.5 Experimental Procedures

1.5.1 General Information

The following reagents were purchased and used as received:

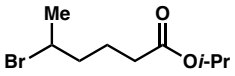
Aldrich: CuI (99.999%; 98% and 99.5% provide comparable results), 1-adamantanecarboxamide, cyclohexanecarboxamide, 2-oxazolidinone, pivalamide, 2-bromoadamantane, bromocyclohexane, bromocycloheptane, 1-bromo-2,2-dimethylpropane, *t*- butyl 4-bromopiperidine-1-carboxylate, 4-bromotetrahydro-2*H*-pyran, and iodocyclohexane; Alfa: LiO*t*-Bu, benzamide, 4-cyanobenzamide, 4-fluorobenzamide, 4-methoxybenzamide, 1-naphthamide, 2-naphthamide, thiophene-2-carboxamide, and 4-bromoheptane; Eastman: furan-2-carboxamide; Oakwood: 2-phenylacetamide; Matrix: 4-(trifluoromethyl)benzamide; Maybridge: *t*-butyl 4-carbamoylpiperidine-1-carboxylate; TCI: nicotinamide, *n*-octanamide.

DMF and CH_3CN were dried in a solvent-purification system with the aid of activated alumina. All reactions were carried out in oven-dried quartz tubes or quartz flasks under an inert atmosphere using a Luzchem LZC–4V photoreactor at 254 nm. ^{1}H and ^{13}C NMR data were collected on a VARIAN 500 MHz spectrometer at ambient temperature. GC analyses were carried out on an Agilent 6890 series system with a DB-1 column (length 30 m, i.d. 0.25 mm) and an Agilent 6850 series system with a G-TA column (length 30 m, i.d. 0.25 mm). GC-MS analyses were performed on an Agilent 6980 series system equipped with an Agilent 5973 Network Mass Selective Detector.

1.5.2 Preparation of Materials

These procedures have not been optimized.

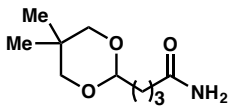
General procedure for the preparation of alkyl bromides. A 300-mL round-bottom flask was charged with PPh_3 (17.0 g, 65.0 mmol, 1.30 equiv), imidazole (4.42 g, 65.0 mmol, 1.30 equiv), and dichloromethane (150 mL). The resulting solution was stirred at 0 °C in an ice bath under a nitrogen atmosphere. Bromine (3.40 mL, 65.0 mmol, 1.30 equiv) was added dropwise over 2 min, yielding a colorless or light-yellow solution. After 5 min, the alcohol (50.0 mmol, 1.00 equiv) was added dropwise over 3 min. The ice bath was then removed, and the reaction mixture was stirred at 23 °C for 20 h. Next, the reaction mixture was concentrated under reduced pressure on a rotary evaporator to a volume of 40 mL, and then it was diluted with a mixture of pentane and ether (4/1, 100 mL). The resulting suspension was filtered and concentrated, and then the residue was purified by column chromatography.



Isopropyl 5-bromohexanoate (25j). The title compound was prepared according to the general procedure, using isopropyl 5-hydroxyhexanoate.[33] The product was obtained as a colorless oil (8.53 g, 72% yield).

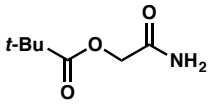
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (hept, J = 6.3 Hz, 1H), 4.17 – 4.07 (m, 1H), 2.34 – 2.24 (m, 2H), 1.91 – 1.67 (m, 7H), 1.23 (d, J = 6.3 Hz, 6H); ^{13}C NMR (126 MHz, CDCl3) δ 172.7, 67.6, 50.8, 40.3, 33.8, 26.4, 23.2, 21.8; FT-IR (neat) 2980, 2935, 1728, 1454, 1373, 1253, 1182, 1107 cm^{-1}; MS (EI) *m/z* ([M – C_3H_7O]$^+$) calcd for $C_6H_{10}BrO$: 177.0, found: 177.1.

Preparation of amides.



4-(5,5-Dimethyl-1,3-dioxan-2-yl)butanamide (24q). The title compound was prepared according to a reported procedure [34] from methyl 4-(5,5-dimethyl-1,3-dioxan-2-yl)butanoate.[35] The product was obtained as a white solid (65% yield).

^{1}H NMR δ (500 MHz, $CDCl_3$) 5.81 (brs, 1H), 5.67 (brs, 1H), 4.43 (t, *J* = 4.8 Hz, 1H), 3.58 (dt, *J* = 11.2, 1.4 Hz, 2H), 3.46 – 3.36 (m, 2H), 2.26 (t, *J* = 7.4 Hz, 2H), 1.84 – 1.62 (m, 4H), 1.16 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 101.8, 77.2, 35.6, 33.8, 30.1, 23.0, 21.8, 20.0; FT-IR (neat) 3387, 3304, 3195, 2966, 2955, 2903, 2872, 2843, 1657, 1631, 1466, 1410, 1346, 1318, 1240, 1216, 1176, 1127, 1097, 1075, 1020, 965, 925, 915, 818, 791 cm^{-1}; MS (EI) m/z (M^+) calcd for $C_{10}H_{19}NO_3$: 201.1, found: 201.2.

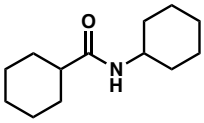


6-Amino-6-oxohexyl pivalate (24s). The title compound was prepared according to a reported procedure[36] from 6-hydroxyhexanamide.[37] The product was obtained as a white solid (61% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (brs, 1H), 5.59 (brs, 1H), 4.04 (t, *J* = 6.6 Hz, 2H), 2.22 (t, *J* = 7.5 Hz, 2H), 1.73 – 1.57 (m, 4H), 1.44 – 1.34 (m, 2H), 1.17 (s, 9H); ^{13}C NMR (126 MHz, CDCl3) δ 178.6, 175.4, 64.1, 38.7, 35.7, 28.4, 27.2, 25.5, 25.0; FT-IR (neat) 3346, 3172, 2970, 2947, 2869, 2812, 1718, 1667, 1629, 1476, 1413, 1395, 1352, 1284, 1176, 1156, 1062, 1032, 953 cm^{-1}; MS (EI) m/z ($[M - C_4H_9]^+$) calcd for $C_7H_{12}NO_3$: 158.1, found: 158.0.

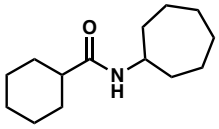
1.5.3 Photoinduced, Copper-Catalyzed Alkylations of Amides

General procedure for the alkylation of amides. CuI (19.5 mg, 0.10 mmol), the amide (1.00 mmol), and LiO*t*-Bu (160 mg, 2.00 mmol) were added to an oven-dried 10-mL quartz test tube that contained a stir bar (3 mm x 13 mm). The test tube was fitted with a rubber septum, the joint was wrapped with electrical tape, and the test tube was evacuated and backfilled with nitrogen (3 cycles). A solution of the alkyl bromide (2.00 mmol) in CH_3CN (5.4 mL) and DMF (0.80 mL) was added in turn by syringe. The test tube was detached from the nitrogen line, and the puncture holes of the septum were covered with vacuum grease. The resulting mixture was stirred vigorously for 5 min, and then the quartz test tube was placed in a Luzchem photoreactor. The stirring mixture was irradiated with a UVC lamp centered at 254 nm for 24 h. During the first 12 h, the reaction tube was occasionally shaken vertically (every 2-3 h) to ensure good mixing of the entire reaction mixture. After 24 h, the reaction mixture was purified by column chromatography.



***N*-Cyclohexylcyclohexanecarboxamide (26a, Figure 1.13) [7474-36-4].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 180 mg (86%). Second run: 189 mg (90%).

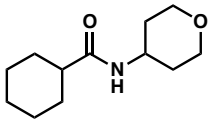
^{1}H NMR (500 MHz, CDCl3) δ 5.31 (brs, 1H), 3.80 – 3.71 (m, 1H), 2.02 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.98 – 1.56 (m, 9H), 1.46 – 1.04 (m, 11H).



***N*-Cycloheptylcyclohexanecarboxamide (26b, Figure 1.13) [550306-49-5].** The title compound was prepared according to the general procedure from

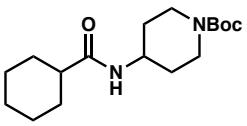
cyclohexanecarboxamide (1.0 mmol) and bromocycloheptane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 131 mg (59%). Second run: 128 mg (57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (d, *J* = 8.3 Hz, 1H), 3.99 – 3.87 (m, 1H), 2.02 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.94 – 1.14 (m, 22H).



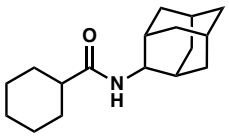
***N*-(Tetrahydro-*2H*-pyran-4-yl)cyclohexanecarboxamide (26c, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and 4-bromotetrahydro-*2H*-pyran (2.0 mmol). The product was purified by column chromatography (hexanes → 50% EtOAc/hexanes). White solid. First run: 191 mg (90%). Second run: 194 mg (92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (d, *J* = 8.0 Hz, 1H), 4.04 – 3.90 (m, 3H), 3.47 (td, *J* = 11.7, 2.2 Hz, 2H), 2.03 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.92 – 1.62 (m, 7H), 1.49 – 1.15 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 66.8, 45.6, 45.3, 33.3, 29.7, 25.7; FT-IR (neat) 3250, 3072, 2969, 2928, 2851, 2832, 1627, 1549, 1446, 1389, 1364, 1335, 1236, 1216, 1142, 1133, 1012, 978, 953, 896, 847, 826, 691 cm^{-1}; MS (EI) m/z (M^+) calcd for $C_{12}H_{21}NO_2$: 211.2, found: 211.2.



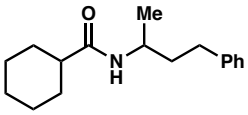
***t*-Butyl 4-(cyclohexanecarboxamido)piperidine-1-carboxylate (26d, Figure 1.13) [1233955- 27-5].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and *t*-butyl 4-bromopiperidine-1-carboxylate (2.0 mmol). The product was purified by column chromatography (5% → 50% EtOAc/hexanes). Off-white solid. First run: 275 mg (89%). Second run: 284 mg (92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (d, *J* = 8.0 Hz, 1H), 4.03 (brs, 2H), 3.97 – 3.87 (m, 1H), 2.91 – 2.79 (m, 2H), 2.03 (tt, *J* = 11.8, 3.4 Hz, 1H), 1.93 – 1.63 (m, 7H), 1.46 (s, 9H), 1.44 – 1.38 (m, 2H), 1.32 – 1.21 (m, 5H).



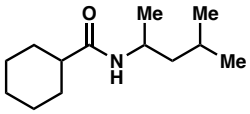
***N*-(Adamantan-2-yl)cyclohexanecarboxamide (26e, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and 2- bromoadamantane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 196 mg (75%). Second run: 189 mg (72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (d, *J* = 8.0 Hz, 1H), 4.03 (dd, *J* = 7.6, 3.6 Hz, 1H), 2.08 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.92 – 1.61 (m, 19H), 1.49 – 1.37 (m, 2H), 1.36 – 1.16 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 52.7, 45.8, 37.5, 37.1, 32.0, 31.9, 29.9, 27.2, 27.1, 25.8; FT-IR (neat) 3324, 2906, 2850, 1733, 1640, 1538, 1471, 1444, 1387, 1310, 1252, 1211, 1179, 1141, 1110, 952, 894, 819, 668, 635 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{17}H_{27}NO$: 261.2, found: 261.3.



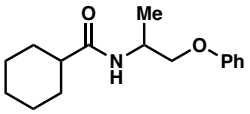
***N*-(4-Phenylbutan-2-yl)cyclohexanecarboxamide (26f, Figure 1.13) [545360-34-7].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and (3-bromobutyl)benzene (2.0 mmol). The product was purified by column chromatograpy (hexanes → 30% EtOAc/hexanes). Beige solid. First run: 192 mg (74%). Second run: 197 mg (76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 5.19 (d, *J* = 8.5, 1H), 4.11 – 4.02 (m, 1H), 2.64 (dd, *J* = 9.4, 6.7 Hz, 2H), 2.00 (tt, *J* = 11.8, 3.4 Hz, 1H), 1.87 – 1.58 (m, 7H), 1.47 – 1.35 (m, 2H), 1.31 – 1.18 (m, 3H), 1.16 (d, *J* = 6.6 Hz, 3H).



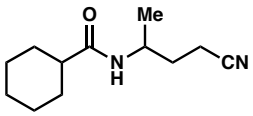
***N*-(4-Methylpentan-2-yl)cyclohexanecarboxamide (26g, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and 2-bromo-4-methylpentane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 171 mg (81%). Second run: 176 mg (83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (d, *J* = 8.6 Hz, 1H), 4.10 – 4.00 (m, 1H), 2.01 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.88 – 1.52 (m, 6H), 1.48 – 1.13 (m, 7H), 1.09 (d, *J* = 6.5 Hz, 3H), 0.90 (dd, *J* = 6.6, 2.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 46.5, 45.8, 43.0, 29.9, 29.6, 25.79, 25.76, 25.74, 25.1, 22.8, 22.5, 21.6; FT-IR (neat) 3289, 3071, 2964, 2928, 2852, 1632, 1541, 1442, 1383, 1259, 1213, 1165, 1127, 953, 896, 697 cm^{-1}; MS (EI) *m/z* (M+) calcd for $C_{13}H_{25}NO$: 211.2, found: 211.3.



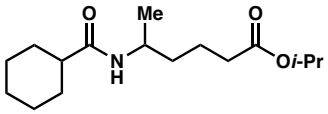
***N*-(1-Phenoxypropan-2-yl)cyclohexanecarboxamide (26h, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and (2-bromopropoxy)benzene (2.0 mmol). The product was purified by column chromatography (20% EtOAc/hexanes → 50% EtOAc/hexanes). Off-white solid. First run: 163 mg (62%). Second run: 166 mg (64%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 6.96 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.93 – 6.90 (m, 2H), 5.70 (d, *J* = 8.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 3.99 – 3.90 (m, 2H), 2.06 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.89 – 1.74 (m, 4H), 1.69 – 1.63 (m, 1H), 1.48 – 1.38 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.28 – 1.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 158.7, 129.5, 121.0, 114.5, 70.5, 45.6, 44.1, 29.6, 27.2, 25.7, 17.7; FT-IR (neat) 3307, 2930, 2919, 2852, 1636, 1533 cm^{-1}; LRMS (LCMS ESI) *m/z* (M^+ + H) calcd for $C_{16}H_{24}NO_2$: 262.2, found: 262.2.



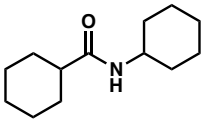
***N*-(4-Cyanobutan-2-yl)cyclohexanecarboxamide (26i, Figure 1.13).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol), 4- bromopentanenitrile (2.0 mmol). The product was purified by column chromatography (20% EtOAc/hexanes → 50% EtOAc/hexanes). Beige solid. First run: 115 mg (55%). Second run: 116 mg (56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (d, *J* = 8.5 Hz, 1H), 4.13 – 4.08 (m, 1H), 2.43 – 2.31 (m, 2H), 2.06 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.93 – 1.55 (m, 7H), 1.49 – 1.37 (m, 2H), 1.31 – 1.21 (m, 3H), 1.19 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 119.8, 45.5, 44.2, 32.7, 29.7, 29.6, 25.7, 20.8, 14.2; FT-IR (neat) 3295, 2974, 2931, 2852, 1637, 1541, 1443, 1428, 1390, 1376, 1261, 1217 cm^{-1}. LRMS (LCMS ESI) *m/z* (M^+ + H) calcd for $C_{12}H_{21}N_2O$: 209.2, found: 209.2.



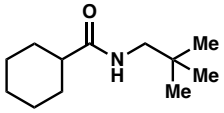
Isopropyl 5-(cyclohexanecarboxamido)hexanoate (26j, Figure 1.13). The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and isopropyl 5-bromohexanoate (2.0 mmol). The product was purified by column chromatography (hexanes → 50% EtOAc/hexanes). Light-tan solid. First run: 110 mg (39%). Second run: 104 mg (37%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (d, *J* = 8.5 Hz, 1H), 4.99 (hept, *J* = 6.3 Hz, 1H), 4.04 – 3.92 (m, 1H), 2.36 – 2.19 (m, 2H), 2.02 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.92 – 1.69 (m, 4H), 1.70 – 1.53 (m, 3H), 1.51 – 1.35 (m, 4H), 1.34 – 1.13 (m, 3H), 1.22 (d, *J* = 6.1 Hz, 6H), 1.11 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 173.1, 67.5, 45.7, 44.5, 36.2, 34.2, 29.8, 29.6, 25.76, 25.74, 25.73, 21.8, 21.4, 21.1; FT-IR (neat) 3277, 3087, 2960, 2928, 2853, 1725, 1634, 1553, 1450, 1417, 1379, 1340, 1259, 1249, 1218, 1191, 1114, 957, 934, 895, 710 cm^{-1}; MS (EI) *m/z* (M+) calcd for $C_{16}H_{29}NO_3$: 283.2, found: 283.3.



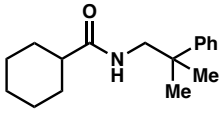
***N*-Cyclohexylcyclohexanecarboxamide (26a, Figure 1.14) [7474-36-4].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 184 mg (88%). Second run: 189 mg (87%).

The ^{1}H NMR spectrum was identical to that obtained for 26a, Figure 1.13.



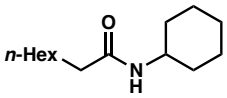
***N*-Neopentylcyclohexanecarboxamide (26k, Figure 1.14).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and 1-bromo-2,2-dimethylpropane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). Off-white solid. First run: 154 mg (78%). Second run: 160 mg (81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (brs, 1H), 3.05 (d, J = 6.3 Hz, 2H), 2.09 (tt, J = 11.8, 3.5 Hz, 1H), 1.91 – 1.83 (m, 2H), 1.83 – 1.76 (m, 2H), 1.71 – 1.63 (m, 1H), 1.50 – 1.40 (m, 2H), 1.33 – 1.17 (m, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) δ 176.1, 110.0, 50.1, 45.9, 31.9, 29.9, 27.2, 25.8; FT-IR (neat) 3280, 3090, 2852, 1644, 1558, 1208 cm^{-1}; LRMS (LCMS EI) *m/z* (M^+ + H) calcd for $C_{12}H_{24}NO$: 198.2, found: 198.2.



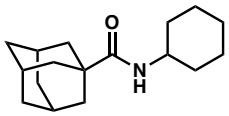
***N*-(2-Methyl-2-phenylpropyl)cyclohexanecarboxamide (26l, Figure 1.14) [1085543-93-6].** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and (1-chloro-2-methylpropan-2-yl)benzene (2.0 mmol) (reaction time: 48 h). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 172 mg (66%). Second run: 177 mg (68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.30 – 7.19 (m, 1H), 5.09 (s, 1H), 3.46 (d, *J* = 6.0 Hz, 2H), 1.94 (tt, *J* = 11.8, 3.3 Hz, 1H), 1.85 – 1.58 (m, 5H), 1.33 (s, 6H), 1.39 – 1.13 (m, 5H).



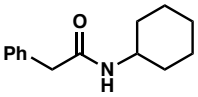
***N*-Cyclohexyloctanamide (26m, Figure 1.15) [42577-04-8].** The title compound was prepared according to the general procedure from *n*-octanamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 30% EtOAc/hexanes). White solid. First run: 194 mg (86%). Second run: 191 mg (85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (brs, 1H), 3.83 – 3.70 (m, 1H), 2.18 – 2.11 (m, 2H), 1.95 – 1.86 (m, 2H), 1.75 – 1.57 (m, 6H), 1.43 – 1.05 (m, 12H), 0.91 – 0.83 (m, 3H).



***N*-Cyclohexyl-1-adamantanecarboxamide (26n, Figure 1.15) [81311-58-2].** The title compound was prepared according to the general procedure from 1-adamantanecarboxamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes). Beige solid. First run: 220 mg (84%). Second run: 237 mg (91%).

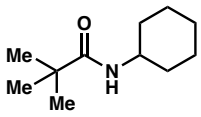
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (brs, 1H), 3.81 – 3.71 (m, 1H), 2.04 (s, 3H), 1.91 – 1.85 (m, 2H), 1.83 (d, *J* = 2.8 Hz, 6H), 1.77 – 1.65 (m, 9H), 1.43 – 1.32 (m, 2H), 1.22 – 1.05 (m, 3H).



***N*-Cyclohexyl-2-phenylacetamide (24o, Figure 1.15) [10264-08-1].** The title compound was prepared according to the general procedure from 2-phenylacetamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography

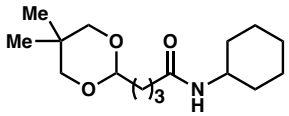
(hexanes → 20% EtOAc/hexanes). White solid. First run: 192 mg (88%). Second run: 201 mg (93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 5H), 5.23 (brs, 1H), 3.80 – 3.71 (m, 1H), 3.55 (s, 2H), 1.90 – 1.49 (m, 5H), 1.39 – 1.26 (m, 2H), 1.18 – 0.95 (m, 3H).



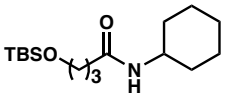
***N*-Cyclohexylpivalamide (26p, Figure 1.15) [4916-82-9].** The title compound was prepared according to the general procedure from pivalamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). Beige solid. First run: 165 mg (90%). Second run: 161 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (brs, 1H), 3.79 – 3.69 (m, 1H), 1.93 – 1.85 (m, 2H), 1.73 – 1.65 (m, 2H), 1.64 – 1.60 (m, 1H), 1.44 – 1.31 (m, 2H), 1.18 (s, 9H), 1.16 – 1.04 (m, 3H).



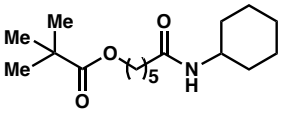
***N*-Cyclohexyl-4-(5,5-dimethyl-1,3-dioxan-2-yl)butanamide (26q, Figure 1.15).** The title compound was prepared according to the general procedure from 4-(5,5-dimethyl-1,3-dioxan-2-yl)butanamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 60% EtOAc/hexanes). Light-tan solid. First run: 251 mg (89%). Second run: 255 mg (90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (d, J = 9.1 Hz, 1H), 4.42 (t, J = 4.8 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.60 – 3.55 (m, 2H), 3.46 – 3.37 (m, 2H), 2.17 (t, J = 7.4 Hz, 2H), 1.93 – 1.54 (m, 9H), 1.40 – 1.28 (m, 2H), 1.22 – 1.03 (m, 3H), 1.17 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 102.0, 77.2, 47.9, 36.6, 33.8, 33.2, 30.1, 25.6, 24.8, 23.0, 21.8, 20.4; FT-IR (neat) 3254, 3074, 2932, 2855, 1630, 1550, 1473, 1448, 1396, 1363, 1176, 1133, 1112, 1090, 1026, 1012, 923, 870, 679 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{16}H_{29}NO_3$: 283.2, found: 283.3.



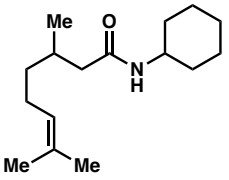
4-((*t*-Butyldimethylsilyl)oxy)-*N*-cyclohexylbutanamide (26r, Figure 1.15). The title compound was prepared according to the general procedure from 4-((*t*-butyldimethylsilyl)oxy)butanamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). Light-tan solid. First run: 245 mg (82%). Second run: 255 mg (85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (d, *J* = 8.1 Hz, 1H), 3.80 – 3.72 (m, 1H), 3.64 (t, *J* = 6.0 Hz, 2H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.95 – 1.78 (m, 4H), 1.74 – 1.65 (m, 2H), 1.64 – 1.57 (m, 1H), 1.42 – 1.31 (m, 2H), 1.21 – 1.04 (m, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 62.1, 48.0, 33.27, 33.25, 28.6, 26.0, 25.6, 24.9, 18.3, 5.3; FT-IR (neat) 3298, 3081, 2927, 2898, 2854, 1635, 1554, 1472, 1461, 1440, 1385, 1254, 1091, 1066, 991, 963, 879, 772, 723, 613 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{16}H_{33}NO_2Si$: 299.2, found: 299.3.



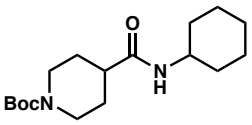
6-(Cyclohexylamino)-6-oxohexyl pivalate (26s, Figure 1.15). The title compound was prepared according to the general procedure from 6-amino-6-oxohexyl pivalate (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 50% EtOAc/hexanes). White solid. First run: 262 mg (88%). Second run: 263 mg (89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (brs, 1H), 4.03 (td, *J* = 6.6, 0.8 Hz, 2H), 3.79 – 3.70 (m, 1H), 2.19 – 2.10 (m, 2H), 1.94 – 1.78 (m, 4H), 1.74 – 1.56 (m, 5H), 1.44 – 1.26 (m, 4H), 1.22 – 1.01 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 171.7, 64.2, 48.1, 38.7, 36.9, 33.3, 28.4, 27.2, 25.6, 25.52, 25.47, 24.9; FT-IR (neat) 3291, 3075, 2930, 2898, 2854, 1728, 1638, 1541, 1480, 1451, 1398, 1363, 1284, 1151, 1039, 891 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{17}H_{31}NO_3$: 297.2, found: 297.3.

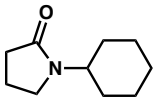


***N*-Cyclohexyl-3,7-dimethyloct-6-enamide (26t, Figure 1.15).** The title compound was prepared according to the general procedure from 3,7-dimethyloct-6-enamide (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). Light-tan solid. First run: 216 mg (86%). Second run: 222 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (d, J = 8.4 Hz, 1H), 5.11 – 5.06 (m, 1H), 3.83 – 3.73 (m, 1H), 2.16 (dd, J = 13.3, 5.7 Hz, 1H), 2.06 – 1.82 (m, 4H), 1.74 – 1.56 (m, 11H), 1.44 – 1.27 (m, 3H), 1.30 – 1.04 (m, 4H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 131.5, 124.4, 48.0, 44.8, 36.9, 33.3, 30.5, 25.7, 25.5, 25.4, 24.9, 19.5, 17.7; FT-IR (neat) 3292, 3079, 2929, 2853, 1634, 1546, 1446, 1376, 1359, 1308, 1250, 1153, 1101, 989, 891, 723, 626 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{16}H_{29}NO$: 251.2, found: 251.3.

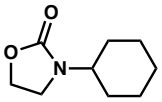


***t*-Butyl 4-(cyclohexylcarbamoyl)piperidine-1-carboxylate (26u, Figure 1.15).** The title compound was prepared according to the general procedure from *t*-butyl 4-carbamoylpiperidine-1-carboxylate (1.0 mmol) and 2-bromobutane (2.0 mmol). The product was purified by column chromatography (hexanes → 70% EtOAc/hexanes). Light-tan solid. First run: 243 mg (85%). Second run: 245 mg (85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (brs, 1H), 4.12 (brs, 2H), 3.79 – 3.70 (m, 1H), 2.72 (br s, 2H), 2.16 (tt, J = 11.6, 3.7 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.81 – 1.74 (m, 3H), 1.74 – 1.53 (m, 4H), 1.48 – 1.42 (m, 9H), 1.42 – 1.29 (m, 2H), 1.21 – 1.03 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 154.7, 79.6, 48.0, 43.5, 33.2, 28.7, 28.4, 25.5, 24.8; FT-IR (neat) 3281, 3072, 2972, 2928, 2877, 2858, 1683, 1634, 1544, 1432, 1365, 1282, 1216, 1177, 1126, 1078, 956, 942, 875, 761, 692 cm^{-1}; MS (ESI) *m/z* ($[M - C_4H_8 + H]^+$) calcd for $C_{11}H_{21}N_2O_3$: 229.2, found: 229.1.



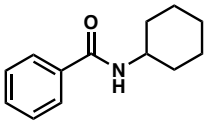
1-Cyclohexylpyrrolidin-2-one (29a, Figure 1.16) [6837-24-7]. The title compound was prepared according to the general procedure (except that no DMF was used; only CH_3CN (6.2 mL)) from 2-pyrrolidone (1.0 mmol) and bromocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 70% EtOAc/hexanes). Light-brown oil. First run: 149 mg (89%). Second run: 147 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 – 3.86 (m, 1H), 3.36 – 3.28 (m, 2H), 2.41 – 2.34 (m, 2H), 2.02 – 1.92 (m, 2H), 1.84 – 1.61 (m, 5H), 1.45 – 1.28 (m, 4H), 1.16 – 1.00 (m, 1H).



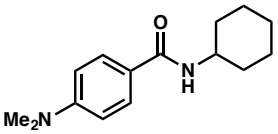
3-Cyclohexyloxazolidin-2-one (29b, Figure 1.16) [55390-61-9]. The title compound was prepared according to the general procedure (except that no DMF was used; only CH_3CN (6.2 mL)) from oxazolidin-2-one (1.0 mmol) and bromocyclohexane. The product was purified by column chromatography (hexanes → 70% EtOAc/hexanes). Light-brown oil. First run: 153 mg (91%). Second run: 150 mg (89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 – 4.25 (m, 2H), 3.72 – 3.63 (m, 1H), 3.57 – 3.46 (m, 2H), 1.87 – 1.74 (m, 4H), 1.72 – 1.62 (m, 1H), 1.45 – 1.28 (m, 4H), 1.17 – 1.01 (m, 1H).



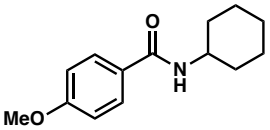
***N*-Cyclohexylbenzamide (31a, Figure 1.17) [1759-68-8].** The title compound was prepared according to the general procedure from benzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (10% EtOAc/hexanes → 30% EtOAc/hexanes). Beige solid. First run: 178 mg (88%). Second run: 177 mg (87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.73 (m, 2H), 7.51 – 7.46 (m, 1H), 7.45 – 7.40 (m, 2H), 5.95 (br s, 1H), 4.01 – 3.94 (m, 1H), 2.08 – 1.99 (m, 2H), 1.81 – 1.71 (m, 2H), 1.69 – 1.62 (m, 1H), 1.49 – 1.38 (m, 2H), 1.29 – 1.19 (m, 3H).



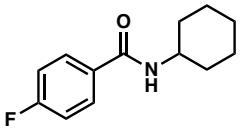
***N*-Cyclohexyl-4-(dimethylamino)benzamide (31b, Figure 1.17) [141557-50-8].** The title compound was prepared according to the general procedure from 4-(dimethylamino)benzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 209 mg (85%). Second run: 213 mg (86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 2H), 6.69 – 6.61 (m, 2H), 5.83 (d, *J* = 8.1 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.01 (s, 6H), 2.01 (dq, *J* = 12.1, 3.8 Hz, 2H), 1.79 – 1.59 (m, 3H), 1.48 – 1.36 (m, 2H), 1.27 – 1.14 (m, 3H).



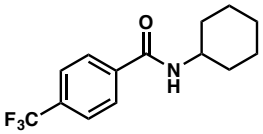
***N*-Cyclohexyl-4-methoxybenzamide (31c, Figure 1.17) [33739-91-2].** The title compound was prepared according to the general procedure from 4-methoxybenzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 40% EtOAc/hexanes). White solid. First run: 184 mg (79%). Second run: 175 mg (75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.67 (m, 2H), 6.96 – 6.86 (m, 2H), 5.91 (d, *J* = 8.1 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.84 (s, 3H), 2.07 – 1.98 (m, 2H), 1.80 – 1.60 (m, 3H), 1.48 – 1.36 (m, 2H), 1.29 – 1.14 (m, 3H).



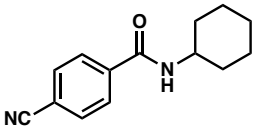
***N*-Cyclohexyl-4-fluorobenzamide (31d, Table 1.17) [2342-50-9].** The title compound was prepared according to the general procedure from 4-fluorobenzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 200 mg (91%). Second run: 200 mg (91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 2H), 7.15 – 7.05 (m, 2H), 5.93 (d, *J* = 7.9 Hz, 1H), 4.01 – 3.91 (m, 1H), 2.07 – 1.98 (m, 2H), 1.81 – 1.61 (m, 3H), 1.48 – 1.36 (m, 2H), 1.29 – 1.14 (m, 3H).



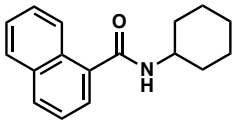
***N*-Cyclohexyl-4-(trifluoromethyl)benzamide (31e, Figure 1.17) [339094-67-6].** The title compound was prepared according to the general procedure from 4-(trifluoromethyl)benzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 197 mg (73%). Second run: 211 mg (78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 2H), 7.72 – 7.65 (m, 2H), 6.00 (d, *J* = 8.0 Hz, 1H), 4.03 – 3.93 (m, 1H), 2.09 – 2.00 (m, 2H), 1.82 – 1.72 (m, 2H), 1.72 – 1.62 (m, 1H), 1.50 – 1.37 (m, 2H), 1.32 – 1.11 (m, 3H).



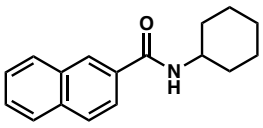
4-Cyano-*N*-cyclohexylbenzamide (31f, Figure 1.17) [167762-78-9]. The title compound was prepared according to the general procedure from 4-cyanobenzamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 40% EtOAc/hexanes). White solid. First run: 190 mg (83%). Second run: 179 mg (79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 2H), 7.76 – 7.69 (m, 2H), 6.01 (d, *J* = 8.1 Hz, 1H), 4.02 – 3.92 (m, 1H), 2.08 – 1.99 (m, 2H), 1.82 – 1.62 (m, 3H), 1.49 – 1.36 (m, 2H), 1.30 – 1.14 (m, 3H).



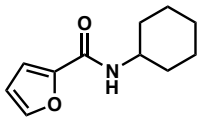
***N*-Cyclohexyl-1-naphthamide (31g, Table 1.17) [32255-83-7].** The title compound was prepared according to the general procedure from 1-naphthamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 239 mg (94%). Second run: 237 mg (94%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 – 8.24 (m, 1H), 7.93 – 7.82 (m, 2H), 7.62 – 7.40 (m, 4H), 5.87 (d, *J* = 8.3 Hz, 1H), 4.15 – 4.06 (m, 1H), 2.17 – 2.08 (m, 2H), 1.83 – 1.63 (m, 3H), 1.54 – 1.41 (m, 2H), 1.33 – 1.15 (m, 3H).



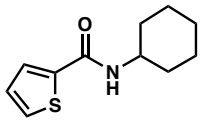
***N*-Cyclohexyl-2-naphthamide (31h, Figure 1.17) [82740-60-1].** The title compound was prepared according to the general procedure from 2-naphthamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 20% EtOAc/hexanes). White solid. First run: 203 mg (80%). Second run: 197 mg (78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H), 7.96 – 7.79 (m, 4H), 7.61 – 7.50 (m, 2H), 6.13 (d, *J* = 8.1 Hz, 1H), 4.10 – 4.00 (m, 1H), 2.13 – 2.04 (m, 2H), 1.84 – 1.64 (m, 3H), 1.52 – 1.40 (m, 2H), 1.35 – 1.17 (m, 3H).



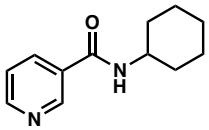
***N*-Cyclohexylfuran-2-carboxamide (31i, Figure 1.17) [10354-47-9].** The title compound was prepared according to the general procedure from furan-2-carboxamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 30% EtOAc/hexanes). Light-tan solid. First run: 165 mg (85%). Second run: 169 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.09 (dd, *J* = 3.5, 0.9 Hz, 1H), 6.49 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.22 (br s, 1H), 3.99 – 3.89 (m, 1H), 2.07 – 1.95 (m, 2H), 1.80 – 1.60 (m, 3H), 1.48 – 1.35 (m, 2H), 1.30 – 1.14 (m, 3H).



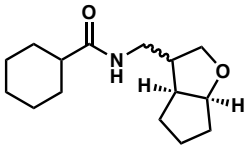
***N*-Cyclohexylthiophene-2-carboxamide (31j, Figure 1.17) [10354-42-4].** The title compound was prepared according to the general procedure from thiophene-2-carboxamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 30% EtOAc/hexanes). Light-tan solid. First run: 145 mg (69%). Second run: 154 mg (74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.40 (m, 2H), 7.06 (dd, *J* = 5.0, 3.7 Hz, 1H), 5.83 (br s, 1H), 4.01 – 3.88 (m, 1H), 2.07 – 1.98 (m, 2H), 1.81 – 1.59 (m, 3H), 1.48 – 1.35 (m, 2H), 1.29 – 1.13 (m, 3H).



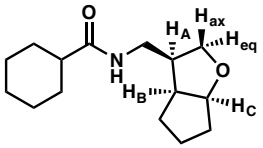
***N*-Cyclohexylnicotinamide (31k, Figure 1.17) [10354-56-0].** The title compound was prepared according to the general procedure from nicotinamide (1.0 mmol) and iodocyclohexane (2.0 mmol). The product was purified by column chromatography (hexanes → 100% EtOAc). White solid. First run: 167 mg (82%). Second run: 171 mg (84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.71 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.12 – 8.08 (m, 1H), 7.37 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 6.06 (d, *J* = 7.7 Hz, 1H), 4.04 –3.94 (m, 1H), 2.09 – 2.00 (m, 2H), 1.82 – 1.62 (m, 3H), 1.50 – 1.37 (m, 2H), 1.32 – 1.15 (m, 3H).

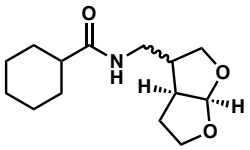


***N*-((Hexahydro-2*H*-cyclopenta[b]furan-3-yl)methyl)cyclohexanecarboxamide (38a, Figure 1.24).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and *trans*-1-(allyloxy)-2-bromocyclopentane (2.0 mmol). The ratio of diastereomers was determined by GC analysis of the unpurified reaction mixture. The product was isolated as a mixture of diastereomers by column chromatography (30% EtOAc/hexanes → 75% EtOAc/hexanes). Yellow solid. First run: 214 mg (85%, 71:29). Second run: 219 mg (87%, 72:28).

Major diastereomer. The major diastereomer could be purified by preparative HPLC (IA column, 5% IPA/hexanes).

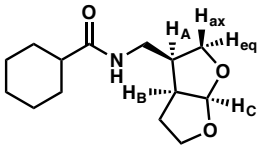


^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (brs, 1H), 4.50 (td, J = 5.8, 2.2 Hz, 1H), 3.84 (dd, J = 8.4, 7.1 Hz, 1H), 3.45 (t, J = 8.8 Hz, 1H), 3.38 – 3.25 (m, 2H), 2.59 – 2.46 (m, 2H), 2.05 (tt, J = 11.8, 3.5 Hz, 1H), 1.88 – 1.13 (m, 16H); 2D NOESY (500 MHz, $CDCl_3$) δ [2.51 (H_A), 3.84 (H_{eq})], [2.51 (H_A), 4.51 (H_C)], [2.56 (H_B), 4.51 (H_C)], [3.85 (H_{eq}), 2.51 (H_A)], [3.84 (H_{eq}), 4.51 (H_C)], [4.51 (H_C), 2.56 (H_B)], [4.51 (H_C), 3.85 (H_{eq})]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 86.3, 70.7, 45.54, 45.48, 43.1, 38.3, 34.2, 29.7, 26.1, 25.7, 25.4. FT-IR (neat) 3280, 3089, 2853, 1638, 1549, 1462, 1448, 1435, 1258, 1217, 1040 cm^{-1}; LRMS (LCMS ESI) *m/z* (M^+ + H) calcd for $C_{15}H_{26}NO_2$: 252.2, found: 252.2.

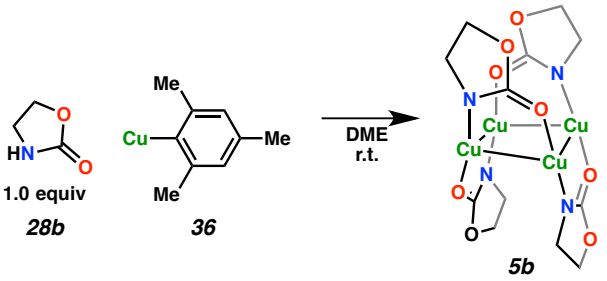


***N*-((Hexahydrofuro[2,3-*b*]furan-3-yl)methyl)cyclohexanecarboxamide (38b, Figure 1.25).** The title compound was prepared according to the general procedure from cyclohexanecarboxamide (1.0 mmol) and *trans*-2-(allyloxy)-3-bromotetrahydrofuran (2.0

mmol). The ratio of diastereomers was determined by ^{1}H NMR analysis of the unpurified reaction mixture. The product was isolated by column chromatography (75% EtOAc/hexanes → EtOAc). Yellow solid. First run: 234 mg (92%, 96:4). Second run: 217 mg (86%, 96:4).



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (d, J = 5.0 Hz, 1H), 5.49 (s, 1H), 3.95 (dd, J = 8.7, 7.3 Hz, 1H), 3.92 – 3.86 (m, 2H), 3.55 (dd, J = 11.2, 8.6 Hz, 1H), 3.47 – 3.39 (m, 1H), 3.36 – 3.29 (m, 1H), 2.87 – 2.80 (m, 1H), 2.58 – 2.48 (m, 1H), 2.06 (tt, J = 11.8, 3.4 Hz, 1H), 1.97 – 1.59 (m, 7H), 1.47 – 1.37 (m, 2H), 1.30 – 1.19 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 109.8, 70.9, 69.2, 45.5, 44.5, 42.5, 37.7, 29.72, 29.68, 25.7, 25.1; FT-IR (neat) 3323, 2977, 2883, 2852, 1644, 1541, 1448, 1442, 1021, 1004, 955 cm^{-1}; LRMS (LCMS ESI) *m/z* (M^+ + H) calcd for $C_{14}H_{24}NO_3$: 254.2, found: 254.2.



Complex 5b. In a nitrogen-filled glovebox, a 20-mL vial was charged with mesitylcopper(I) (183 mg, 1.00 mmol) and 2-oxazolidone (87.0 mg, 1.00 mmol, 1.00 equiv). 1,2-Dimethoxyethane (18.0 mL) was added, and the reaction mixture was stirred at room temperature for 4 h, resulting in a pale-yellow precipitate. The suspension was allowed to settle overnight, and then the solvent was decanted. The solid was washed with pentane (2x3 mL) and dried under vacuum, affording complex **4** as a pale-yellow solid (124 mg, 83% yield).

Anal. calcd for $C_{12}H_{16}Cu_4N_4O_8$: C, 24.08; H, 2.69; N, 9.36. Found: C, 24.23; H, 2.69; N, 9.33.

Preparation of X-ray quality crystals. In a nitrogen-filled glovebox, a 4-mL vial was charged with mesitylcopper(I) (37 mg, 0.20 mmol, 1.0 equiv) and 2-oxazolidone (17 mg, 0.20 mmol, 1.0 equiv). 1,2-Dimethoxyethane (4.0 mL) was added, and the reaction mixture was stirred at room temperature for 30 min. The resulting suspension was filtered through an acrodisc, and the filtrate was kept at room temperature for 24 h, furnishing pale-yellow crystals that were suitable for X-ray diffraction.

A crystal of $C_{12}H_{16}Cu_4N_4O_8$ was selected and mounted in a nylon loop in immersion oil. All measurements were made on a Bruker APEX-II with filtered Mo-K" radiation at a temperature of 100 K. Using Olex2,[38] the structure was solved with the ShelXS[39] structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization.

1.6 Notes and Citations

(1) For recent reviews, see (a) Ribas, X.; Güell, I. *Pure Appl. Chem.* **2014**, *86*, 345–360. (b) Sambiagio, C.; Marsden, S.P.; Blacker, A.J.; McGowan, P.C. *Chem. Soc. Rev.* **2014**, *43*, 3225–3550.

(2) Ullman, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174–2185.

(3) Ullman, F. *Chem. Ber.* **1903**, *34*, 2174–2185.

(4) Ullman, F.; Sponagel, P. *Chem. Ber.* **1905**, *38*, 2211–2212.

(5) Goldberg, I. *Chem. Ber.* **1906**, *39*, 1691–1692.

(6) Hurtley, W.R.H. *J. Chem. Soc.* **1929**, 1870–1873.

(7) (a) Marcoux, J.-F.; Doye, S.; Buchwald, S.L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540. (b) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S.L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660.

(8) (a) Kelkar, A.A.; Patil, N.M.; Chaudhari, R.V. *Tetrahedron Lett.* **2002**, *43*, 7143–7146. (b) Ouali, A.; Spindler, J.-F.; Jutand, A.; Taillefer *Adv. Synth. Catal.* **2007**, *349*, 1906–1916.

(9) (a) Strieter, E.R.; Blackmond, D.G.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, *127*, 4120–4121. (b) Strieter, E.R.; Bhayana, B.; Buchwald, S.L. *J. Am. Chem. Soc.* **2009**, *131*, 78–88.

(10) (a) Tye, J.W.; Weng, Z.; Johns, A.M.; Incarvito, C.D.; Hartwig, J.F. *J. Am. Chem. Soc.* **2008**, *130*, 9971–9983. (b) Giri, R.; Hartwig, J.F. *J. Am. Chem. Soc.* **2010**, *132*, 15860–15863. (c) Tye, J. W.; Weng, Z.; Giri, R.; Hartwig, J.F. *Angew. Chem. Int. Ed.* **2010**, *49*, 2185–2189. (d) Chen, C.; Weng, Z.; Hartwig, J.F.

Organometallics **2012**, *31*, 8031–8037. (e) Liu, X.; Zhang, S.-L.; Ding, Y. *Dalton Trans.* **2012**, *41*, 5897–5902.

(11) (a) Zhang, S.-L. Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546–4554. (b) Zhang, S.-L.; Ding, Y. *Organometallics* **2011**, *30*, 633–641. (c) Zhang, S.-L. *Dalton Trans.* **2012**, *41*, 1382–13840. (d) Zhang, S.-L.; Fan, H.-J. *Organometallics* **2013**, *32*, 4944–4951.

(12) Jones, G.O.; Liu, P.; Houk, K.N.; Buchwald, S.L. *J. Am. Chem. Soc.* **2010**, *132*, 6205–6213.

(13) There is some experimental evidence for radical intermediates in systems using highly specialized aryl halides: (a) Arai, S.; Yamagishi, T.; Ototake, S.; Hida, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 547–548. (b) Arai, S.; Hida, M.; Yamagishi, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 277–282.

(14) Annunziata, A.; Galli, C.; Marinelli, M.; Tullia, P. *Eur. J. Org. Chem.* **2001**, 1323−1329.

(15) Creutz, S.E.; Lotito, K.J.; Fu, G.C.; Peters, J.C. *Science* **2012**, *338*, 647–651.

(16) (a) Ziegler, D.T.; Choi, J.; Muñoz-Molina, J.M.; Bissember, A.C.; Peters, J.C.; Fu, G.C. *J. Am. Chem. Soc.* **2013**, *135*, 13107–13112. (b) Uyeda, C.; Tan, Y.; Fu, G.C.; Peters, J.C. *J. Am. Chem. Soc.* **2013**, *135*, 9548–9552. (c) Tan, Y.; Muñoz-Molina, J.M.; Fu, G.C.; Peters, J.C. *Chem. Sci.* **2014**, 2831–2835.

(17) Paradies, J. Palladium-Catalyzed Aromatic Carbon-Nitrogen Bond Formation. In *Metal-Catalyzed Cross-Coupling Reactions and More;* De Meijere, A.; Brase, S.; Oestreich, M., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2014, pp 995-1065.

(18) (a) Rao, K.S.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735–7754. (b) Fischer, C.; Koenig, B. *Beilstein J. Org. Chem.* **2011**, *7*, 59–74.

(19) Wang, C.; Xiao, J. Asymmetric Reductive Amination. In *Topics in Current Chemistry*; Li, W.; Zhang, X.; Springer Berlin Heidelberg, 2014; Vol. 343; pp 261–282.

(20) Hultzsch, K.C.; *Adv. Synth. Catal.* **2005**, *347*, 367–391.

(21) (a) Aydın, A.; Kaya, I.; *Electrochim. Acta.* **2012**, *65*, 104–114. (b) Tu, X.; Fu, X.; Jiang, Q.; Liu, Z.; Chen, G. *Dyes Pigm.* **2011**, *88*, 39–43. (c) Kozuka, M.; Tsuchida, T.; Mitani, M.; *Tetrahedron Lett.* **2005**, *46*, 4527–4530.

(22) Bissember, A.C.; Lundgren, R.J.; Creutz, S.E.; Peters, J.C. Fu, G.C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129–5133.

(23) Carey, J.S.; Laffan, D.; Thomson, C.; Williams, M.T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

(24) Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. *Nat. Prod. Rep.* **2004**, *21*, 15–61.

(25) Knight, A.S.; Zhou, E.Y.; Francis, M.B.; Zuckermann, R.N. *Adv. Mater.* **2015**, doi:10.1002/adma.201500275.

(26) For reviews, see (a) Lanigan, R.M.; Sheppard, T.D. *Eur. J. Org. Chem.* **2013**, 7453–7465. (b) González-Rosende, M.E.; Castillo, E.; Lasri, J.; *Sepúlveda*-Arques, J. *Prog. React. Kinet. Mech.* **2004**, *29*, 311–332.

(27) For a review, see Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L.J. *Chem. Rev.* **2015**, *115*, 2596–2697.

(28) Tran, B.L.; Li, B.; Driess, M.; Hartwig, J.F. *J. Am. Chem. Soc.* **2014**, *136*, 2555–2563.

(29) Aryl amides were observed to be particularly insoluble in CH_3CN.

(30) Pandey, G.; Rao, K.S.S.P.; Palit, D.K.; Mittal, J.P. *J. Org. Chem.* **1998**, *63*, 3968–3978.

(31) Hackmann, C.; Schäfer, H.J. *Tetrahedron* **1993**, *49*, 4559–4574.

(32) Isse, A.A.; Lin, C.Y.; Coote, M.L.; Gennaro, A. *J. Phys. Chem. B* **2011**, *115*, 678–684.

(33) Nemoto, H.; Zhong, W.; Kawamura, T.; Kamiya, M.; Nakano, Y.; Sakamoto, K. *Synlett* **2007**, 2343–2346.

(34) Bundesmann, M.W.; Coffey, S.B.; Wright, S.W. *Tetrahedron Lett.* **2010**, *51*, 3879–3882.

(35) The ester was synthesized from 4-(5,5-dimethyl-1,3-dioxan-2-yl)butanal (Alfa) using a literature method: Maki, B.E.; Scheidt, K.A. *Org. Lett.* **2008**, *10*, 4331–4334.

(36) Miranda, M.O.; Pietrangelo, A.; Hillmyer, M.A.; Tolman, W.B. *Green Chem.* **2012**, *14*, 490–494.

(37) Zhou, J.; Fu, G.C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530.

(38) Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339–341.

(39) Sheldrick, G.M. *Acta Cyrst. A* **2008**, *64*, 112–122.