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Halogen- and *N*-Haloimide-Promoted Homo- and Heterocoupling of α-(*N*-Carbamoyl)alkylcuprates and α-(Alkoxy)alkylcuprates

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Abstract: Both homo- and mixed lithium di-α-(heteroatom)-alkylcuprates readily dimerize upon addition of halogens (e.g., I_2, Br_2) or *N*-halosuccinimides to afford the coupled products in excellent yields. Higher yields result when the requisite α-(heteroatom)alkyllithium reagents are generated via deprotonation rather than by transmetalation of the corresponding stannanes. Mixed lithium dialkyl- or alkyl(aryl)cuprate reagents containing one α-(heteroatom)alkyl ligand and one simple alkyl or aryl ligand give significantly lower yields of coupled product. Low enantioselectivity has been achieved in the oxidative coupling of lithium (*n*-Bu)(2-pyrrolidinyl)cuprate.

The oxidative coupling of lithium dialkylcuprates was first reported by Whitesides[1] over 30 years ago and reexamined by Bertz,[2] who suggested that product distributions in the couplings of unsymmetrical lithium dialkylcuprates could be related to proposed cuprate structures. Although many oxidants have been examined, dioxygen and nitrobenzenes are the most frequently employed and effective oxidants.[3] In Bertz's study, the combined yields of coupled products were significantly higher with CuI (80−90%) than with CuCN (64−77%); a result confirmed by subsequent applications.[4] Homocoupling products have been observed as byproducts in the reactions of scalemic acyclic α-(alkoxy)alkylcuprates[5a] prepared via a tin−lithium−copper transmetalation cascade but not with the corresponding cyclic[5b] analogues. Several studies have explored the reaction for the *N*-arylation or *N*-alkylation of amines and developed new oxidant combinations that significantly improved chemical yields for these amidocuprate reagents.[6] The biaryl coupling and its asymmetric variants developed by Lipshutz[7] and extended by Schreiber[8] are more effective with CuCN. They remain the most useful application of the reaction to date. Recently, aryl nitriles have been prepared in modest yields by the oxidative decomposition of arylcyanocuprates.[9] Little mechanistic work[10] has been done on these oxidative couplings, and the observations noted above remain to be accounted for within a coherent mechanistic picture. We now report a highly efficient oxidative coupling of homo and mixed α-(heteroatom)alkylcuprates[11] effected by halogens or *N*-halosuccinimides. The reaction provides a rapid entry to vicinal diamines[12] and bis-protected amino alcohols[13] and sheds new insights into mechanistic aspects of these oxidative couplings. This rapid entry to vicinal diamines[12] is attractive given the synthetic utility of scalemic vicinal diamines with C_2 symmetry[12b] in asymmetric synthesis. Synthetic routes to these scalemic vicinal diamines are often long and tedious, and even a rapid synthesis of the racemic vicinal diamines would provide convenient opportunities for chemical resolution. Intriguing hints in the literature[1,5a] suggesting that some of these oxidative couplings could proceed with retention of configuration about a stereogenic C−Cu bond indicated potential opportunities employing our scalemic α-(*N*-carbamoyl)alkylcuprate chemistry.[14]

During our development of α-(*N*-carbamoyl)alkylcuprate chemistry we frequently encountered minor amounts of homocoupling dimers from pyrrolidinylcuprates. Early efforts to prepare these dimers from lithium dialkylcuprates (i.e., $R_2CuLi{\cdot}LiCN$) and dioxygen gave modest yields of the dimer from the *N*-Boc-*N*,*N*-dimethylamine-derived cuprate (46%) and complicated reaction mixtures from the *N*-Boc-2-pyrrolidinylcuprate.[15] Subsequently, in a study examining the palladium-promoted arylation of α-lithiocarbamates, we explored the role of copper by utilizing stoichiometric amounts of the α-(*N*-carbamoyl)-alkylcuprate reagent.[16] Under these conditions, the major product proved to be the pyrrolidine dimer **1** (eq 1). Considering RI (R = *N*-Boc-2-pyrrolidinyl) as a possible intermediate in the transformation, the cuprate reagent was treated with I_2 and afforded **1** in high yield. Subsequent experimentation revealed that nearly quantitative

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(3) Oxidative coupling of a variety of lithium dialkylcuprates has been achieved with dioxygen, nitrobenzene, *o*-, *m*-, and *p*-dinitrobenzene, 2,4-dinitrobenzenesulfonyl chloride, 2,4-dinitrobenzene-1-fluorobenzene, lithium 2,4-dinitrobenzoate, 1,1′-diheptyl-4,4′bipyridinium dibromide, iron(III) chloride, iodine, 2,4,6-tri-*tert*-butylnitrobenzene, or tris(4-bromophenyl)aminium hexachloroantimonate (see ref 3) and of amidocuprates with dioxygen/*o*-nitrobenzene (20 mol %), $Cu(NO_3)_2/O_2$, $CuCl_2$, RuO_2, $VOCl_3Me_3SiOOSiMe_3$, or copper(II) 2-ethylhexanoate (see ref 6).

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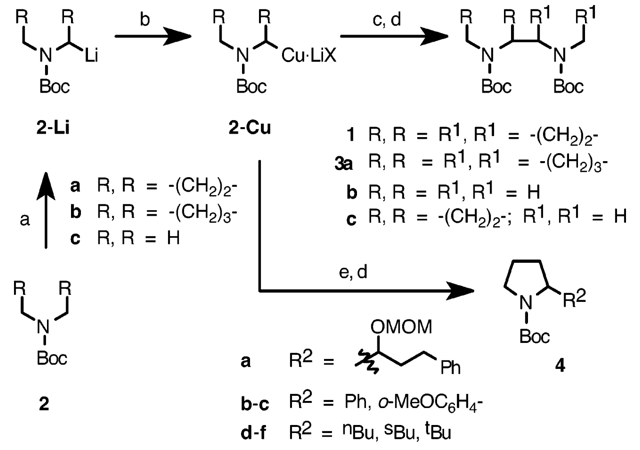
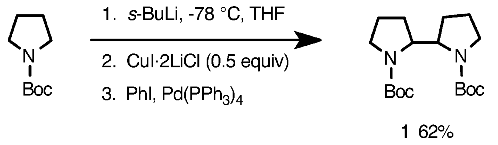
10.1021/jo035715+ CCC: $27.50

SCHEME 1[a]



[a] Key: (a) *s*-BuLi, THF, −78 °C, 2 h; (b) CuX·2LiCl (X = CN, I); (c) THF, (**2a**−**c**)−**Li**, −78 °C; (d) I_2, −78 °C; (e) R^2Li, THF, −78 °C.

yields of homocoupled dimers could be obtained by addition of halogens or *N*-haloimides (Scheme 1, Table 1).



(1)

The characteristics of this reaction were explored by the systematic variation of copper(I) salt, cuprate reagent, oxidant, and the ligands to be coupled (Scheme 1, Table 1). *N*-Boc-2-lithiopyrrolidine and iodine gave low yields of *N*,*N*′-bis(Boc)-2,2′-bipyrrolidine (**1**, Table 1, entry 1). Similarly low yields were obtained upon addition of iodine to either the alkylcyanocuprate (i.e., RCuCN, entry 2), the lithium dialkylcuprate reagent prepared from CuCN (entry 3), or the alkylcopper reagent (or alkylhalocuprate, RCuILi) prepared from CuI (entry 4). Excellent yields of homocoupled product could be obtained from lithium dialkylcuprates prepared from CuI with 1 equiv of Br_2 or I_2 (entries 5 and 6) while slightly lower yields were obtained with *N*-bromosuccinimide or *N*-iodosuccinimide (entries 11 and 12) with the latter giving the lowest yield (76%). An excellent yield was obtained with 0.5 equiv of I_2 and monotonically decreased with decreasing amounts of I_2 (entries 7−10). At quantities of I_2 less than 0.5 equiv, the chemical yields of **1** were roughly twice the value of I_2 equivalents employed. In all cases, a nearly 1:1 mixture of the two diastereomers (i.e., *meso*-*R**,*S**-**1** and *dl*-*R**,*R**-**1**) were obtained. The homocoupling reaction could be extended to the lithium dialkylcuprates derived from *N*-Boc-2-piperidinyllithium (**2b-Li**) or *N*-Boc-*N*-methylaminomethyllithium (**2c-Li**) (entries 13 and 14).

We next turned our attention to the heterocoupling of two different ligands. The mixed cuprate generated from *N*-Boc-2-lithiopyrrolidine and *N*-Boc-*N*-methyl-1-lithiomethylamine gave the heterocoupled product in 65−70% (entries 15 and 16) yield along with minor amounts of the two homocoupled products in 10% (bis-pyrrolidine **1**) and 3−4% (**3b**), respectively. The coupling of the 2-pyrrolidinyl ligand with an α-alkoxyalkyl ligand failed to occur under the standard conditions (Table 1, entry 17), although a low yield of coupled product could be achieved with 3 equiv of iodine (entry 18). The α-(alkoxy)alkyl ligand did not undergo homocoupling when the cuprate reagent was prepared from CuI (entry 19) even when excess iodine was employed. Preparation of the lithium di-α-(alkoxy)alkylcuprate reagent from CuCN and utilization of excess I_2 afforded a modest yield of the homocoupled product **5** (entry 20).

Attempts to couple the 2-pyrrolidinyl ligand with simple alkyl (e.g., *n*-Bu, *s*-Bu, *t*-Bu) or aryl (e.g., Ph, *o*-C_6H_4−) ligands afforded modest yields of heterocoupled products that decreased along the series *n*-Bu > *s*-Bu > *t*-Bu, Ar (Table 1, entries 21−33). The presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) appeared to facilitate the coupling of the 2-pyrrolidinyl and *n*-Butyl ligands (entries 21−23). The use of *trans*-1,2-diaminocyclohexane resulted in a lower yield than when no diamine was present (entries 23 and 24). The use of *n*-Bu_3P (6.0 equiv) gave a modest yield of the coupled product (entry 25) where TMEDA was not used to facilitate deprotonation. Similarly, higher yields of heterocoupled product were obtained in the presence of TMEDA than in its absence for coupling of the 2-pyrrolidinyl and *sec*-butyl ligands (entries 26 and 27), and the same result was obtained for coupling of the *tert*-butyl ligand (entries 28 and 29). Attempted coupling of the 2-pyrrolidinyl and aryl ligands gave low yields at −78 °C where **1** and the biaryl homo coupling products were the major products formed (entries 30 and 32). Better yields of *N*-Boc-2-arylpyrrolidines could be achieved if the coupling reaction was conducted at −125 °C in 2-methyltetrahydrofuran (entries 31 and 33).

Several experiments involving the coupling of simple alkyl ligands were performed for comparison with the α-(heteroatom)alkyl chemistry described above. Consistent with the report by Bertz,[2] the coupling of unfunctionalized homo- and mixed lithium dialkylcuprates (e.g., *n*-Bu, *s*-Bu combinations) with iodine gave only minor amounts (<20%) of the desired product. The presence or absence of TMEDA did not significantly alter the outcome.

Although the homocoupling of the 2-pyrrolidinyl ligand gave nearly 1:1 mixtures of *meso* and *dl* diastereomers, enantioselective coupling from scalemic 2-pyrrolidinylcuprates was examined. Asymmetric deprotonation of *N*-Boc-pyrrolidine [*s*-BuLi, (−)-sparteine, Et_2O, −78 °C, 1 h][14,17] followed by oxidative coupling gave no to low enantioselectivity (Table 2). The enantioselectivity in the 2-pyrrolidinyl homo coupling reactions appeared to be sensitive to the Cu(I) salt employed (entries 1−3), while the mixed *n*-Bu/2-pyrrolidinyl coupling was largely insensitive (entries 4, 5, and 7). Low enantioselectivity resulted when deprotonation was effected in Et_2O at −95 °C followed by cuprate formation at −95 °C with CuBr·2LiCl (entry 6). The yields in these reactions employing mixed Et_2O/THF solvent mixtures (Table 2) uniformly gave chemical yields lower than those observed in THF alone (Table 1).

Several interesting observations, relative to existing precedents, have emerged from this work. Iodine is an effective reagent for the oxidative dimerization of ketone

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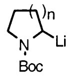
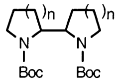
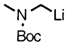
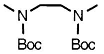
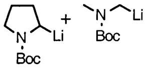
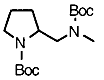
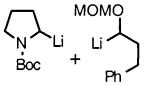
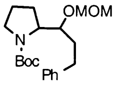
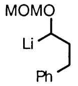
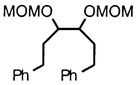
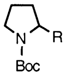
TABLE 1. Homo- and Heterocoupling of Lithium α-(*N*-Carbamoyl)alkylcuprates and of Heterodialkylcuprates

entry	RLi[a]	CuX	equiv[b]	oxidant[c]	product	n or R	% yield[d]	R*S*/ R*R*[e]
1		-	-	I_2 (1.0)		1	35	-
2		CN	1.0	I_2 (1.0)		1	30	-
3		CN	0.5	I_2 (1.0)		1	42	-
4		I	1.0	I_2 (1.0)		1	43	-
5	**2a-Li** n = 1	I	0.5	Br_2 (1.0)		1	96	46:54
6		I	0.5	I_2 (1.0)	**1** n = 1	1	98	44:56
7		I	0.5	I_2 (0.5)		1	95	46:54
8		I	0.5	I_2 (0.4)		1	78	42:58
9		I	0.5	I_2 (0.3)		1	57	43:57
10		I	0.5	I_2 (0.25)		1	47	45:55
11		I	0.5	NBS (1.0)		1	88	48:52
12		I	0.5	NIS (1.0)		1	76	47:53
13	**2b-Li** n = 2	I	0.5	I_2 (1.0)	**3a** n = 2	2	85[f]	-
14		I	0.5	I_2 (1.0)	 **3b**	-	80[g]	
15		I	1.0	I_2 (1.0)		-	70	
16		I	1.0	I_2 (0.5)	**3c**	-	65	
17		I	1.0	I_2 (1.0)		-	0	
18		I	1.0	I_2 (3.0)	**4a**	-	20[h]	
19		I	0.5	I_2 (3.0)			0	
20		CN	0.5	I_2 (3.0)	**5**		53	
21	**2a-Li** + *n*-BuLi	I	1.0	I_2 (1.0)		*n*-Bu	75	-
22	**2a-Li** + *n*-BuLi	I	1.0	I_2 (1.0)		*n*-Bu	70[i]	-
23	**2a-Li** + *n*-BuLi	I	1.0	I_2 (1.0)		*n*-Bu	50[j]	-
24	**2a-Li** + *n*-BuLi	I	1.0	I_2 (1.0)		*n*-Bu	22[k]	-
25	**2a-Li** + *n*-BuLi	I	1.0	I_2 (1.0)	**4b** R = Ph	*n*-Bu	40[l]	-
26	**2a-Li** + *s*-BuLi	I	1.0	I_2 (1.0)	**c** R = $MeOC_6H_4$	*s*-Bu	50	-
27	**2a-Li** + *s*-BuLi	I	1.0	I_2 (1.0)	**d** R = *n* -Bu	*s*-Bu	30[j]	-
28	**2a-Li** + *t*-BuLi	I	1.0	I_2 (1.0)	**e** R = *s* - Bu	*t*-Bu	30	-
29	**2a-Li** + *t*-BuLi	I	1.0	I_2 (1.0)		*t*-Bu	20[j]	-
30	**2a-Li** + PhLi	I	1.0	I_2 (1.0)	**f** R = *t* -Bu	Ph	10	-
31	**2a-Li** + PhLi	I	1.0	I_2 (1.0)		Ph	35[m]	-
32	**2a-Li** + *o*-$MeOC_6H_4Li$	I	1.0	I_2 (1.0)		*o*-$MeOC_6H_4$	20	-
33	**2a-Li** + *o*-$MeOC_6H_4Li$	I	1.0	I_2 (1.0)		*o*-$MeOC_6H_4$	40[m]	-

[a] The α-lithiocarbamates were generated by direct deprotonation (TMEDA, THF, −78 °C, 2 h). The α-(alkoxy)alkyllithium was generated from the corresponding stannanes via *n*-BuLi-mediated transmetalation. [b] Equivalents of CuX·2LiCl in THF used unless otherwise noted. The R_2CuLi (0.5 equiv of CuX·2LiCl) and RCuXLi (1.0 equiv of CuX·2LiCl, X = I, CN) cuprates were employed. [c] Equivalents of oxidant employed. [d] Yields based upon isolated products purified by column chromatography. [e] Diastereomeric ratio was determined from LC−MS analysis of the crude reaction product. [f] Deprotonation was effected in Et_2O (TMEDA, −78 °C, 3.5 h) followed by a THF solution of CuI·2LiCl. [g] *N*-Boc-*N*-methyl-*N*-[2-(methyl)butyl]amine was obtained as a byproduct. [h] Isolated 23% **1**, 7% **4e**, and <5% **5**. [i] TMEDA (10 equiv). [j] No diamine was employed. [k] *trans*-1,2-Diaminocyclohexane was employed. [l] *n*-Bu_3P (6.0 equiv), 10% homocoupled product formed. [m] 2-Methyltetrahydrofuran was employed at −125 °C for the oxidative coupling step.

and ester enolates[18] and the cyclopentyldienyl anion[19] but becomes problematic with increasing basicity of the carbanion.[20] Although lithium acetylides have a basicity comparable to ester enolates, they react with I_2 at low temperatures to afford 1-iodoalkynes.[21] Aryl and vinyl iodides can be prepared from the corresponding lithium reagents upon reaction with I_2[22a] and an aryllithium is preferentially iodinated in the presence of a lithium acetylide.[22b] Similarly, I_2, NBS, and NCS react with vinyl copper reagents to afford the corresponding vinyl halides[23,24] but induce oxidative dimerization of lithium dialkylcuprates[2] in low yields. In marked contrast to the lithium dialkylcuprates, I_2, Br_2, NBS, and NIS are particularly effective in the oxidative dimerization of lithium di[α-(*N*-carbamoyl)alkyl]cuprates. The coupling of diarylcuprates[7,8] affords higher yields of dimer when the cuprate is prepared from CuCN than when prepared from CuI while just the opposite is observed in the coupling of lithium dialkycuprates.[2] The yields of coupled products is nearly quantitative when both ligands contain proximate heteroatom functionality and diminish as the

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(23) For iodination of vinyl copper reagents, see: (a) Normant, J. F.; Chuit, C.; Cahiez, G.; Villieras, J. *Synthesis* **1974**, 803. (b) Westmijze, H.; Meijer, J.; Vermeer, P. *Rec. Trav. Chim. Pays-Bas* **1977**, *96*, 168. (c) Gardette, M.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1985**, *41*, 5887.

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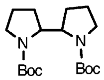
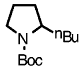
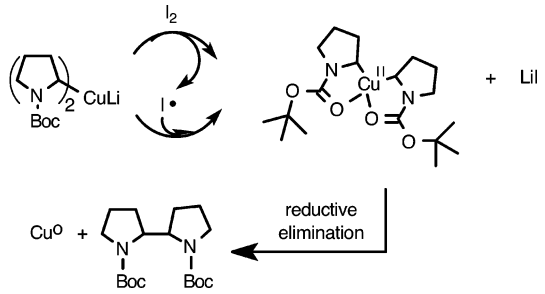
TABLE 2. Asymmetric Deprotonation and Oxidative Coupling of Scalemic α-(*N*-Carbamoyl)alkylcuprates

entry	*N*-Boc^a + (RLi)	CuX	equiv^b	product^c	% yield^d	% ee^e
1	**2a**	CN	0.5	 **1**	60^f	0
2	**2a**	I	0.5		67^f	8
3	**2a**	Br	0.5		50^f	30
4	**2a** + ^{n}BuLi	CN	1.0	 **4d**	24^g	20
5	**2a** + ^{n}BuLi	I	1.0		30^g	20
6	**2a** + ^{n}BuLi	Br	1.0		55	10^h
7	**2a** + ^{n}BuLi	Br	1.0		40^g	22^i

[a] The scalemic α-lithiocarbamate was generated by direct deprotonation [*s*-BuLi, (−)-sparteine (1.1 equiv), Et_2O, −78 °C, 1 h] followed by cuprate formation (CuX·2LiCl, THF, −78 °C) to give a 1:1 Et_2O/THF solvent mixture unless otherwise noted. [b] Equivalents of CuX·2LiCl employed. [c] Oxidative coupling was achieved with I_2 (1.0 equiv). [d] Products purified by column chromatography. [e] Enantiomeric excess (% ee) was calculated from the enantiomeric ratio (er) measured by chiral stationary- phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel]. [f] Yield for meso and *dl* diastereomers. [g] $^nBu_3P$ (2.0 equiv) was employed instead of LiCl; 30% homocoupled product **1** was formed. [h] Deprotonation in Et_2O (−95 °C, 1 h) followed by addition of CuBr·2LiCl (THF, −95 °C, 1 h). [i] Deprotonation in Et_2O followed by addition of CuBr·2$^nBu_3P$ in Et_2O.

SCHEME 2



heteroatom functionality is removed from one ligand and then from both ligands. The use of a large excess of external ligands such as TMEDA or *n*-Bu_3P does not increase the yields of the coupled products but does seem to diminish the yields of the homocoupled products when mixed lithium dialkylcuprates are coupled. Upon addition of I_2, the solution initially turns a bright yellow and then after several minutes black with the formation of colloidal particles appearing along the solvent edge consistent with the formation of Cu^0. The correlation of the yield of the coupled product with twice the amount of I_2 employed (for 0.5−0.25 equiv of I_2) suggest that both iodine atoms are involved in the oxidation of the cuprate reagent. A mechanism consistent with prior suggestions accounts for these observations (Scheme 2). Iodine oxidation of the cuprate reagent affords LiI, the neutral Cu(II) complex and an iodine atom which can oxidize a second molecule of cuprate to afford LiI and the Cu(II) complex. Reductive elimination from the Cu(II) complex affords the coupled product along with Cu^0. This reductive elimination may be particularly facile for the α-(*N*-carbamoyl)alkylcuprates where intramolecular chelation between the carbonyl oxygen and the Cu(II) metal center is possible. Similarly, α-(alkoxy)alkyl ligands also participate in facile coupling reactions.

Several questions remain. Why does CuCN prove superior to CuI for biaryl coupling while CuI proves superior for dialkyl coupling? Are there competing pathways for product formation involving radical combinations and reductive eliminations? Can ligands effective for Cu(II) intermediates favor higher chemical yields, diastereoselectivities and enantioselectivities? Is dynamic thermodynamic resolution a viable asymmetric strategy if effective ligands can be found? These questions await further experimentation.

In summary, excellent yields of homo- and heterocoupled products can be obtained by the oxidative coupling of lithium dialkylcuprates when both ligands contain α-heteroatoms. Modest yields are obtained when only one of the ligands contains an α-heteroatom and very low yields when nonfunctionalized ligands are employed. Chemical yields are related to both the nature of the ligands and the Cu(I) salt employed revealing considerable subtlety in these oxidative cuprate couplings and opportunities for stereochemical control.

Experimental Section

General Procedure A: Oxidative Homocouplings of α-(*N*-Carbamoyl)alkylcuprate Reagents. At room temperature, the *N*-Boc-protected amine was mixed with TMEDA (2.0 equiv), and the mixture was dissolved in dry THF to form a homogeneous solution. The solution was cooled to −78 °C and stirred for a few minutes. Then *s*-BuLi (1.2 equiv) was added dropwise, whereupon the solution became a yellow to deep yellow color. The yellow solution was stirred at −78 °C for an additional 2 h. The copper(I) salt (CuX = CuCN, purified CuI; 1.0 equiv for the alkylcuprate and 0.5 equiv for the lithium dialkylcuprate) and lithium chloride (2.0 equiv per CuX) were dried by hot air or flame under a dry nitrogen atmosphere and cooled to room temperature. Dry THF was added, and the mixture was stirred at room temperature until a slightly green or blue homogeneous solution was achieved. The solution was cooled to −78 °C. At this temperature, the copper(I) solution was transferred into the α-(*N*-carbamoyl)alkyllithium reagent (note: the inverse transfer afforded similar results for the cuprate formation). The yellow to deep yellow solution was then stirred at −30 °C for 0.5 h and recooled to −78 °C. The oxidant (Br_2, I_2, NBS, NIS) was dissolved in dry THF or just mixed with dry THF and cooled to −78 °C. Either the oxidant solution was transferred into the stirred cuprate solution (the color of the oxidant disappeared immediately and became yellowish turbid) or the cuprate solution was transferred into the coupling reagent. The reaction mixture was stirred at −30 °C for 2 h and at room temperature for 1 h whereupon the color changed from yellow to black. The reaction mixture was diluted with Et_2O, and the organic phase was washed with NH_4Cl (satd), followed by concentration in vacuo to afford the crude product. Pure product was obtained from either preparative TLC or flash column chromatography.

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Supporting Information Available: General experimental information, data reduction for **1**, **3a**−**c** and **4b**−**f**, and ^{13}C NMR spectra for **4c**−**f** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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