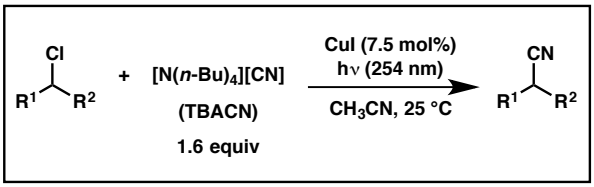
CHAPTER 2

Photoinduced, Copper-Catalyzed Carbon–Carbon Bond Formation: Cyanation of Unactivated Secondary Alkyl Chlorides at Room Temperature[†]



[†]This work was performed in collaboration with Tanvi Ratani and was partially adapted from the publication: Ratani, T.S.[‡]; Bachman, S.[‡]; Fu, G.C.; Peters, J.C. *J. Am. Chem. Soc.* **2015**, *137*, 13902–13907. [‡]Contributed equally

2.1 Introduction

Nitriles are a prevalent class of molecules in pharmaceuticals,[1] natural products,[2] and industrial processes.[3] The unique properties of the nitrile group include minimal steric demand, high polarization, and ability to act as a hydrogen bond acceptor and a hydroxyl or carboxyl isostere.[4] In addition, nitriles provide a versatile synthetic handle for transformations such as α-alkylation, [5] α-arylation, [6] conjugate addition, [7] cycloaddition,[8] hydration,[9] hydrolysis,[10] hydrogenation,[11] and cyclopropanation.[12]

With respect to the conversion of alkyl halides to the corresponding nitriles, S_N2-type conditions are generally employed for primary and secondary halides.[13] Radical cyanation of alkyl halides has been described but is limited to alkyl iodides.[14] While some transition metal-mediated cyanation reactions of benzylic alkyl chlorides have been developed,[15] there have been no similar advancements for unactivated alkyl halides.

Nucleophilic substitution of unactivated primary and secondary alkyl halides by cyanide typically requires the use of phase transfer reagents,[13a−f] cyanide-impregnated inorganic solid support systems,[13g−i] or the combination of elevated temperature and polar solvent.[13k−m] These conditions often result in competitive or even exclusive elimination of unactivated secondary alkyl halides.[13e, 13f, 13n] There are only limited examples of room temperature S_N2 reactions of unactivated secondary alkyl bromides and iodides,[13n] and there are virtually no examples of unactivated secondary alkyl chlorides undergoing the transformation at temperatures less than 75 °C.[13o]

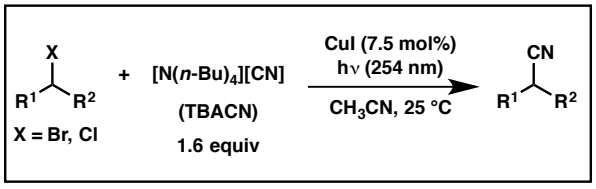
A potential alternative to direct nucleophilic substitution of unactivated secondary alkyl halides is the transition metal-catalyzed cross coupling of cyanide with alkyl

halides. Thus, we were interested in developing such a method for the cyanation of challenging S_N2 substrates, for example unactivated secondary alkyl chlorides.

We have recently reported photoinduced, copper-catalyzed cross-couplings of unactivated alkyl iodides and bromides with nitrogen nucleophiles.[16] We postulate that these and related processes involve one electron reduction of the electrophile by a photoexcited copper–nucleophile species.[16, 17] Achieving the desired cyanation reaction could therefore be dependent on the ability of a relevant copper−cyanide complex to undergo photoexcitation and subsequently reduce a secondary unactivated alkyl chloride.[18]

Prior to this study, we were uncertain as to whether either carbon nucleophiles or unactivated secondary alkyl chlorides would be appropriate coupling partners in these photoinduced, copper-catalyzed bond-forming processes; herein we report that the room temperature C−C coupling of cyanide and a variety of unactivated secondary alkyl halides can indeed be achieved (Scheme 2.1).

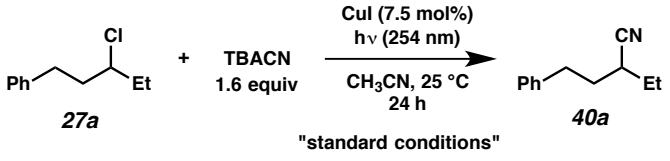
Scheme 2.1 Photoinduced, Cu-catalyzed cyanation of unactivated secondary alkyl halides



2.2 Results and Discussion

After optimization of various reaction parameters, cyanation of an unactivated secondary alkyl chloride (**27a**) proceeded in good yield using tetrabutylammonium cyanide (TBACN) as the cyanide source, CuI as the precatalyst, and 15-watt UVC compact fluorescent light bulbs[19] as the irradiation source (Table 2.1, entry 1).[20] This C−C coupling was efficient even at 0 °C (entry 2). By contrast, in the absence of CuI and light, efficient cyanation required heating to 92 °C (82% yield after 24 h).

Table 2.1 Effect of reaction parameters on photoinduced, Cu-catalyzed cyanation



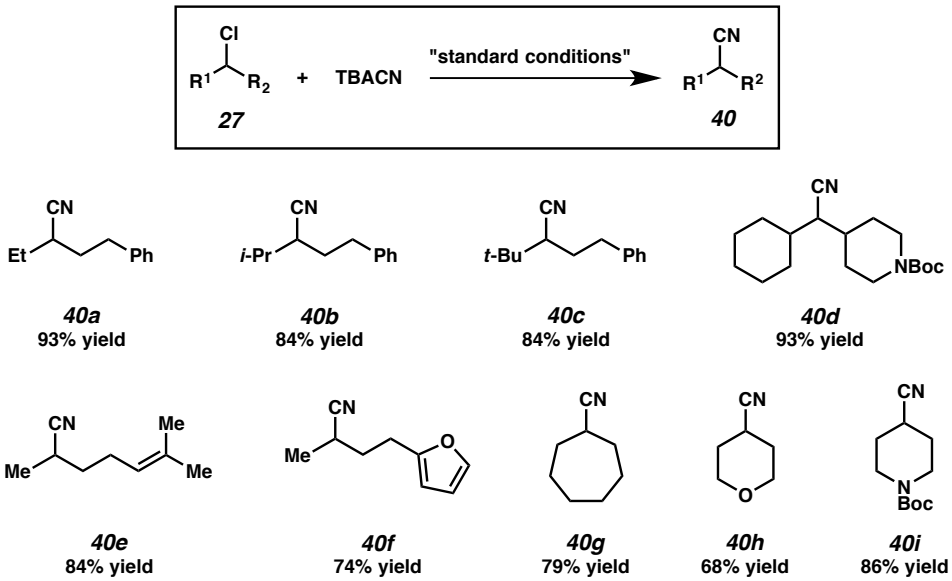
entry	change from the "standard conditions"	yield (%)[a]
1	none	88
2	0 °C (60 h)	85
3	no CuI	<1
4	no hν	<1
5	no CuI and no hν	<1
6	hν (photoreactor at 254 nm)	86
7	hν (photoreactor at 300 nm)	15
8	hν (photoreactor at 350 nm)	12
9	CuBr, instead of CuI	42
10	CuCl, instead of CuI	48
11	15 mol% CuCl, instead of CuI	66
12	Cu_2O, instead of CuI	32
13	$CuCl_2$, instead of CuI	44
14	$Cu(OTf)_2$, instead of CuI	42
15	Cu nanopowder (60-80 nm), instead of CuI	23
16	NaCN, instead of TBACN	25
17	KCN, instead of TBACN	27
18	$K_4[Fe(CN)_6]$, instead of TBACN	<1
19	CuI (5.0 mol%)	83
20	CuI (2.5 mol%)	78
21	CuI (1.0 mol%)	47
22	12 h	82
23	1.2, instead of 1.6, equiv TBACN	75
24	under an atmosphere of air, instead of nitrogen	32
25	0.1 equiv H_2O added	87

[a]All data are the average of two or more experiments. The yield was determined through GC analysis with the aid of a calibrated internal standard.

In the absence of light, copper, or both light and copper, formation of the nitrile (**40a**) was not observed (Table 1, entries 3−5), and longer wavelengths of light resulted in dramatically reduced reaction efficiency (entries 7 and 8). Substituting CuI by other copper(I) halides furnished the product in significantly lower yield (entries 9 and 10), but a moderate yield could be obtained when the amount of CuCl was increased to 15 mol% (entry 11). Copper(I) oxide, copper(II) sources, and copper nanopowder provide inferior results compared to CuI (entries 12−15). Metal cyanides were significantly less effective cyanide sources than TBACN (entries 16–18). The amount of CuI precatalyst could be reduced to as low as 2.5 mol% and still effect cross-coupling in good yield (entries 19, 20), and even 1 mol% CuI afforded a moderate yield of the nitrile (entry 21). Using a smaller excess of TBACN or shorter reaction time decreased the amount of product formation slightly (entries 22 and 23). The reaction is sensitive to air (entry 24) but not highly sensitive to water (entry 25).

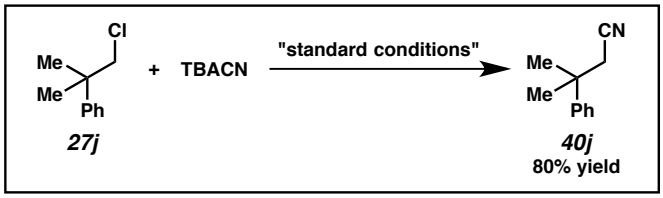
A variety of unactivated secondary alkyl chlorides can be converted to the corresponding nitriles at room temperature (Scheme 2.2). Both acyclic (**40a–f**) and cyclic (**40g–i**) alkyl chlorides are good coupling partners in this cyanation reaction. The reaction is tolerant of sterically demanding alkyl side chains, including isopropyl and *tert*-butyl groups at the α-position (**40b** and **40c**). Even when both alkyl substituents are α-branched, C−C bond formation occurs in good yield (**40d**). The reaction is compatible with various functional groups, including a Boc-protected amine (**40d** and **40i**), a trisubstituted olefin (**40e**), a furan (**40f**), and an ether (**40h**). This method is also effective for a gram-scale (1.3 g of product) synthesis of **40a** in 94% yield.

Scheme 2.2 Scope with respect to unactivated secondary alkyl chlorides

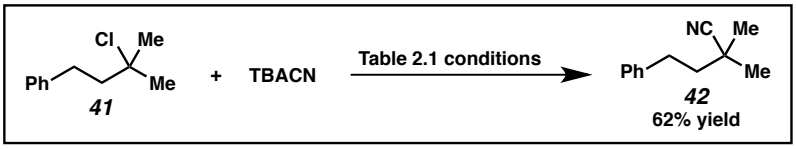


Under our standard reaction conditions, a particularly poor S_N2-substrate, neophyl chloride (**27j**), can be cross-coupled in good yield (Scheme 2.3), whereas under thermal conditions (DMF, 80 °C), <1% of the product was observed after 24 h. In addition, an unactivated tertiary alkyl chloride (**41**) can be converted to the nitrile in moderate yield, generating a quaternary center (Scheme 2.4). In a competition experiment, a tertiary alkyl chloride undergoes cyanation more rapidly than a secondary alkyl chloride (Scheme 2.5), which could be because the tertiary alkyl chloride has a greater propensity to undergo one electron reduction.[18]

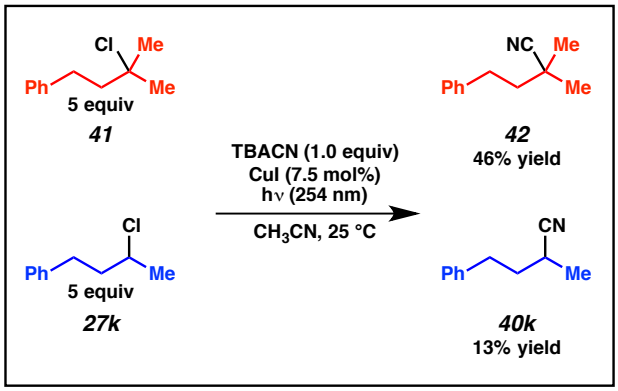
Scheme 2.3 Cyanation of neophyl chloride



Scheme 2.4 Cyanation of a tertiary chloride

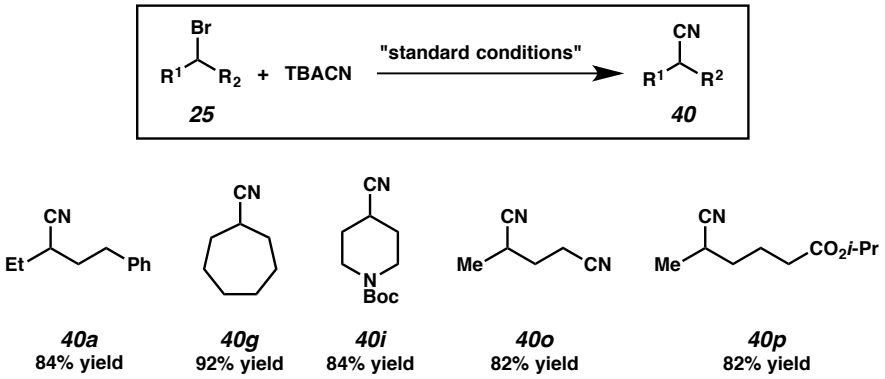


Scheme 2.5 Relative reactivity of a tertiary and secondary alkyl chloride

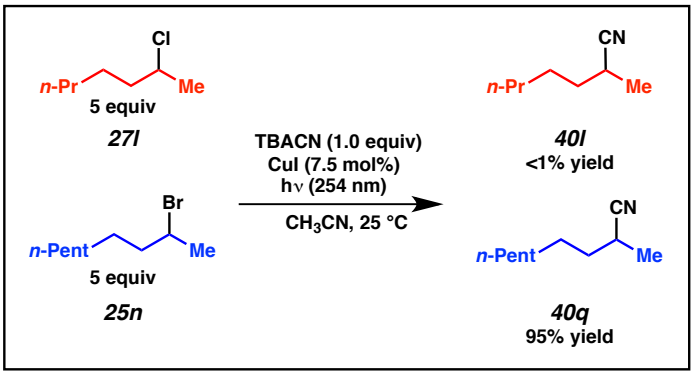


Without modification of the reaction conditions, a variety of unactivated secondary alkyl bromides are also effective in this photoinduced, copper-catalyzed cyanation reaction (Scheme 2.6). Although a background cyanation of alkyl bromides is observed in the absence of copper and light, the catalyzed process is at least five times faster. The reaction is compatible with both cyclic and acyclic alkyl bromides and tolerates a Boc-protected amine (**40i**), a nitrile (**40o**), and an ester (**40p**). An unactivated secondary alkyl bromide (**25n**) can be selectively coupled in the presence of a secondary alkyl chloride (**27l**, Scheme 2.7).

Scheme 2.6 Scope with respect to unactivated secondary alkyl bromides

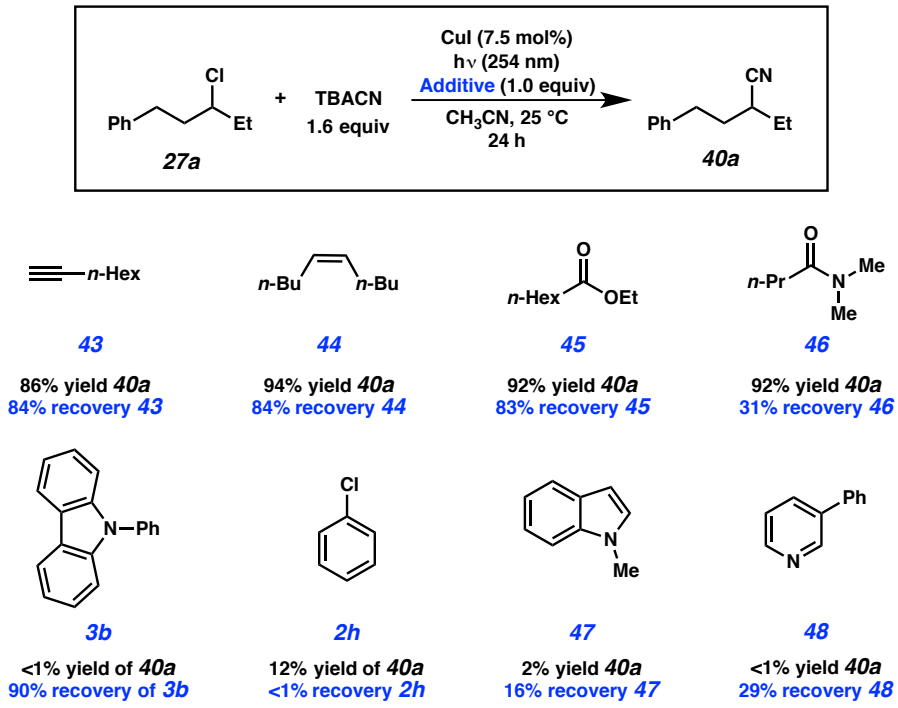


Scheme 2.7 Relative reactivity of a secondary alkyl chloride and bromide



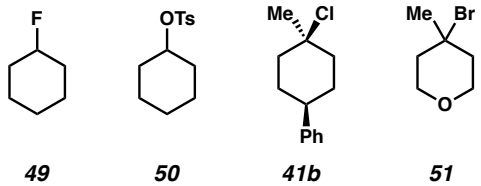
We further explored the functional group compatibility of this reaction with a robustness screen (Scheme 2.8).[21] This photoinduced, Cu-catalyzed cyanation is compatible with a terminal alkyne (**43**), an internal olefin (**44**), and an ester (**45**). A tertiary amide (**46**) was recovered in poor yield but did not inhibit product formation, whereas *N*-phenyl carbazole (**3b**) could be recovered in good yield but resulted in no observable C−C coupling. An aryl chloride (**2h**) and nitrogen-containing heterocycles **47** and **48** were not tolerated.

Scheme 2.8 Additional exploration of functional group tolerance



With respect to the limitations of this methodology, in preliminary studies, we were not able to couple a secondary alkyl fluoride (**49**) or tosylate (**50**) using these conditions (Figure 2.1). Although we have established the first example of a tertiary alkyl halide as a coupling partner in these photoinduced, Cu-catalyzed processes, this is not yet a general method. Attempts to couple other tertiary halides (e.g. **41b** and **51**) resulted in low conversion of the electrophile even at increased reaction times.

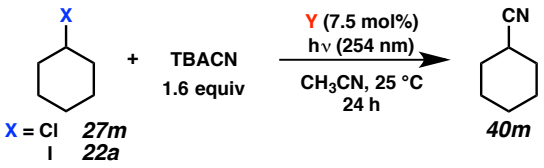
Figure 2.1 Examples of unsuccessful substrates



2.3 Mechanistic studies

During reaction optimization, it was observed that the use of CuI as a precatalyst resulted in significantly better yield than CuCl or CuBr (Table 2.1, entries 9−11). This effect is also pronounced when chlorocyclohexane (**27m**) is used as the electrophile (Table 2.2, entries 1 and 2). In addition, the combination of both catalytic CuCl and TBAI provides dramatically better results than iodide-free conditions (Table 2.2, entry 3).

Table 2.2 Increased reaction efficiency in the presence of an iodide source



entry	X	Y	yield (%)[a]
1	Cl	CuCl	34
2	Cl	CuI	82
3	Cl	CuCl + TBAI	78
4	I	CuI	57
5	Cl	TBAI	5
6	I	none	26
7	I	none (no light)	<1
8	Cl	$[Cu(CN)_2]TBA$	26
9	Cl	$[Cu(CN)_2]TBA$ + TBAI	76

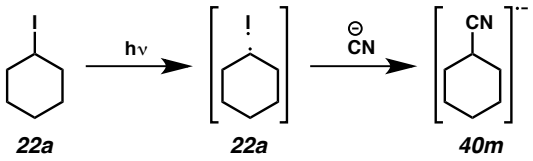
[a]The yield was determined through GC analysis with the aid of a calibrated internal standard (average of two runs).

One possible rationalization for this effect could be the *in situ* conversion of the alkyl chloride to a catalytic amount of the alkyl iodide, which undergoes cyanation more rapidly. When the analogous alkyl iodide (**22a**) is used as the substrate, a modest yield of the corresponding nitrile (**40m**) is observed (Table 2.2, entry 4), which could be due to unproductive consumption of the alkyl iodide in the presence of UV light.[22] Thus, generation of only a catalytic amount of the alkyl iodide, followed by rapid conversion to the nitrile, could be advantageous compared to cyanation of an alkyl iodide substrate. A

catalytic amount of tetrabutylammonium iodide, instead of CuI, does not result in significant product formation (entry 5), indicating that copper is still essential to the overall transformation.

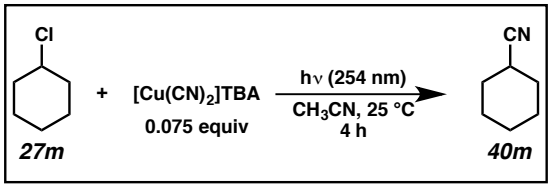
When iodocyclohexane (**22a**) is used as a substrate in the absence of copper, a small amount of the nitrile is generated, whereas no product formation is observed in the absence of both light and copper (Table 2.2, entries 6 and 7). This suggests that, if the alkyl iodide is generated *in situ*, conversion to the nitrile by S_N2 substitution is not a major pathway. However, direct photolysis of the alkyl iodide and recombination with cyanide could still be a minor contributor (Scheme 2.9).

Scheme 2.9 Possible contribution of a photoinduced, Cu-free pathway for cyanation of an in situ-generated alkyl iodide



In light of our working hypothesis that the photoexcitation of a relevant Cu−Nu complex is critical in these photoinduced, Cu-catalyzed coupling reactions, we also attempted the cyanation of chlorocyclohexane (**27m**) using catalytic $[Cu(CN)_2]TBA$[23] instead of CuI. Consistent with our previous observations, these iodide-free conditions result in a low yield of C−C coupling (Table 2.2, entry 8), but the combination of catalytic $[Cu(CN)_2]TBA$ and TBAI results in restored reaction efficiency (entry 9). Similarly, in the absence of additional TBACN, this copper−cyanide complex reacts stoichiometrically with chlorocyclohexane to generate the nitrile in low yield, whereas a 1:1 ratio of $[Cu(CN)_2]TBA$ and TBAI results in efficient cyanation (Scheme 2.10).

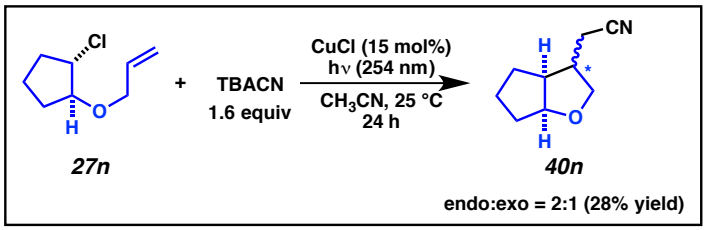
Scheme 2.10 Chemical competence of a copper–cyanide complex



Above conditions: 14% yield
0.075 equiv. TBAI added: 98% yield
(yields based on copper)

In order to gain insight into the possible intermediacy of alkyl radicals in this C−C coupling, we subjected alkyl chloride **27n** to our iodide-free reaction conditions (Scheme 2.11). While we are aware that iodide-free conditions are not optimal for generating high yields of product (Table 2.1, entry 1 vs. 11) this ensures that alkyl radical formation does not occur by halogen exchange followed by direct photolysis.[24] The alkyl chloride reacts to form exclusively the cyclized/coupled product with a diastereoselectivity consistent with that observed for radical cyclization of the corresponding alkyl bromide.[25]

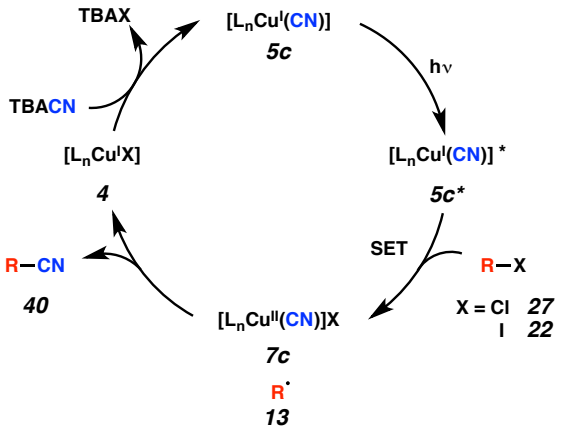
Scheme 2.11 Cyclization and coupling of an alkyl chloride bearing a pendant olefin



Our preliminary mechanistic observations are thus consistent with the intermediacy of alkyl radical intermediates and suggest the intermediacy of $[Cu(CN)_2]TBA$ and alkyl iodides. A possible mechanism for this photoinduced, copper-catalyzed cyanation is shown in Figure 2.2. The copper(I)−halide complex (**4**) reacts

with TBACN to yield a copper−cyanide complex (**5c**). Irradiation of **5c** and SET to the alkyl halide result in the formation of a copper(II) species (**7c**) and an alkyl radical. Reaction of the alkyl radical with the copper(II)−cyanide complex then generates the nitrile (**40**) and regenerates a copper(I)−halide complex (**4**).

Figure 2.2 Cyclization and coupling of an alkyl chloride bearing a pendant olefin



2.4 Conclusion

We have developed, to the best of our knowledge, the first method for the transition metal-catalyzed cyanation of unactivated secondary alkyl halides. This photoinduced, copper-catalyzed cyanation reaction uses a commercially available and inexpensive light source and proceeds efficiently at room temperature. Under a single set of conditions, unactivated secondary alkyl chlorides and bromides, including sterically hindered substrates, undergo C−C bond formation in generally good yield. For the first time, we have established that both carbon nucleophiles, as well as unactivated secondary alkyl chlorides, are appropriate coupling partners in photoinduced, copper-catalyzed bond forming processes. Initial mechanistic observations are consistent with the formation of an alkyl radical intermediate during the course of the reaction.

2.5 Experimental Procedures

2.5.1 General Information

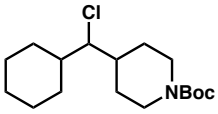
The following reagents were purchased and used as received: Copper(I) iodide (Aldrich; 99.999%), tetrabutylammonium cyanide (Aldrich; 95%), 4-chlorotetrahydro-*2H*-pyran (Acros), *tert*-butyl 4-bromopiperidine-1-carboxylate (Aldrich), (1-chloro-2-methylpropan-2-yl)benzene (Aldrich). CH_3CN was deoxygenated and dried by sparging with nitrogen followed by passage through an activated alumina column (S. G. Water) prior to use.

^{1}H and ^{13}C spectroscopic data were collected on a Varian 500 MHz spectrometer or a Varian 400 MHz spectrometer at ambient temperature. GC analyses were carried out on an Agilent 6890 series system with an HP-5 column (length 30 m, I.D. 0.25 mm). All photoreactions were carried out in oven-dried quartz test tubes or a quartz flask, under an inert atmosphere, with the use of 15W, 120V, UV Germicidal Compact Lamps (Norman Lamps, Inc.) and a Fantec 172 x 150 x 51 mm Dual Ball Bearing AC high speed fan (240 CFM).

2.5.2 Preparation of Materials

These procedures have not been optimized.

General Procedure for the Chlorination of Secondary Alcohols. To an oven-dried 500-mL round-bottom flask containing a stir bar was added dry CH_2Cl_2 (0.2 M) and the alcohol (1.00 equiv). The mixture was cooled to 0 °C in an ice bath, and PPh_3 (1.00 equiv) and NCS (1.00 equiv) were slowly added in turn. The round-bottom flask was then capped with a rubber septum and placed under a nitrogen atmosphere with the use of a needle attached to a vacuum manifold. The reaction was allowed to warm to room temperature as it remained in the water bath. After 5−8 hours, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The organic phase was separated, dried over anhydrous Na_2SO_4, and then concentrated carefully by rotary evaporator (careful concentration was important for volatile products). The product was purified by column chromatography (hexanes or Et_2O/hexanes).

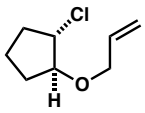


***tert*-Butyl 4-(chloro(cyclohexyl)methyl)piperidine-1-carboxylate (27d, Figure 2.2)**.

Cyclohexylmagnesium chloride (2.0 M in Et_2O; 23.5 mL, 46.9 mmol) was added dropwise to a solution of *tert*-butyl 4-formylpiperidine-1-carboxylate (10.0 g, 46.9 mmol) in THF (230 mL) at −78 °C (dry ice/acetone bath). The resulting solution was allowed to warm to room temperature while remaining in the acetone bath and stirring for 6 h. Next, the reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL), and the resulting mixture was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated by rotary evaporator. The residue was passed through a plug of silica gel (60% Et_2O/hexanes), and the resulting filtrate was concentrated by rotary evaporator and used in the next step without further purification.

The title compound was prepared according to the general procedure for chlorination of secondary alcohols, using the unpurified *tert*-butyl 4-

(cyclohexyl(hydroxy)methyl)piperidine-1-carboxylate. The product was purified by flash chromatography (5%→30% Et_2O/hexanes). Off-white solid (1.05 g, 7% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 – 4.12 (m, 2H), 3.58 (dd, 1H, *J* = 6.8, 5.5 Hz), 2.73 – 2.62 (m, 2H), 1.96 – 1.75 (m, 5H), 1.73 – 1.65 (m, 2H), 1.65 – 1.57 (m, 2H), 1.47 (s, 9H), 1.45 – 1.17 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 79.8, 74.7, 40.8, 39.9, 31.5, 28.8, 26.61, 26.60, 26.2; ATR-IR (neat) 2928, 2848, 1682, 1445, 1417, 1368, 1284, 1265, 1246, 1163, 1121, 773 cm^{-1}; HRMS (ESI) *m/z* $[M–(isobutylene)–(CO_2)+H]^+$ calcd for $C_{13}H_{23}ClNO_2$: 216.1519, found: 216.1504.

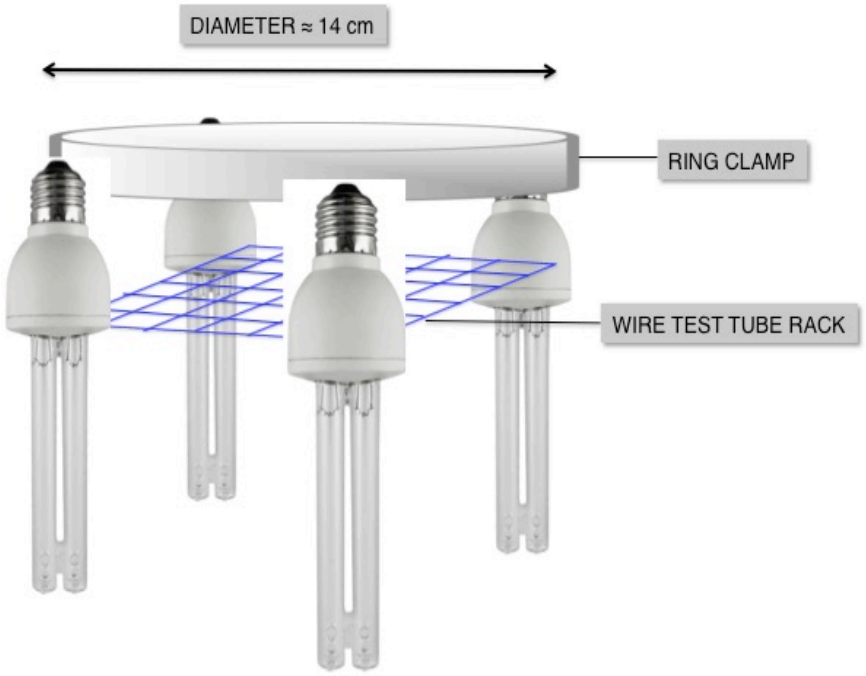


(1*S*,2*S*)-1-(allyloxy)-2-chlorocyclopentane (27n, Figure 2.12). This procedure was adapted from a literature procedure.[26] Cyclopentene (5.00 mL, 56.6 mmol) was added dropwise over 30 minutes to a suspension of *N*-chlorosuccinimide (7.60 g, 56.6 mmol) in dry CH_2Cl_2 (100 mL). The resulting suspension was stirred at room temperature for 2 h, and then allyl alcohol (7.70 mL, 113.2 mmol) was added dropwise by syringe pump over 2 h. The reaction mixture was stirred at room temperature for 6 h. The solvent was then removed by rotary evaporator, and the crude residue was poured into a separatory funnel containing H_2O (100 mL). The mixture was extracted with Et_2O (3 x 50 mL), and the combined organic phases were washed with water (50 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The product was purified by column chromatography (100% hexanes). Clear oil (695 mg, 4% yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddt, 1H, *J* = 17.2, 10.4, 5.6 Hz), 5.28 (dq, 1H, *J* = 17.2, 1.7 Hz), 5.21 – 5.16 (m, 1H), 4.22 – 4.17 (m, 1H), 4.08 – 4.01 (m, 2H), 4.00 – 3.95 (m, 1H), 2.27 – 2.06 (m, 2H), 1.93 – 1.72 (m, 3H), 1.70 – 1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 117.0, 87.2, 70.5, 63.1, 34.2, 29.9, 21.4; ATR-IR (neat) 3100, 2960, 2861, 1651, 1463, 1433, 1341, 1256, 1082, 1013, 922, 793, 702, 655, 560 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_8H_{13}ClO$: 160.1, found: 160.1.

2.5.3 Photoinduced, Copper-Catalyzed Cyanation Reactions

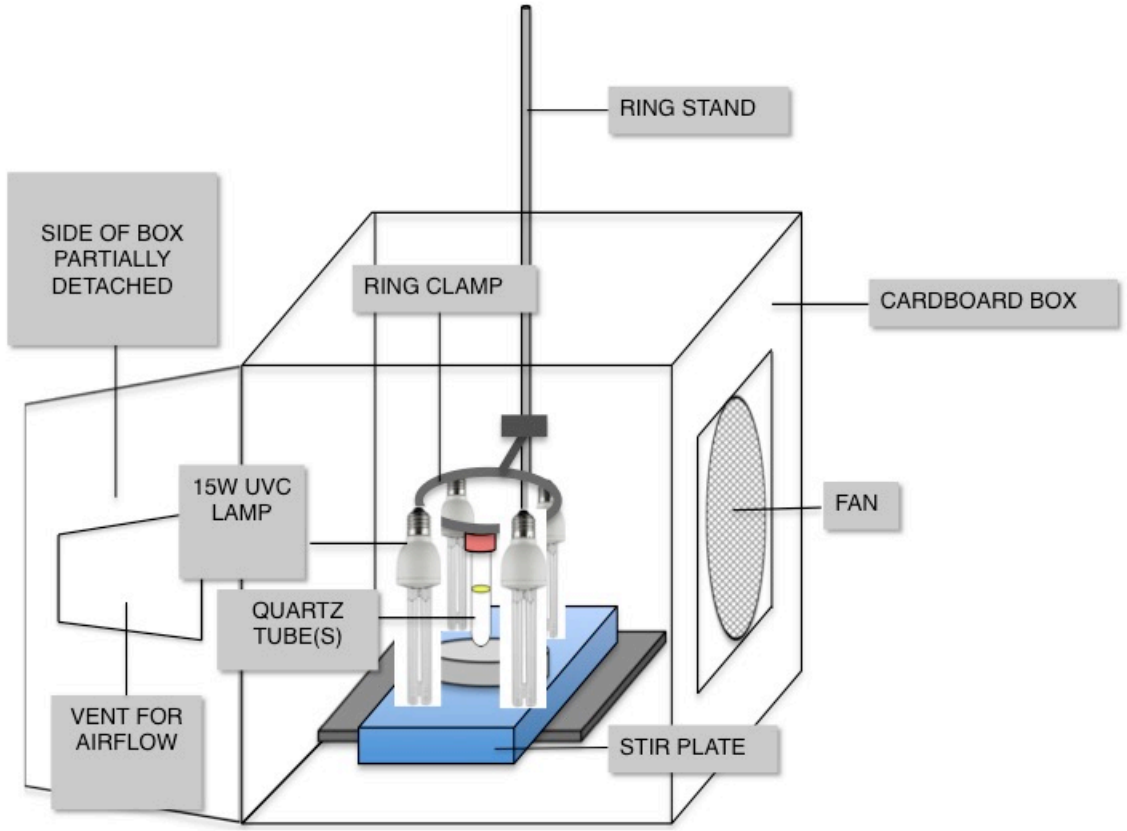
Four 15W, 120V UV germicidal CFL lamps were suspended from a ring clamp on a ring stand (Figure 2.13). The lamps were spaced approximately evenly around the circumference of the ring clamp with a diameter of ≈14 cm. In a second clamp below the ring clamp, the top of a wire test tube rack was placed interior to the lamps.

Figure 2.13 Placement of CFL lamps around a ring clamp



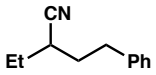
A stir plate covered in aluminum foil was placed underneath the lamps (Figure 2.14). A cardboard box lined with aluminum foil was placed over the ring stand, lamps, and stir plate. In one side of the cardboard box, a space was cut out, and a 172 x 150 x 51 mm high-speed (240 CFM) fan was fitted into this side of the box. In the side of the box directly opposite the fan, a vent was cut out. Photoreactions were carried out in quartz tubes or a quartz flask placed approximately in the center of the wire test tube rack, ensuring that the reaction vessels were within the line of airflow from the fan and did not directly touch the lamps.

Figure 2.14 Placement of cardboard box and fan relative to the CFL lamps



General Procedure. Inside a glovebox, an oven-dried 20-mL vial equipped with a stir bar was charged with TBACN (***Caution: Highly toxic!*** 601 mg, 2.24 mmol, 1.60 equiv) and capped with a PTFE-lined pierceable cap sealed with electrical tape. The vial was then removed from the glovebox, and MeCN (18.0 mL) was added via syringe. The mixture was vigorously stirred for 5 minutes, resulting in a colorless suspension. An oven-dried 20-mL quartz tube containing a stir bar was then charged with CuI (20.0 mg, 0.105 mmol, 0.0750 equiv), capped with a rubber septum, and sealed with electrical tape. The tube was evacuated and backfilled with nitrogen three times (through a needle attached to a vacuum manifold), and the TBACN suspension was added via syringe, followed by the electrophile (1.40 mmol, 1.00 equiv) via microsyringe (if the electrophile is a solid, then it was added immediately after the addition of CuI). The reaction mixture was stirred vigorously for one minute. The quartz tube was then removed from the manifold, and the resulting mixture was then stirred vigorously and irradiated in the

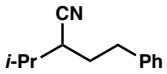
center of four, 15W UVC compact fluorescent light bulbs at room temperature for 24 h. Then, the reaction mixture was transferred to a 100-mL round-bottom flask and concentrated using a rotary evaporator in a well-ventilated fume hood. The residue was purified by column chromatography.



2-Ethyl-4-phenylbutanenitrile (40a, Figure 2.2) [1126479-77-3]. The title compound was prepared according to the General Procedure from (3-chloropentyl)benzene (258 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (5→10% EtOAc/hexanes). Tan oil. First run: 223 mg (92% yield). Second run: 227 mg (94% yield).

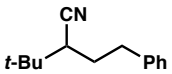
Gram-scale reaction. In a glove box, a 200-mL quartz flask was charged with TBACN (3.44 g, 12.8 mmol, 1.60 equiv), and a stir bar was added. The flask was capped with a rubber septum and sealed with electrical tape and then removed from the glove box. A separate 250-mL flask (borosilicate glass) was then charged with CuI (114 mg, 0.600 mmol, 0.0750 equiv), and acetonitrile (110 mL) and a stir bar were added. The CuI/acetonitrile solution was vigorously stirred for 1 minute under a nitrogen atmosphere, after which the homogeneous solution was cannula transferred to the quartz flask containing TBACN. Then, the alkyl chloride (1.50 mL, 8.00 mmol, 1.00 equiv) was added via syringe. The reaction mixture was irradiated for 24 h using the same irradiation set-up as described above. Then, the stir bar was removed, and the reaction mixture was concentrated using a rotary evaporator in a well-ventilated fume hood. The product was purified by column chromatography on silica gel (10→20% Et_2O/hexanes). Tan oil. 1.30 g, 94% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.26 – 7.19 (m, 3H), 2.91 (ddd, 1H, *J* = 14.2, 9.1, 5.2 Hz), 2.75 (ddd, 1H, *J* = 13.8, 8.9, 7.6 Hz), 2.49 – 2.43 (m, 1H), 2.01 – 1.92 (m, 1H), 1.90 – 1.82 (m, 1H), 1.70 – 1.63 (m, 2H), 1.09 (t, 3H, *J* = 7.4 Hz).

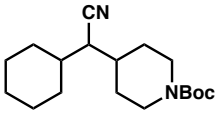


2-Isopropyl-4-phenylbutanenitrile (40b, Figure 2.2). The title compound was prepared according to the General Procedure from (3-chloro-4-methylpentyl)benzene (280 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (5→10% EtOAc/hexanes). Tan oil. First run: 220 mg (84% yield). Second run: 222 mg (85% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 7.25 – 7.19 (m, 3H), 2.92 (ddd, 1H, *J* = 14.1, 9.2, 5.0 Hz), 2.71 (ddd, 1H, *J* = 13.8, 9.0, 7.6 Hz), 2.40 (dt, 1H, *J* = 10.4, 5.0 Hz), 1.96 (dddd, 1H, *J* = 13.9, 10.7, 9.0, 5.0 Hz), 1.89 – 1.78 (m, 2H), 1.08 – 1.02 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 129.0, 128.8, 126.7, 121.3, 38.8, 33.9, 32.2, 30.4, 21.3, 19.0; ATR-IR (neat) 3028, 2964, 2932, 2900, 2874, 2236, 1603, 1497, 1455, 1391, 1373, 751, 701 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{13}H_{17}N$: 187.1, found 187.2.

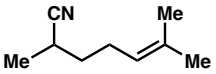


3,3-Dimethyl-2-phenethylbutanenitrile (40c, Figure 2.2). The title compound was prepared according to the General Procedure from (3-chloro-4,4-dimethylpentyl)benzene (95.0 μL, 0.440 mmol) as the electrophile. The product was purified by column chromatography on silica gel (hexanes→10% Et_2O/hexanes). Yellow oil. First run: 75.0 mg (85% yield). Second run: 74.1 mg (84% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.25 – 7.20 (m, 3H), 3.01 (ddd, 1H, *J* = 13.8, 8.9, 4.9 Hz), 2.67 (dt, 1H, *J* = 13.8, 8.5 Hz), 2.25 (dd, 1H, *J* = 11.6, 4.3 Hz), 1.92 – 1.79 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 129.0, 128.8, 126.7, 121.6, 43.8, 34.5, 33.3, 29.5, 27.8; ATR-IR (neat) 3028, 2963, 2938, 2875, 2233, 1602, 1498, 1488, 1472, 1463, 1456, 1399, 1375, 1368, 1317, 1233, 1030, 770, 757, 701 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_{14}H_{19}N$: 201.2, found 201.2.



***t*-Butyl 4-(cyano(cyclohexyl)methyl)piperidine-1-carboxylate (40d, Figure 2.2)**. The title compound was prepared according to the General Procedure from tert-butyl 4-(chloro(cyclohexyl)methyl)piperidine-1-carboxylate (442 mg, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (20→60% Et_2O/hexanes). Off-white solid. First run: 392 mg (91% yield). Second run: 406 mg (95% yield).

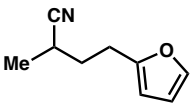
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 – 4.06 (m, 2H), 2.74 – 2.61 (m, 2H), 2.22 (t, 1H, J = 7.0 Hz), 1.91 – 1.84 (m, 2H), 1.83 – 1.72 (m, 3H), 1.72 – 1.56 (m, 4H), 1.45 (s, 9H), 1.36 – 1.10 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 120.3, 80.0, 44.9, 36.0, 35.0, 32.0, 30.7, 29.8, 26.4, 26.3, 26.1; ATR-IR (neat) 2930, 2923, 2855, 2236, 1692, 1452, 1431, 1365, 1285, 1235, 1179, 1135 cm^{-1}; HRMS (ESI) *m/z* $[M–(isobutylene)–(CO_2)+H]^+$ calcd for $C_{13}H_{23}N_2$: 207.1861, found: 207.1848.



2,6-Dimethylhept-5-enenitrile (40e, Figure 2.2) [54088-65-2].

The title compound was prepared according to the General Procedure from 6-chloro-2-methylhept-2-ene (205 mg, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (4% Et_2O/hexanes). Clear oil. First run: 161 mg (84% yield). Second run: 164 mg (85% yield).

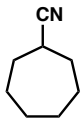
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 – 5.02 (m, 1H), 2.67 – 2.55 (m, 1H), 2.23 – 2.11 (m, 2H), 1.72 – 1.62 (m, 7H), 1.59 – 1.49 (m, 1H), 1.33 – 1.29 (m, 3H).



4-(Furan-2-yl)-2-methylbutanenitrile (40f, Figure 2.2) [71649-14-4]. The title compound was prepared according to the General Procedure from 2-(3-chlorobutyl)furan (221 mg, 1.40 mmol) as the electrophile. The product was purified by column

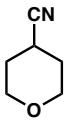
chromatography on silica gel (10% Et_2O/hexanes). Yellow oil. First run: 160 mg (77% yield). Second run: 148 mg (71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.30 (m, 1H), 6.31 – 6.27 (m, 1H), 6.08 – 6.04 (m, 1H), 2.92 – 2.75 (m, 2H), 2.67 – 2.56 (m, 1H), 2.01 – 1.85 (m, 2H), 1.36 – 1.31 (m, 3H).



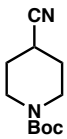
Cycloheptanecarbonitrile (40g, Figure 2.2) [32730-85-1]. The title compound was prepared according to the General Procedure from chlorocycloheptane (193 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (10→20% EtOAc/hexanes). Clear oil. First run: 138 mg (80% yield). Second run: 135 mg (78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 (tt, 1H, J = 7.9, 4.6 Hz), 1.96 – 1.82 (m, 4H), 1.80 – 1.70 (m, 2H), 1.67 – 1.53 (m, 6H).



Tetrahydro-2*H*-pyran-4-carbonitrile (40h, Figure 2.2) [4295-99-2]. The title compound was prepared according to the General Procedure from 4-chlorotetrahydro-2*H*-pyran (152 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (10→50% EtOAc/hexanes). Tan oil. First run: 103 mg (66% yield). Second run: 111 mg (71% yield).

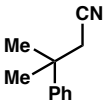
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 – 3.85 (m, 2H), 3.62 – 3.56 (m, 2H), 2.86 (tt, 1H, J = 8.2, 4.3 Hz), 1.96 – 1.90 (m, 2H), 1.89 – 1.82 (m, 2H).



***t*-Butyl 4-cyanopiperidine-1-carboxylate (40i, Figure 2.2) [91419-52-2]**. The title compound was prepared according to the General Procedure from *tert*-butyl 4-

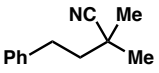
chloropiperidine-1-carboxylate (277 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (40→70% Et_2O/hexanes). Off-white solid. First run: 262 mg (89% yield). Second run: 248 mg (84% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 – 3.60 (m, 2H), 3.37 – 3.29 (m, 2H), 2.83 – 2.76 (m, 1H), 1.91 – 1.83 (m, 2H), 1.82 – 1.74 (m, 2H), 1.47 – 1.43 (m, 9H).



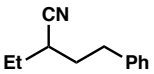
3-Methyl-3-phenylbutanenitrile (40j, Figure 2.3) [17684-33-2]. The title compound was prepared according to the General Procedure from (1-chloro-2-methylpropan-2-yl)benzene (226 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (10→20% EtOAc/hexanes). Tan oil. First run: 184 mg (83% yield). Second run: 174 mg (78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.28 – 7.24 (m, 1H), 2.62 (s, 2H), 1.52 (s, 6H).



2,2-Dimethyl-4-phenylbutanenitrile (42, Figure 2.4) [75490-38-9]. The title compound was prepared according to the General Procedure from (3-chloro-3-methylbutyl)benzene (256 mg, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (hexanes→10% Et_2O/hexanes). Clear oil. First run: 149 mg (61% yield). Second run: 153 mg (63% yield).

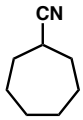
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.25 – 7.18 (m, 3H), 2.85 – 2.76 (m, 2H), 1.88 – 1.78 (m, 2H), 1.42 (s, 6H).



2-Ethyl-4-phenylbutanenitrile (40a, Figure 2.6) [1126479-77-3]. The title compound was prepared according to the General Procedure from (3-bromopentyl)benzene (259 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on

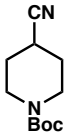
silica gel (10→20% Et_2O/hexanes). Tan oil. First run: 202 mg (83% yield). Second run: 205 mg (84% yield).

The ^{1}HNMR spectrum of the product was identical to that of **40a**, Figure 2.2.



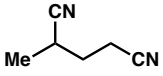
Cycloheptanecarbonitrile (40g, Figure 2.6) [32730-85-1]. The title compound was prepared according to the General Procedure from bromocycloheptane (208 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (20→40% Et_2O/hexanes). Yellow oil. First run: 157 mg (91% yield). Second run: 160 mg (93% yield).

The ^{1}HNMR spectrum of the product was identical to that of **40g**, Figure 2.2.



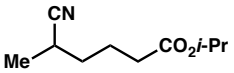
***t*-Butyl 4-cyanopiperidine-1-carboxylate (40i, Figure 2.6) [91419-52-2]**. The title compound was prepared according to the General Procedure from *tert*-butyl 4-bromopiperidine-1-carboxylate (276 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (40→80% Et_2O/hexanes). Off-white solid. First run: 242 mg (82% yield). Second run: 250 mg (85% yield).

The ^{1}HNMR spectrum of the product was identical to that of **40i**, Figure 2.2.



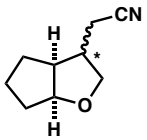
2-Methylpentanedinitrile (40o, Figure 2.6) [4553-62-2]. The title compound was prepared according to the General Procedure from 4-bromopentanenitrile (162 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (40→80% Et_2O/hexanes). Yellow oil. First run: 124 mg (82% yield). Second run: 122 mg (81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 – 2.79 (m, 1H), 2.65 – 2.51 (m, 2H), 2.02 – 1.91 (m, 2H), 1.42 – 1.39 (m, 3H).



Isopropyl 5-cyanohexanoate (40p, Figure 2.6). The title compound was prepared according to the General Procedure from isopropyl 5-bromohexanoate (237 μL, 1.40 mmol) as the electrophile. The product was purified by column chromatography on silica gel (20→60% Et_2O/hexanes). Yellow oil. First run: 211 mg (82% yield). Second run: 208 mg (81% yield).

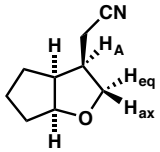
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 – 4.96 (m, 1H), 2.66 – 2.58 (m, 1H), 2.32 (t, 2H, J = 7.2 Hz), 1.89 – 1.70 (m, 2H), 1.69 – 1.55 (m, 2H), 1.34 – 1.31 (m, 3H), 1.23 (d, 6H, J = 6.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 122.8, 68.0, 34.0, 33.4, 25.5, 22.5, 22.0, 18.0; ATR-IR (neat) 2982, 2940, 2878, 2239, 1729, 1457, 1420, 1375, 1340, 1294, 1274, 1253, 1181, 1146, 1110 cm^{-1}; MS (EI) *m/z* $[M - (C_3H_7O)]^+$ calcd for $C_7H_{10}NO$: 124.1, found: 124.1.



2-((3a*S*,6a*S*)-Hexahydro-2*H*-cyclopenta[*b*]furan-3-yl)acetonitrile (40n, Figure 2.12). In an N_2-atmosphere glovebox, a 20-mL vial was charged with TBACN (266 mg, 0.991 mmol) and a stir bar. To this vial was added 8.3 mL of MeCN, and the solution was stirred vigorously for 5 minutes. Next, CuCl (9.33 mg) was weighed into an oven-dried 20-mL quartz test tube, and the TBACN solution was added to the tube. To this suspension was added trans-1-(allyloxy)-2-chlorocyclopentane (100 mg, 0.622 mmol), and the tube was capped with a rubber septum and sealed with electrical tape. The solution was stirred for another 3 minutes, and was then brought out of the glovebox and irradiated in the center of four, 15 watt UVC compact fluorescent light bulbs at room temperature` for 24 h. 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 (5% Et_2O/hexanes→Et_2O). Clear liquid. First run: 25 mg (27%, 2.3:1). Second run: 28 mg (30%, 2.1:1).

Major diastereomer. The major diastereomer could be purified by preparative HPLC (ZORBAX RX-SIL column, 9.4 x 250 mm, 20% EtOAc/hexanes).



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (td, 1H, J = 5.8, 2.5 Hz), 3.97 – 3.89 (m, 1H), 3.48 (t, 1H, J = 8.3 Hz), 2.75 – 2.62 (m, 2H), 2.46 – 2.33 (m, 2H), 1.87 – 1.58 (m, 5H), 1.53 – 1.41 (m, 1H); 2D NOESY (400 MHz, $CDCl_3$) δ [4.55 (H_C), 3.91 (H_{eq})], [4.55 (H_C), 2.68 (H_A/H_B)], [3.91 (H_{eq}), 4.55 (H_C)], [3.91 (H_{eq}), 2.68 (H_A/H_B)], [2.68 (H_A/H_B), 3.91 (H_{eq})], [2.68 (H_A/H_B), 4.55 (H_C)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.9, 86.5, 71.5, 46.1, 39.6, 34.2, 26.2, 25.7, 16.7; ATR-IR (neat) 2955, 2869, 2246, 1483, 1468, 1451, 1426, 1339, 1307, 1261, 1205, 1154, 1080, 1043, 960, 950, 922, 901, 806, 649 cm^{-1}; MS (EI) *m/z* (M^+) calcd for $C_9H_{13}NO$: 151.1, found: 151.1.

1.6 Notes and Citations

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