Copper Cyanide-Catalyzed Palladium Coupling of *N-tert*-Butoxycarbonyl-Protected α-Lithio Amines with Aryl Iodides or Vinyl Iodides

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Treatment of (α-aminoalkyl)lithium reagents with aryl iodides in the presence of catalytic amounts of CuCN and $PdCl_2(PPh_3)_2$ or $[(p\text{-}MeOC_6H_4)_3P]_4Pd$ affords 2-aryl substituted amines in modest to good yields. The yields can be improved by use of softer ligands such as $AsPh_3$ and $SbPh_3$ or by use of bis(diphenylphosphino)ferrocene (dppf). Coupled products are obtained with electron-rich aryl iodides (XArI, X = Me, OMe), and the reaction fails with electron-poor aryl iodides (XArI, X = NO_2, CO_2Li). Treatment of the (α-aminoalkyl)lithium reagents with vinyl iodides and Pd(0)/dppf/CuCN afforded the coupling products in low to modest yields.

Introduction and Background

The direct α-lithiation of amines is possible when the nitrogen atom is protected with a dipole stabilizing group that can participate in complex-induced proximity (CIP) effects.[1] α-Aminoalkyl carbanions are readily accessible from formamidines[2] and carbamates[3] as a result of the pioneering work of Meyers and Beak, respectively.[4] These carbanions react with typical carbonyl electrophiles and with alkyl halides, chlorosilanes, and chlorostannanes. We have extended the range of α-aminoalkyl metal chemistry with the development of the corresponding cuprate and/or copper reagents[5] which react with enones,[5a,b], enoates,[5e] allylic substrates,[5f] acid chlorides,[5d] and cyclic vinyl triflates.[5c] Although the organolithium and organocopper reagents react with a wide range of carbonyl and saturated electrophiles, the direct introduction of an aryl or vinyl substituent remains problematic.

α-Arylation of amines has been achieved principally by reaction of Grignard,[6] organocopper,[7] or organozinc[8] reagents with N,O and/or N,S mixed acetals which are prepared either by electrochemical oxidation of the amine[8] or via reduction[6a] of the corresponding lactam. Reaction of Grignard reagents with chiral 1,3-oxazolidines provides an asymmetric version of the N,O-acetal protocol.[9] α-Arylpyrrolidines and -piperidines have been prepared by alkylation of α-aryl-α-lithio amines with dihaloalkanes[10] followed by cyclization onto the nitrogen atom or by intramolecular reaction of the α-lithio amine[11] with an alkyl chloride or epoxide functionality. A palladium-catalyzed[12a] tandem α-arylation−isomerization of cyclic enamides has been used to prepare α-arylpyrrolidines and -piperidines while the 2-(1-alkenyl) derivatives have been prepared by Pd(0)-catalyzed coupling of vinyl halides with olefinic sulfonamides.[12b]

Addition of a suitable α-aminoalkyl organometallic reagent to a *σ*-aryl or vinyl palladium(II) complex provides a potential solution for the direct introduction of an aryl or vinyl substituent adjacent to a N atom.[13] Although an (α-aminoalkyl)(tri-*n*-butyl)stannane has been reported to undergo palladium/CuCN-mediated coupling with acid chlorides,[14] the butyl group transferred competitively with the α-aminoalkyl group consistent with our own observations. We reported[15] the first successful palladium-promoted coupling of (α-aminoalkyl)-lithium reagents with aryl iodides and now describe the full details of our investigation along with efforts to extend the coupling reaction to vinyl iodides.

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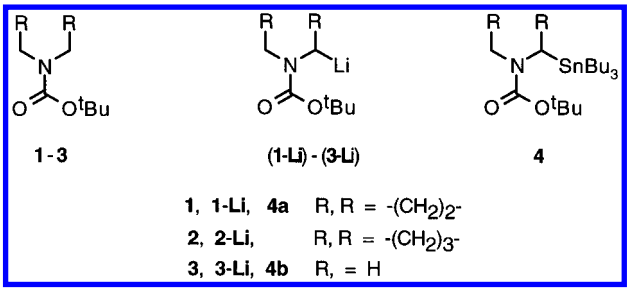
Results

The *N*-Boc protected amines (**1**−**3**) were prepared in high yields from pyrrolidine, piperidine, and *N*,*N*-dimethylamine [*tert*-butoxycarbonate anhydride, triethylamine (TEA), (dimethylamino)pyridine (DMAP), CH_2Cl_2, rt] and were purified by vacuum distillation. The iodoalkenes[16] and 1-iodohexyne[17] were prepared by established procedures.



Initial attempts to couple [(*N*-Boc-*N*-methylamino)-methyl]stannane **4b** with iodobenzene in the presence of bis(dibenzylideneacetone)palladium [$Pd(dba)_2$][18a] and PPh_3 [PhMe/THF, sealed tube, 140 °C][14] failed to yield any coupled products. The α-stannyl derivatives **4a**[3a] and **4b** also failed to afford coupling products when 5 mol % of several palladium catalysts such as $PdCl_2(PPh_3)_2$,[18b] $PdCl_2$ + 4 Ph_3P, and $[(p\text{-}MeOC_6H_4)_3P]_4Pd$[18a] were used. Transmetalation of **4a** [*n*-BuLi, TMEDA, THF, −78 °C, 1 h][3c,19] into the lithium derivative followed by cannula transfer into a mixture of $PdCl_2(Ph_3P)_2$ (5 mol %) and CuCN (10 mol %)[20] containing iodobenzene, with stirring at −78 °C to room temperature over a period of 10 h, afforded the coupled product **5** in 29% yield.

Efforts to optimize the yield of **5** were focused on the reactions of the α-lithio carbamate **1-Li**, derived from pyrrolidine, with iodobenzene in the presence of palladium and CuCN catalysts (eq 1). The α-lithio carbamate **1-Li** was generated by deprotonation of **1** [*s*-BuLi, TMEDA (2.2 equiv), THF, −78 °C, 2 h][3a] and then transferred by cannula to a mixture of iodobenzene or, in one case bromobenzene, and the palladium and CuCN co-catalyst at −78 °C (Table 1). Initial experiments with $[(p\text{-}MeOC_6H_4)_3P]_4Pd$ (5 mol %)/CuCN (10 mol %) revealed that the coupling process did not occur at −78 °C, but moderate yields of **5** could be obtained, with variable results, at temperatures between 25 and 74 °C (Table 1, entries 1−5). Utilization of $[(p\text{-}MeOC_6H_4)_3P]_4Pd$ absorbed on Celite gave a lower yield (Table 1, entry 6), while use

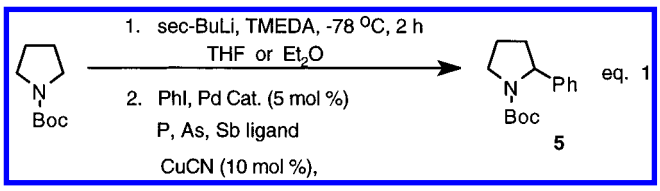


Table 1. Effect of Pd Catalysts and Ligands on the Coupling Reaction of *N*-(*tert*-Butoxycarbonyl)-2-lithiopyrrolidine (1-Li) with PhI To Afford *N*-Boc-2-phenylpyrrolidine (eq 1, 5)[a]

entry	Pd cat[b]	ligand	equiv[c]	temp °C[d]	time (h) (at higher temp)	solvent	yield (%)[e]
1	A			−78	3	PhMe/Et_2O	0
2	A			−78 (75)	2 (18)	PhMe/Et_2O	54
3	A			−78 (75)	2.5 (18)	PhMe/Et_2O	39
4	A			−78 (40)	2 (24)	Et_2O	47
5	A			−78 (rt)	8 (64)	Et_2O	38
6	B			−30[f] (40)	4 (12)	Et_2O	26
7	C			rt[f] (70)	3 (24)	THF	57
8	D			−78 to rt	18	THF	0
9	D	PBu_3	4		19	THF	38
10	D	PPh_3	2		18	THF	52
11	D	PPh_3	4		17	THF	58
12	D	$AsPh_3$	2		18	THF	71
13	D	$SbPh_3$	2		18	THF	72
14	D	dppb	1		13	THF	43
15	D	dppp	1		13	THF	46
16	D	BNAP	1		15	THF	55
17	D	dppf	1		13	THF	79

[a] *N*-Boc-2-lithiopyrrolidine (**1-Li**) was generated by deprotonation (TMEDA, *s*-BuLi, THF, or Et_2O, −78 °C, 2 h) of *N*-Bocpyrrolidine (**1**). [b] A = $[(p\text{-}MeOC_6H_4)_3]_4Pd$ (5 mol %)/CuCN (10 mol %). B = $[(p\text{-}MeOC_6H_4)_3]_4Pd$ on Celite (5 mol %)/CuCN (10 mol %). C = $PdCl_2(PPh_3)_2$ (5 mol %)/CuCN (10 mol %). D = Pd^0 (5 mol %)/CuCN (10 mol %) prepared by K reduction of $PdCl_2$/CuCN/ligand. [c] dppb = 1,4-bis(diphenylphosphino)butane. dppp = 1,3-bis(diphenylphosphino)propane. BINAP = 2,2'-bis(diphenylphosphino)-binaphthalene. dppf = bis(diphenylphosphino)ferrocene. [d] The temperature was held at −78 °C for the indicated period of time and then at a higher temperature for an additional period of time or allowed to rise from −78 °C to room temperature and then stirred at room temperature. [e] Yields are based upon isolated products purified by column chromatography. [f] Allowed to rise from −78 °C to this temperature.

of $PdCl_2(PPh_3)_2$ (5 mol %)/CuCN (10 mol %) gave 57% yield (Table 1, entry 7; 20% yield with bromobenzene[15]) of **5**. In an effort to produce a more reactive palladium catalyst, a $PdCl_2$/CuCN/P, As, or Sb ligand mixture was reduced with K metal to afford activated Pd(0).[21] This active Pd(0) catalyst gave no coupled product in the absence of added phosphine ligands (Table 1, entry 8). Addition of 4 equiv of PBu_3 gave **5** in 38% yield which could be increased to 52−58% yield by using 2 or 4 equiv of Ph_3P (Table 1, entries 8−11). Slightly lower yields of **5** could be obtained with the bidentate ligands dppb and dppp, while higher yields could be obtained with softer ligands[20,22] such as $AsPh_3$ and $SbPh_3$ (Table 1, entries 12−15). Modest yields of **5** were obtained with BINAP as added ligand, while the best results were obtained with the phosphinyl-substituted ferrocence catalyst dppf[23] (Table 1, entries 16, 17).

The effect of the Cu(I) salt co-catalyst[20] was briefly examined with 10 mol % of $SbPh_3$ as added ligand (Table 2). The absence of a Cu(I) salt resulted in a low yield of **5**, while 2 equiv of CuBr, CuI, or CuSCN per 1 equiv of palladium catalyst gave **5** in yields between 37 and 58% (Table 2, entries 2−4). Two equiv of CuCN per 1 equiv of palladium catalyst proved the most effective, and yields varied in a nonlinear way as the amount of CuCN was increased and diminished to zero at 10 equiv and above per 1 equiv of palladium catalyst (Table 2, entries 9, 10).

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Table 2. Effect of Co-Catalysts, MX, on the Coupling Reaction of *N*-Boc-2-lithiopyrrolidine (1-Li) with Iodobenzene Catalyzed by Pd(0) (5 mol %)/$SbPh_3$ (10 mol %)/MX (m equivs) To Afford 5[a]

entry	m equiv[b]	MX[c]	time (h)[d]	yield (%) **5**[e]
1	none	none	18	15.3
2	0.10	CuBr	15	43.7
3	0.10	CuI	22	58
4	0.10	CuSCN	18	37
5	0.10	CuCN	18	72
6	0.20	CuCN	18	39.6
7	0.25	CuCN	18	37.9
8	0.33	CuCN	18	53.8
9	0.50	CuCN	15	0
10	1.10	CuCN	18	0
11	0.10	ZnI_2	18	0
12	1.10	ZnI_2	15	0

[a] TMEDA was present in the reaction mixture from the deprotonation step (*s*-BuLi, diamine, THF, −78 °C, 2 h). [b] equiv with respect to 1 mmol of *N*-Boc-2-lithiopyrrolidine. [c] All copper(I) salts and ZnI_2 were purchased from Aldrich and used as received. [d] After transferring of *N*-Boc-2-lithiopyrrolidine (**1-Li**) into the catalysts' [active Pd(0) and co-catalyst were prepared by K metal reduction of a $PdCl_2/SbPh_3$/CuCN mixture] flask, the mixture was stirred in the cold bath and then warmed naturally to room temperature for the time indicated. [e] Yields are based on isolated product purified by column chromatography.

Table 3. Effect of the Diamine Ligand on the Coupling Reaction of *N*-Boc-2-lithiopyrrolidine (1-Li) with Iodobenzene Catalyzed by Pd(0) (5 mol %)/$SbPh_3$ (10 mol %)/CuCN (10 mol %) To Afford 5[a]

entry	amine[b]	equiv[c]	time (h)[d]	yield (%) **5**[e]
1	TMEDA	2.2	18	72
2	(−)-sparteine	1.0	15	46
3	(−)-sparteine	2.2	15	38.8
4	Proton Sponge	1.0	17	25
5	Proton Sponge	2.0	17	27.5
6	DPTMEDA	1.0	14	0
7	DPTMEDA	2.2	15	0

[a] 1 mmol of *N*-Bocpyrrolidine (**1**) was used for deprotonation (*s*-BuLi, diamine, THF, −78 °C, 2 h); about 1.5 mL of cyclohexane was introduced from *s*-BuLi. [b] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. Proton Sponge = 1,8-bis(dimethylamino)naphthalene. DPTMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diphenylethylenediamine. [c] Number of equivalents with respect to 1 mmol of *N*-Boc-pyrrolidine; 2.2 equiv of TMEDA was always used for deprotonation. [d] After *N*-Boc-2-lithiopyrrolidine was transferred into the catalysts' flask, the mixture was stirred for the time indicated. [e] Yields are based upon isolated products purified by column chromatography.

Attempted use of ZnI_2 proved completely ineffective (Table 2, entries 11, 12).[24]

The yield of coupled product was also found to depend upon the diamine utilized to aid in the deprotonation of the carbamates (Table 3). Utilization of TMEDA afforded the highest yield of **5**, which significantly decreased when TMEDA was replaced by sparteine or 1,8-bis(dimethylamino)naphthalene (Proton Sponge) (Table 3, entries 1−5). Interestingly, use of 1 equiv of sparteine gave a higher yield of **5** than did the use of 2 equiv. Use of 1,2-diphenyl-*N*,*N*,*N*′,*N*′-tetramethylethylenediamine gave no coupled product **5** (Table 3, entries 6, 7).

With the optimum conditions established, the scope of the reaction was examined with a range of aryl iodides and vinyl iodides (Table 4). The active Pd(0)/CuCN-catalyzed coupling of **1-Li** with iodobenzene occurred with nearly equal facility when either dppf or $SbPh_3$ were used as ligands (Table 4, entries 1, 2), while lower yields were obtained when $PdCl_2(PPh_3)_2$/CuCN was employed (Table 4, entry 3). It should be noted, however, that 10 mol % of the organolithium reagent could be consumed in reducing 5 mol % of the $PdCl_2(PPh_3)_2$ catalyst precursor to Pd^0 via R_2PdL_2. The latter catalyst system promoted the coupling of *N*-Boc-2-lithiopyrrolidine (**1-Li**) and *N*-Boc-2-lithiopiperidine (**2-Li**) with 4-iodoanisole (Table 4, entries 4, 5), *o*-iodotoluene (Table 4, entries 6, 7), and *p*-iodotoluene (Table 4, entries 8, 9) in modest to good yields. The more electron-rich anisole derivative gave lower yields of coupling product than did the toluene derivatives. The $PdCl_2(PPh_3)_2$/CuCN or $[(p\text{-}MeOC_6H_4)_3P]_4Pd$ catalyst system was completely ineffective in promoting the coupling of 1-iodonaphthalene, 2-iodothiophene,(*E*)-1-iodo-1-hexene,and2-iodo-1-hexene. These aryl iodides could be coupled with **1-Li** and **2-Li** in modest yields when the active Pd(0)/CuCN catalyst system was employed with either dppf, $AsPh_3$, or $SbPh_3$ serving as added ligands (Table 4, entries 10−13). These conditions also promoted the coupling of **1-Li** and **2-Li** to (*E*)-1-iodo-1-hexene in low to moderate yields (Table 4, entries 14−17), while coupling with 2-iodo-1-hexene could be achieved only in low yields (Table 4, entries 18, 19). The attempted coupling of **1-Li** with either (*E*)-1-iodo-1-hexene or 2-iodo-1-hexene gave as the major product *N*-Boc-2-hydroxypyrrolidine. The active Pd(0)/CuCN/$SbPh_3$ catalyst system promoted the coupling of **1-Li** and **2-Li** to 1-iodohexyne in modest to low yields, respectively (Table 4, entries 20, 21). Trace amounts of symmetrical biaryl or 1,3-divinyl coupling products were observed in the reactions of **1-Li** with 1-iodonaphthalene, 2-iodothiophene, and (*E*)-1-iodo-1-hexene. The acyclic derivative, **3-Li**, was coupled with PhI [$Pd^0(SbPh_3)_2$ (5 mol %), CuCN (10 mol %), THF, −75 °C to room temperature, 18 h] to afford *N*-(*tert*-butoxycarbonyl)-*N*-methylbenzylamine in 49% yield.

In an effort to probe the dynamics of this reaction process, the thermal stability of *N*-Boc-2-lithiopyrrolidine was examined by allowing the reagent to stir at a given temperature for 30 min, quenching the anion with chlorotrimethylsilane, and then measuring the yield of *N*-Boc-2-(trimethylsilyl)pyrrolidine (**23**) as an indication of the amount of **1-Li** that did not decompose. The reagent **1-Li** was found to be stable at −78 °C (94% **23**), moderately stable at −50 °C (71.5% **23**), and unstable at 0 °C (1.5% **23**) or room temperature (1.5% **23**).

In a limited study, **1-Li** was treated with either $MgBr_2$ or ZnX_2 (X = Br, I) and the putative Grignard or organozinc reagent was added to a Pd^0 (5 mol %)/CuCN (10 mol %)/ligand ($SbPh_3$ or PPh_3, 10 mol %) mixture at −78 °C and warmed to room temperature. Although traces of 2-aryl- or 2-vinylpyrrolidines were observed in a few experiments, these reaction conditions generally failed to give the desired products and usually resulted in recovered *N*-Bocpyrrolidine (**1**).

Discussion

Crucial mechanistic questions concerning the copper cyanide-catalyzed palladium-promoted coupling of (α-aminoalkyl)lithium reagents with aryl iodides are the following. (1) What is the rate-determining step in the catalytic cycle? (2) What is the nature of the organome-

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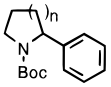
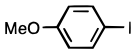
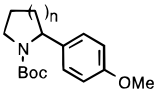
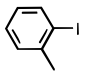
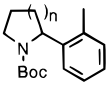
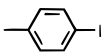
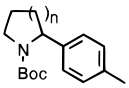
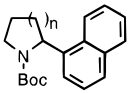
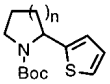
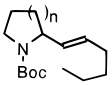
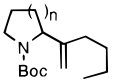
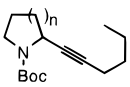
Table 4. Effect of Pd Catalysts and Ligands on the Coupling Reaction of *N*-(*tert*-butoxycarbonyl)-2-lithiopyrrolidine (1-Li) and the Corresponding Piperidine (2-Li) with Aryl, Vinyl, and 1-Alkynyl Iodides

entry	amine[a]	RI[b]	Pd cat.[c]	ligand[d]	equiv[e]	temp (°C)[f]	time (h)[g] (higher temp)	product	compd no.	*n*	yield (%)[h]
1	**1**		Pd(0)	dppf	1	−78 to rt	13		**5**	1	79
2	**2**		Pd(0)	$SbPh_3$	2		18		**6**	2	75
3	**2**		$PdCl_2$	PPh_3	2	−78 to rt	10 (24)		**6**	2	55
4	**1**		$PdCl_2$	PPh_3	2	−78 to rt (75)	8 (5)		**7**	1	34
5	**2**		$PdCl_2$	PPh_3	2	−78 to rt (40)[i]	24 (20)		**8**	2	43
6	**1**		$PdCl_2$	PPh_3	2	−78 to −12 (75)	4.5 (14)		**9**	1	64
7	**2**		$PdCl_2$	PPh_3	2	−78 to rt (75)	11 (18)		**10**	2	65
8	**1**		$PdCl_2$	PPh_3	2	−78 to −12 (75)	4.5 (14)		**11**	1	67
9	**2**		$PdCl_2$	PPh_3	2	−78 to rt (75)	11 (8)		**12**	2	71
10	**1**		Pd(0)	dppf	1	−78 to rt	13		**13**	1	39[j]
11	**2**		Pd(0)	$SbPh_3$	2	−78 to rt	15		**14**	2	42
12	**1**		Pd(0)	$AsPh_3$	2	−78 to rt	18		**15**	1	36[j]
13	**2**		Pd(0)	$SbPh_3$	2	−78 to rt	18		**16**	2	42
14	**1**		Pd(0)	$SbPh_3$	2	−78 to rt	14		**17**	1	35[k]
15	**1**		Pd(0)	dppf	1	−78 to rt	13		**17**	1	12[j]
16	**1**		Pd(0)	$AsPh_3$	2	−78 to rt	13		**17**	1	20[j]
17	**2**		Pd(0)	$SbPh_3$	2	−78 to rt	23		**18**	2	17
18	**1**		Pd(0)	$SbPh_3$	2	−78 to rt	14		**19**	1	10[k]
19	**2**		Pd(0)	$SbPh_3$	2	−78 to rt	23		**20**	2	<5[l]
20	**1**		Pd(0)	$SbPh_3$	2	−78 to rt	20		**21**	1	34[j]
21	**2**		Pd(0)	$SbPh_3$	2	−78 to rt	20		**22**	2	<9[l]

[a] The carbamate was deprotonated (TMEDA, *s*-BuLi, −78 °C) in THF unless otherwise noted. [b] 1.2 equiv of the aryl iodide, vinyl iodide, or 1-alkynyl iodide was used. [c] The Pd(0) catalyst was prepared by potassium metal reduction of a $PdCl_2$/CuCN/ligand mixture. $PdCl_2$ was employed as a preformed $PdCl_2(PPh_3)_2$ complex (ref 18b). [d] dppf = bis(diphenylphosphino)ferrocene. [e] Equivalents of ligand per equivalent of palladium catalyst. [f] The temperature range over which the reaction was carried out. [g] The temperature was held at −78 °C for the indicated period of time and then at the higher temperature for an additional period of time, or allowed to rise from −78 °C to room temperature and then stirred at room temperature. [h] Yields are based upon isolated products purified by column chromatography. [i] Et_2O was used as solvent. [j] Small amounts of biaryl or 1,3-dienyl homocoupled products were observed. [k] *N*-Boc-2-hydroxypyrrolidine was formed in 36% yield. [l] Product yield was estimated from MS−GC analysis.

tallic reagent acting as the nucleophile? (3) What is the role of the Cu(I) salt? (4) What roles does the diamine play? (5) Why do chemical yields decrease with 1-iodonaphthalene, 2-iodothiophene, and vinyl iodides? (6) Why do Grignard and organozinc analogs fail in this reaction? A perspective on these questions can be obtained by examining known facts in the context of current mechanistic proposals for palladium-promoted coupling of aryl iodides and organometallic reagents.

Pd(0)- and Ni(0)-catalyzed couplings of organometallic reagents with electrophiles are thought to proceed via a catalytic cycle involving oxidative addition−transmetalation−reductive elimination.[25] Oxidative addition of a Pd^0 species to aryl or vinyl halides affords an aryl or vinyl Pd^{II} halide which can then undergo a transmetalation reaction with the organometallic reagent giving rise to either a *cis* or *trans* diorganopalladium species (Scheme 1) with the latter being thermodynamically more stable.[25a,26] Reductive elimination from the *cis* complex affords the coupled product and regenerates the Pd(0) or Ni(0) catalyst. Recent studies have suggested that effective catalytic cycles involve rapid transmetalation of an initially formed *cis* organopalladium halide, and that involvement of the *trans* complex represents a slower, less efficient catalytic cycle. These mechanistic modifications involve tetracoordinate or pentacoordinate palladium complexes (Scheme 1).[26,30]

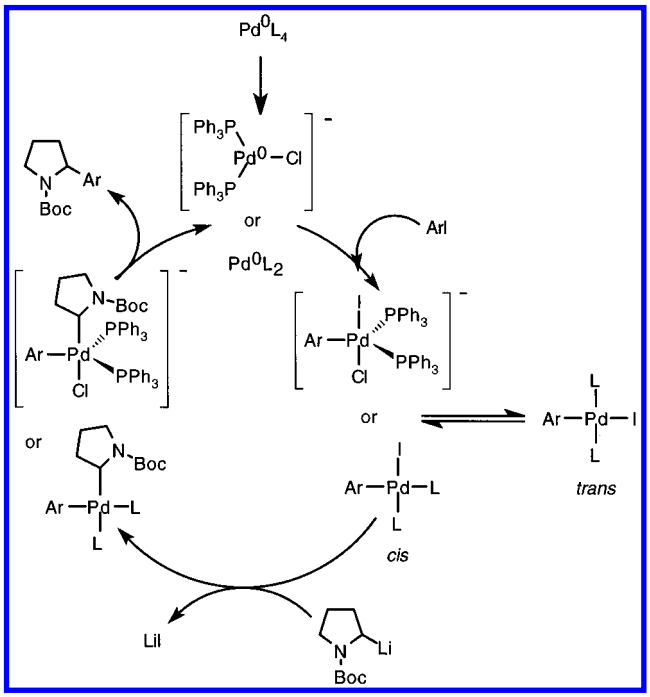
Although the vast range of Pd(0)- and Ni(0)-catalyzed coupling reactions can be accommodated by this descriptive catalytic cycle, each step is open to kinetic complications and mechanistic possibilities.[26] Any of the three steps can, depending upon electrophile/organometallic combination and particular reaction conditions, function as the rate-determining step.[26] The oxidative addition of zero-valent palladium to aryl iodides is generally rapid at room temperature,[13a,26] and the rate is increased by electron-withdrawing groups[25,27] on the aromatic ring. The oxidative addition proceeds via a dissociative mechanism involving a coordinatively unsaturated palladium species (i.e., Pd^0L_2) and is inhibited by increased ligand

(25) For reviews detailing mechanistic aspects of organopalladium chemistry, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Yamamoto, A. *Organotransition Metal Chemistry—Fundamental Concepts and Applications*; Wiley: New York, 1986.

(26) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531 and references cited therein.

(27) (a) Fauvarque, J. F.; Pflüger, F.; Troupel, M. *J. Organomet. Chem.* **1981**, *208*, 419. (b) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995.

Scheme 1



stoichiometry favoring formation of Pd^0L_4.[25a,26] Difficulties in the reaction are often attributed to the transmetalation step.[13a] Grignard, organozinc, and organotin reagents are the most widely employed,[13a] while organolithium[21a] reagents are infrequently used. Transmetalation from copper[28] to palladium is generally slow, and organolithium reagents can form ate complexes (e.g., $[PdR_3L]^-Li^+$ and $[PdR_4]Li_2$).[29] Reductive elimination occurs via a nondissociative nonassociative mechanism for *cis* diaryl- and divinylpalladium complexes and via a dissociative mechanism for dialkylpalladium complexes.[25a] The dissociative pathway is inhibited by excess phosphine ligands, and the effect of particular ligands is related to their binding affinity to palladium (dppe > PEt_3 > PEt_2Ph > $PMePh_2$ > $PEtPh_2$ > PPh_3);[25a] the lower the binding affinity to palladium the greater the rate of reductive elimination.

The oxidative addition of (dppf)Pd^0 to (*E*)-2-halo-1-(4-methoxyphenyl)ethene displays the characteristic halide reactivity pattern of I > Br >> Cl (−70, −40, and >25 °C, respectively),[30] while the oxidative addition of $(PPh_3)_2Pd^0$ with PhI is instantaneous[26] at 20 °C. The addition of aryl Grignard reagents to the above vinylpalladium halides is rapid at −80 °C, and reductive elimination is so fast at −80 °C that only the product olefin−palladium complex can be observed by ^{31}P NMR. Utilization of benzylmagnesium chloride results in transmetalation at −80 °C, but reductive elimination begins to occur at temperatures > −30 °C with a half-life of 4 min at −15 °C. We have observed that α-aminoalkyl cuprates are formed from the organolithium reagents at around −50 °C,[5] whereas simple lithium dialkyl or diaryl cuprates form at lower temperatures (−120 to −78 °C). *It seems plausible, therefore, that all three steps in the coupling of α-aminoalkyl anions with aryl iodides occur between −50 and 20 °C and that the oxidative addition and reductive elimination steps are slower than the transmetalation step (e.g., RLi to RPdAr).*

Table 1 reveals that ligand effectiveness is in the order of dppf ≈ $AsPh_3$ ≈ $SbPh_3$ > $(p\text{-}MeOC_6H_4)_3P$ ≈ PPh_3 ≈ BINAP > PBu_3 ≈ dppb ≈ dppp. The effect of the heteroatom ligands (P, As, and Sb) was examined in conjunction with a more reactive Pd(0) generated by potassium metal reduction. No coupling product was observed in the absence of an added phosphine ligand, and this can be attributed to catalyst decomposition in the absence of stabilizing ligands.[22] The yield of coupled product increased as the softness of the ligand ($SbPh_3$, $AsPh_3$ > PPh_3 > PBu_3) increased (Table 1, entries 8−13). This trend is also consistently observed in the bisphosphine ligands with the diarylalkylphosphines dppb and dppp giving higher yields than PBu_3 but lower yields than PPh_3 and BINAP (Table 1, entries 14, 15 vs 9, 10, 16). Soft ligands (e.g., $AsPh_3$ and $SbPh_3$) and bisphosphines with a large bite angle all are relatively effective in promoting the coupling reaction of **1-Li** with PhI. The soft ligands facilitate, through facile ligand dissociation, formation of a coordinately unsaturated Pd(0) intermediate necessary for the oxidative addition, while bisphosphines (particularly dppf) may facilitate reductive elimination,[31] relative to β-hydrogen elimination, and prevent formation of the *trans* diorganopalladium complex leading to a nonproductive or a slower and less effective catalytic cycle (Scheme 1).[26] These observations are consistent with a rate-limiting dissociative process occurring among some or all[32] of the steps of the catalytic cycle. The more tightly bound the heteroatom is to the Pd intermediate, the slower the ligand dissociation necessary for the oxidative addition step and perhaps the transmetalation step and hence the slower the overall rate of the catalytic cycle.

The Pd-catalyzed coupling of α-aminoalkyl anions with aryl halides requires the use of a Cu(I) salt as a co-catalyst in order to achieve good yields. Copper co-catalysts are frequently used in the Stille coupling of organostannanes, and a mechanistic study attributed the resultant increase in reaction rates and product yields to the ability of Cu(I) to scavenge free phosphine ligand.[20] Formation of a copper−phosphine complex facilitates ligand dissociation from palladium intermediates which may be necessary for transmetalation to occur. In more polar solvents, Sn/Cu transmetalation followed by Cu/Pd transmetalation may also contribute to the observed rate accelerations. The "copper effect" is not nearly as dramatic when soft ligands (e.g., $AsPh_3$) are used since ligand dissociation is not a problem. In contrast, Cu(I) co-catalysts are required in the α-aminoalkyl anion couplings regardless of the ligands employed (i.e., PPh_3, $AsPh_3$, or $SbPh_3$). Potassium metal reduction of a $PdCl_2(Ph_3P)_2$/CuCN mixture is assumed to afford KCl, $Pd^0(PPh_3)_2$ or $Pd^0(PPh_3)_2Cl^-Li^+$, and CuCN. Addition of an α-lithio carbamate to this mixture will rapidly consume the CuCN at −50 °C to afford a cuprate reagent, removing 20% of the lithium reagent when 10 mol % CuCN is employed and perhaps more if higher order cuprate compositions are involved. These cuprate reagents are also capable of binding phosphine and nitro-

(28) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 607; and references cited therein.
(29) Nakazawa, H.; Ozawa, F.; Yamamoto, A. *Organometallics* **1983**, *2*, 241.
(30) Brown, J. M.; Cooley, N. A. *Organometallics* **1990**, *9*, 353.
(31) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
(32) For descriptions of reductive elimination promoted by ligand dissociation, see: (a) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1720. (b) Ozawa, F.; Kurihara, K.; Yamamoto, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 399.

gen ligands[33] and could accelerate the α-aminoalkyl anion couplings in a manner similar to that proposed for the "copper effect" in Stille couplings.[20] In this regard, it should be remembered that the 2 equiv of diamine used to facilitate carbamate deprotonation are present in the reaction medium. Amines form complexes with palladium species in palladium-promoted amination of aryl halides,[34] and methyllithium readily reacts with $PdBr_2$(TMEDA) to form Me_2Pd(TMEDA) and eventually Me_4PdLi_2.[29] The effect of the Cu(I) salts (i.e., CuCN > CuI > CuBr > CuSCN) on product yield could reflect either cuprate reactivity if they are involved in the transmetalation process or cuprate instability resulting in removal of the α-aminoalkyl group from the catalytic cycle upon cuprate decomposition. Increasing the amount of Cu(I) co-catalyst generally results in diminished product yield, although 33 mol % CuCN per equivalent of the α-lithio carbamate provides an anomaly in an otherwise uniform trend. Utilization of sufficient CuCN to consume all the α-lithio carbamate and form either $R_2CuLi{\cdot}LiCN$ or RCuCNLi (50 and 100 mol %, respectively) results in no product formation. *These results are consistent with either decomposition of the Pd(0) catalyst with increasing copper content or the failure of the cuprate reagent to participate in the transmetalation step.* Cuprate reagents can exist in equilibrium with the organolithium precursors, and the cuprate reagents formed from the CuCN co-catalyst could return some of the alkyllithium reagent to the catalytic cycle.[35]

It is difficult to ascertain the nature of the organometallic reagent undergoing transmetalation to palladium under these reaction conditions. The 2-lithiopyrrolidine derivative begins to undergo decomposition at −55 °C and rapidly decomposes at 0 °C in THF. Our own experience with the α-aminoalkyl cuprates[5] is that the onset of their thermal decomposition is around −40 °C. It seems reasonable that Li/Pd transmetalation should be faster than Cu/Pd transmetalation and that a crucial factor is the temperature at which Pd(0) undergoes oxidative addition to the aryl halide. Since cuprate reagents are in equilibrium with the alkyllithium species from which they were formed,[35] they could be an equilibrium source of the lithium reagents as the latter are removed by the catalytic cycle. *Since utilization of sufficient CuCN to convert all of the (α-aminoalkyl)lithium reagent into a cuprate reagent results in no coupling, it seems reasonable to assume that the organometallic nucleophile participating in the transmetalation with a Pd^{II} species is an organolithium reagent.*

The diamine employed to facilitate deprotonation of the carbamate moiety also effects the observed yield of the coupling reaction. Both TMEDA and sparteine effectively facilitate deprotonation of the carbamates, and in the α-aminoalkyl cuprate conjugate addition reactions use of sparteine afforded higher yields.[5b] For these reasons the dependence of coupling yield on diamine does not appear to reflect deprotonation efficiencies. The diamines could influence these coupling reactions through ion-pairing effects,[26] functioning as ligands for palladium intermediates, promoting stability of the Pd(0) catalysts, or promoting stability of the organolithium reagent. Diamine ligands have been used in place of phosphine ligands in Pd-catalyzed reactions.[36] *The necessity of CuCN as a co-catalyst, even with soft ligands such as $SbPh_3$, is plausibly related to the presence of these nitrogen ligands in the reaction mixture and the increased stoichiometry of ligands capable of binding to palladium species.*

The coupling of α-aminoalkyl carbanions with 1-iodonaphthalene, 2-iodothiophene, and 1-iodo-1-hexene proceeds in modest yields when soft ligands, such as $AsPh_3$ or $SbPh_3$, or dppf were employed. A major side reaction in the vinyl iodide couplings involved halogen metal exchange affording 2-iodopyrrolidine, which hydrolyzed to the hydroxy derivative upon workup. The lower yields obtained with these substrates can also be due to a slower rate of reductive elimination. The rate of reductive elimination is reported to be in the order of diaryl > aryl(alkyl) > dipropyl > diethyl > dimethyl.[25a] The formation of trace amounts of homocoupling products (Table 4, entries 10, 12, 15, and 16, legend *f*) are consistent with either halogen−metal exchange or decreased rate of reductive elimination with resultant increased formation of the *trans* diorganopalladium complex, given the observation[26] that stoichiometric *trans*-$PhPdI(PPh_3)_2$ affords homocoupled product (i.e., biphenyl) in the presence of nucleophiles. Given the thermal instability of the (α-aminoalkyl)lithium and α-aminoalkyl cuprate reagents above −40 °C, a decrease in the rate of the catalytic cycle will result in a competitive nonproductive decomposition of the organometallic nucleophile.

The failure of α-aminoalkyl Grignard and zinc reagents to participate in these coupling reactions is in marked contrast to the general superiority of Grignard and organozinc reagents over organolithium reagents in palladium-promoted coupling reactions.[13a] If the α-aminoalkyl Grignard and zinc reagents undergo transmetalation to palladium more slowly than the lithium reagents, more of the initial *cis*-$ArPdIL_2$ complex formed upon oxidative addition may undergo isomerization to the *trans*-$ArPdIL_2$ complex resulting in a nonproductive pathway if the subsequent *trans*-aryl(α-aminoalkyl)palladium complexes are significantly more stable than the corresponding *cis* isomers. In this regard it is interesting to note that alkyllithium reagents promote isomerization of *trans*-PdR_2L_2 to the *cis* isomer.[29] These considerations could account for the failure of α-aminoalkyl Grignard and zinc reagents to couple with aryl iodides under these reaction conditions.

Conclusions

In summary, (α-aminoalkyl)lithium reagents can be coupled with aryl iodides in the presence of palladium catalysts and CuCN as a co-catalyst. The reaction is largely limited to phenyl iodides, and diminished yields are observed with polyaromatic and heteroaromatic halides. The success of the reaction appears to depend

(33) (a) van Koten, G.; Jastrzebski, J. T. B. H. *J. Am. Chem. Soc.* **1985**, *107*, 697. (b) Hallnemo, G.; Ullenius, C. *Tetrahedron Lett.* **1986**, *27*, 395. (c) Dieter, R. K.; Lagu, B.; Deo, N.; Dieter, J. W. *Tetrahedron Lett.* **1990**, *31*, 4108. (d) Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernandez, A. E.; Vickers, D.; Fluckiger, E.; Patterson, R. G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965. (e) Alexakis, A.; Mutti, S.; Normant, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 6332.

(34) (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (b) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215 and references cited therein.

(35) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1995**, *107*, 3197.

(36) (a) Markies, B. A.; Wijkens, P.; Boersma, J.; Kooijman, H.; Veldman, N.; Spek, A. L.; van Koten, G. *Organometallics* **1994**, *13*, 3244. (b) van Asselt, R.; Elsevier, C. J. *Organometallics* **1994**, *13*, 1972. (c) van Asselt, R.; Elsevier, C. J. *Tetrahedron* **1994**, *50*, 323. (d) Wright, M. E.; Lowe-Ma, C. K. *Organometallics* **1990**, *9*, 347.

on a fine balance between the rates of each step of the oxidative addition−transmetalation−reductive elimination sequence. Rate reduction of either the oxidative addition or reductive elimination steps as a result of substrate structure or ligand composition may result in competitive decomposition of the organolithium reagent. Reduction in the rate of the transmetalation step may result in either catalyst decomposition or pathways that do not favor eventual coupling. Recent insights (Scheme 1)[26,30] into the mechanism of palladium-catalyzed nucleophilic substitution, outlined in the discussion, suggest that mechanistic studies of this reaction may be particularly useful in expanding its scope and synthetic utility.

Experimental Section

Materials. House nitrogen gas was passed sequentially through concentrated sulfuric acid, potassium hydroxide, and anhydrous calcium chloride before being introduced into the reaction flask. The reaction flasks were flame-dried and cooled to room temperature in a dry nitrogen atmosphere before use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone (dark blue-purple color) under a N_2 atmosphere. *N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diphenylethylenediamine was prepared according to a literature procedure.[37]

General Procedure A: Coupling Reactions Employing Cu(I) Salts and Preformed Palladium Catalysts. Under a N_2 atmosphere, the *N*-Bocpyrrolidine (**1**) or *N*-Bocpiperidine (**2**) (1.0 mmol), tetramethylethylenediamine (2.2 mmol), and THF (2 mL) were put into a flame-dried flask. The contents cooled to −78 °C (acetone−dry ice), whereupon *s*-BuLi (1.2 mmol) was added in one portion, and the mixture was stirred for 2 or 3 h at −78 °C to form the α-lithio amines (**1-Li** and **2-Li**) as yellow-orange solutions.

Under a N_2 atmosphere, THF (2.0 mL), the palladium catalyst (0.05 mmol), CuCN (0.10 mmol), and the aryl iodide (1.2−2.0 mmol) were placed into another flask. The mixture was cooled to −78 °C. The α-lithio amine solution was transferred by cannular into the flask containing the aryl iodide and catalyst, and the mixture was stirred and warmed to room temperature naturally (ca. 8 h). The mixture was heated to reflux (75 °C) until the disappearance of the *N*-Bocpyrrolidine (**1**, $R_f = 0.43$) or *N*-Boc piperidine (**2**, $R_f = 0.35$) as indicated by TLC analysis (silica gel, 10% Et_2O−petroleum ether, v/v).

The reaction mixture was cooled to room temperature, diluted with Et_2O (8−15 mL), quenched with aqueous saturated NH_4Cl (2 mL), and filtered through Celite or paper. The organic layer was separated and the aqueous layer was extracted with Et_2O (5 mL × 4). The combined organic phase was washed with 1 N HCl (15 mL × 2), $NaHCO_3$ (saturated, 15 mL × 2), and brine (15 mL × 2) and dried over K_2CO_3/Na_2SO_4. The crude product was obtained by evaporation of solvent *in vacuo*.

The pure product was isolated by column chromatography (silica gel, 10% Et_2O−petroleum ether, v/v, gravity or flash), medium-pressure liquid chromatography (MPLC), or preparative TLC (silica gel).

General Procedure B: Coupling Reactions Employing Cu(I) Salts and Active Pd(0) Generated *in Situ*. $PdCl_2$ (5 mol %), the P, As, or Sb ligand (listed in Tables 1 and 4), CuCN (10 mol %) or other metal salt, and potassium (5 mol %) were put into one flask. THF (2 mL) was added, and the flask was vacuum degassed (5 mmHg) and flushed with dry N_2. The mixture was heated in an oil bath (75 °C) for 2 h (reddish mixture became black slurry) and cooled to room temperature. The aryl iodide (2 mmol) or vinyl iodide was added, and the mixture was stirred at room temperature for 1 h.

N-Bocamine (1 mmol), TMEDA (2.2 mmol) or (−)-sparteine (1 or 2.2 mmol) or other appropriate tertiary diamines, and THF (2 mL) were placed into another flask. The flask was cooled by a dry ice−acetone bath (−78 °C), and the mixture was stirred for 10 min. Then *s*-BuLi (1.2 mmol) was added in one portion, and the mixture was stirred for an additional 2 or 3 h.

At the same time, the flask containing the Pd(0) species was cooled in the same cold bath. The α-lithio amine was transferred into the flask containing the Pd(0) species by cannula. The mixture was stirred, warmed naturally overnight, and monitored by TLC (silica gel, 10% Et_2O−petroleum ether, v/v) until no starting material was observed.

The mixture was diluted with 15−20 mL of Et_2O, quenched with 5 mL of H_2O, and filtered. The residue was washed with Et_2O (5 mL × 3). The organic layer was separated, and the aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic extracts were washed with 1 N HCl (5 mL × 2), $NaHCO_3$ (saturated, 5 mL × 2), and brine (5 mL × 3), then dried over Na_2SO_4/K_2CO_3, and filtered. Upon concentration *in vacuo*, the crude material was obtained as a pale yellow or colorless oil. Pure product was obtained by gravity or flash column chromatography (silica gel, 200−400 or 60−200 mesh), MPLC, or preparative TLC.

***N*-(*tert*-Butoxycarbonyl)pyrrolidine (1).** Under a N_2 atmosphere, pyrrolidine (**1**, 3.56 g, 50 mmol) was stirred together with *tert*-butoxy carbonate anhydride (12.15 g, 55.7 mmol), *p*-(dimethylamino)pyridine (6.60 g, 50 mmol), and NEt_3 (7.5 mL, 50 mmol) in CH_2Cl_2 (75 mL) for 24 h. The reaction mixture was diluted with Et_2O (120 mL), then washed with 10% HCl, K_2CO_3 (saturated), and brine, and finally dried over K_2CO_3/Na_2SO_4. Pure **1** (8.27 g, 96.7% yield) was obtained as a colorless oil (lit.[3a,d]): bp 70−75 °C (0.05 mmHg); IR 2977 (vs), 2876 (s), 1702 (vs), 882 (s), 774 (s) cm^{-1}; ^1H NMR δ 1.46 (s, 9 H), 1.84 (m, 4 H), 3.30 (m, 4 H); ^{13}C NMR δ 25.2, 28.4, 45.6, 78.7, 154.6; mass spectrum *m*/*z* (intensity) EI 172 (0.3, $M^+ + 1$), 171 (3, M^+), 156 (0.3, $M^+ - CH_3$), 114 (16, $M^+ - C_4H_9$), 98 (28.5, $M^+ - C_4H_9O$), 57 (100, C_4H_9).

***N*-(*tert*-Butoxycarbonyl)piperidine (2).** The same procedure used for preparing (**1**) was employed. From 4.26 g (50 mmol) of piperidine was obtained 8.92 g of pure **2** (bulb-to-bulb distillation, 79 °C, 0.05 mmHg) in 96.4% yield (lit.[3d]): IR 2973 (s), 2937 (s), 2859 (s), 1695 (vs), 1423 (vs), 1030 (s) cm^{-1}; ^1H NMR δ 1.46 (s, 10 H), 1.47−1.72 (m, 5 H), 3.36 (t, $J = 5.78$ Hz, 4 H); ^{13}C NMR δ 24.4, 25.6, 28.3, 44.5, 78.9, 154.8; mass spectrum *m*/*z* (intensity) EI 187 (0.05, $M^+ + 2$), 186 (0.9, $M^+ + 1$), 185 (6.4, M^+), 170 (0.1, $M^+ - CH_3$), 128 (34, $M^+ - C_4H_9$), 57 (100, C_4H_9).

***N*,*N*-Dimethyl-*N*-(*tert*-butoxycarbonyl)amine (3).** The same procedure employed for preparing **1** was used. From 8.18 g (100 mmol) of dimethylamine hydrochloride was obtained 11.95 g (82% yield) of pure **3** (lit.[3a]): bp 75−80 °C (16−17 mmHg); IR 2981 (s), 2933 (s), 1702 (vs), 1391 (s), 1167 (vs) cm^{-1}; ^1H NMR δ 1.43 (s) and 1.45 (s, 9 H), 2.84 (s) and 2.85 (s, 6 H); ^{13}C NMR δ 28.4, 36.0, 79.1, 156.0; mass spectrum *m*/*z* (intensity) EI 146 (0.4, $M^+ + 1$), 145 (4.6, M^+), 130 (1.2, $M^+ - CH_3$), 90 (34), 88 (3.1), 72 (74.8), 57 (100).

***N*-[(Tributylstannyl)methyl]-*N*-(*tert*-butoxycarbonyl)-methylamine (4b).** *N*-Boc-*N*,*N*-dimethylamine (**3**, 0.7298 g, 5 mmol) was mixed with TMEDA (0.75 mL, 5 mmol) and Et_2O (10 mL) under N_2, and the colorless mixture was cooled to −78 °C and reacted with *s*-BuLi (4.6 mL, 5 mmol) for 1 h. Bu_3SnCl (1.36 mL, 5 mmol) was syringed into the pale-yellow solution. The mixture was stirred and warmed to room temperature overnight (white turbid), quenched with saturated aqueous NH_4Cl (5 mL), washed with brine, and dried over K_2CO_3/Na_2SO_4. Concentration *in vacuo* followed by bulb-to-bulb distillation after column chromatography (silica gel, 100−200 mesh, 20% Et_2O−petroleum ether, v/v) of the crude product gave 1.44 g of pure **4b** in 66% yield as a colorless oil: bp 100 °C (0.005 mmHg); IR 2924 (s), 1683 (s), 1485 (s), 767 (m) cm^{-1}; ^1H NMR δ 0.88 (m, 14 H), 1.32 (m, 8 H), 1.39−1.68 (br m, 16 H), 2.95 (m, 3 H); ^{13}C NMR δ 8.7, 9.4, 10.2, 13.7, 17.5, 26.8, 27.4, 27.8, 28.5, 28.9, 29.1, 29.2, 32.2, 34.8, 36.3, 37.3, 78.7, 155.4.

***N*-(*tert*-Butoxycarbonyl)-2-(tributylstannyl)pyrrolidine (4a).** The same procedure for preparing **4b** was used. From 0.855 g (5 mmol) of **1** was obtained 1.961 g (colorless liquid, 85.3% yield) of **4a** (lit.[3a]): IR 2961 (s), 2932 (s), 2875

(37) Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255.

(m), 2853 (m), 1683 (s) cm^{-1}; ^1H NMR δ 0.65−1.03 (m, 15 H), 1.03−1.38 (m, 8 H), 1.38−1.74 (m, 14 H), 1.74−2.32 (m, 3 H), 3.09−3.79 (m, 3 H); ^{13}C NMR δ 8.2, 9.9, 13.6, 26.9, 27.3, 27.9, 29.1, 30.3, 46.2, 78.2, 154.0.

***N*-(*tert*-Butoxycarbonyl)-2-phenylpyrrolidine (5).** *N*-Boc-2-phenylpyrrolidine (**5**) was obtained as a colorless oil in three ways: (1) the reduction of 3,4-dihydro-5-phenyl-2*H*-pyrrole (2-phenyl-1-pyrroline) and the subsequent protection of 2-phenylpyrrolidine with the Boc group (64% yield); (2) the coupling reaction catalyzed by preformed palladium catalyst (general procedure A, up to 57% yield); and (3) the coupling reaction catalyzed by CuCN and active Pd(0) generated *in situ* (general procedure B, up to 79% yield). **5** (lit.[11]): IR 3064 (w), 3031 (w), 2983 (s), 2925 (m), 2873 (m), 1698 (vs), 1397 (vs), 1370 (m), 1168 (s), 1120 (m), 753 (m), 708 (s) cm^{-1}; ^1H NMR δ 1.17 (s, 6 H), 1.46 (s, 3 H), 1.72−2.03 (m, 3 H), 2.30 (br s, 1 H), 3.62 (br s, 2 H), 4.76 and 4.97 (2 br s, 1 H, rotamer), 7.06−7.42 (m, 5 H); ^{13}C NMR δ 23.0, 28.0 (28.3), 35.8 (34.8), 46.9, 61.1 (60.4), 78.9, 125.2, 126.3, 128.0, 144.9 (143.6), 154.3; mass spectrum *m/z* (intensity) EI 248 (22, $M^+ + 1$), 246 (11, $M^+ - 1$), 192 (100, $M^+ - C_4H_7$), 170 (17, $M^+ - C_6H_5$), 146 (83, $M^+ - {}^tBuCO_2$).

Under a N_2 atmosphere, 3,4-dihydro-5-phenyl-2*H*-pyrrole[38] (2.08 mmol), $NiCl_2$ (0.52 g, 4 mmol), and MeOH (anhydrous, 20 mL) were stirred together and cooled to −30 °C. Then $NaBH_4$ (0.78 g, 20 mmol) was added in one portion, and the mixture changed color from gold to blue, finally becoming a black slurry. The mixture was stirred overnight (−30 °C to rt, 14 h),[39] treated with 2 N NaOH (10 mL), and extracted with Et_2O (20 mL × 3). The combined organic phase was washed with brine (15 mL × 3) and dried over K_2CO_3. The crude 2-phenylpyrrolidine (yellowish liquid, 0.2426 g, 79% yield) obtained upon filtration and concentrated *in vacuo* was used without further purification.

2-Phenylpyrrolidine (0.2426 g, ca. 1.65 mmol), *tert*-butoxy carbonate anhydride (0.72 g, 3.3 mmol), 4-(dimethylamino)pyridine (0.22 g, 1.65 mmol), NEt_3 (0.25 mL, ca. 1.7 mmol), and CH_2Cl_2 (20 mL) were stirred together under a N_2 atmosphere at room temperature for 16 h. The mixture was diluted with 50 mL of Et_2O and washed with 1 N HCl (20 mL × 3) and saturated aqueous $NaHCO_3$ (25 mL × 3). The organic phase was dried over K_2CO_3 (yellowish clear solution), filtered, and concentrated *in vacuo* to afford 0.458 g of a yellow liquid. Pure **5** (0.260 g colorless oil, 64% yield) was obtained by column chromatography (silica gel, 200−400 mesh, 20% Et_2O−petroleum ether, v/v, gravity, $R_f = 0.37$).

***N*-(*tert*-Butoxycarbonyl)-2-phenylpiperidine (6).** General procedure A was employed. $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) and CuCN (9 mg, 0.10 mmol) were used as catalysts on a 1 mmol reaction scale. Pure **6** was isolated as a colorless oil (lit.[11]) in 55% yield by column chromatography (silica gel, 10% Et_2O−petroleum ether, v/v, $R_f = 0.35$).

General procedure B was employed. TMEDA (0.33 mL, 2.2 mmol) or (−)-sparteine (0.23 mL, 1 mmol) was used in THF as solvent. $PdCl_2$ (9 mg, 0.05 mmol), CuCN (9 mg, 0.10 mmol), $SbPh_3$ (70.6 mg, 0.10 mmol), and K (2 mg, 0.05 mmol) were used to generate the catalyst mixture. *N*-Bocpiperidine (**2**, 0.185 g, 1 mmol) was converted into lithio amine **2-Li** which reacted with PhI (0.16 mL, 2 mmol) to afford crude product (0.541 g, yellow oil). Pure **6** (0.195 g, 75% yield) was obtained as colorless oil by preparative TLC (silica gel, 10% Et_2O−petroleum ether, v/v, $R_f = 0.35$): (lit.[11]) IR 3088 (w), 3065 (w), 3015 (w), 2980 (m), 2944 (s), 2870 (m), 1701 (vs), 1499 (m), 1481 (m), 1457 (s), 1420 (vs), 1371 (s), 1279 (s), 1249 (s), 1182 (s), 1163 (vs), 1022 (s), 863 (m), 741(w), 692 (m) cm^{-1}; ^1H NMR δ 1.46 (s, 9 H), 1.36−1.72 (m, 4 H), 1.78−2.03 (m, 1 H), 2.30 (d, $J = 14.02$ Hz, 1 H), 2.67−2.86 (m, 1 H), 4.05 (d, $J = 13.45$, 1 H), 5.42 (br s, 1 H), 7.08−7.53 (m, 5 H); ^{13}C NMR δ 19.3, 25.4, 28.0, 28.3, 40.0, 53.1, 79.4, 126.2, 126.4, 128.4, 140.3, 155.5; mass spectrum, *m/z* (intensity) EI 262 (14, $M^+ + 1$), 206 (98), 205 (98, $M^+ - C_4H_8$), 188 (52, $M^+ - C_4H_9O$), 160 (100, $M^+ - C_4H_9 - CO_2$), 77 (63, C_6H_5).

***N*-(*tert*-Butoxycarbonyl)-2-(4-methoxyphenyl)pyrrolidine (7).** General procedure A was employed. $PdCl_2(PPh_3)_2$ (35 mg, 5 mol %) and CuCN (9 mg, 10 mol %) were used as catalysts. *N*-Bocpyrrolidine (**1**, 0.171 g, 1 mmol) was converted into *N*-Boc-α-lithiopyrrolidine (**1-Li**) which reacted with *p*-$MeOC_6H_4I$ (0.351 g, 1.5 mmol), affording 0.505 g of crude product (orange oil). Half of the crude material was subjected to preparative TLC (silica gel, 20 cm × 20 cm × 0.2 cm, 10% Et_2O−petroleum ether, v/v), and 0.0466 g of pure **7** (pale yellow oil) was obtained (34% yield): IR 3065 (w), 2965 (s), 1698 (vs), 1615 (m), 1516 (s), 1398 (s), 1252 (s), 1170 (m), 1117 (m), 1041 (m), 835 (m), 777 (w) cm^{-1}; ^1H NMR δ 1.21 (s, 6 H), 1.47 (br s, 3 H), 1.69−2.06 (m, 3 H), 2.26 (br s, 1 H), 3.42−3.69 (m, 2 H), 3.79 (s, 3 H), 4.73 and 4.80 (2 br s, 1 H, rotamer), 6.84 (d, $J =$ 8.31 Hz, 2 H), 7.08 (d, $J = 8.31$ Hz, 2 H); ^{13}C NMR δ 23.2, 28.2, 36.0, 47.0, 55.2, 60.7, 79.1, 113.5, 114.7, 126.5, 133.9, 158.2; mass spectrum, *m/z* (intensity) EI 278 (21, $M^+ + 1$), 277 (60, M^+), 276 (12, $M^+ - 1$), 203 (11, $M^+ - C_4H_9OH$), 175 (30, $M^+ - C_4H_9OCHO$). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.31; H, 8.30; N, 5.05. Found: C, 69.13; H, 8.39; N, 5.10.

***N*-(*tert*-Butoxycarbonyl)-2-(4-methoxyphenyl)piperidine (8).** General procedure A was employed. $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) and CuCN (9 mg, 0.10 mmol) were used as catalysts. *N*-Bocpiperidine (**2**, 0.185 g, 1 mmol) was converted into α-lithio amine **2-Li** which was mixed with *p*-methoxyiodobenzene (0.351 g, 1.5 mmol)/catalyst mixture affording crude product (0.247 g, yellow oil). Pure **8** (pale yellow oil) was obtained by column chromatography (silica gel, 10% Et_2O−petroleum ether, v/v, $R_f = 0.27$) in 43% yield. When the oil was placed in a freezer, it became a white solid: mp 76.9−78 °C; IR 3061 (w), 3018 (w), 2962 (m), 2925 (m), 2882 (m), 2845 (w), 1686 (vs), 1612 (s), 1520 (s), 1471 (m), 1421 (s), 1267 (s), 1163 (s), 1039 (s), 842 (m) cm^{-1}; ^1H NMR δ 1.47 (s, 9 H), 1.33−1.67 (m, 4 H), 1.78−1.94 (m, 1 H), 2.26 (d, $J = 13.38$ Hz, 1 H), 2.64−2.69 (m, 1 H), 3.80 (s, 3 H), 4.02 (d, $J = 12.10$ Hz, 1 H), 5.37 (br s, 1 H,), 6.88 (d, $J = 8.63$ Hz, 2 H), 7.14 (d, $J = 8.81$ Hz, 2 H); ^{13}C NMR δ 19.3, 25.5, 28.4, 28.0, 39.9, 52.6, 55.2, 79.4, 113.9, 127.6, 132.3, 155.6, 158.1; mass spectrum, *m/z* (intensity) EI 292 (2, $M^+ + 1$), 291 (7, M^+), 235 (93), 218 (30), 190 (100, $M^+ - C_4H_9 - CO_2$), 57 (100, C_4H_9). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.10; H, 8.59; N, 4.81. Found: C, 70.19; H, 8.25; N, 5.40.

4-Methoxybenzonitrile was formed as a byproduct present in up to 26 mol %: IR 2216 cm^{-1}; ^1H NMR δ 4.04 (s, 3 H), 7.14 (d, $J = 9$ Hz, 2 H), 7.60 (d, $J = 9$ Hz, 2 H); ^{13}C NMR δ 55.4, 103.9, 114.7, 119.1, 133.9, 162.8 (calcd δ 56.0, 104.8, 114.8, 116.5, 133.0, 166.3).

***N*-(*tert*-Butoxycarbonyl)-2-(2-methylphenyl)pyrrolidine (9).** General procedure A was employed. $PdCl_2(PPh_3)_2$ (35 mg, 5 mol %) and CuCN (9 mg, 10 mol %) were used as catalysts. *N*-Bocpyrrolidine (**1**, 0.171 g, 1 mmol) was converted into *N*-Boc-α-lithiopyrrolidine (**1-Li**) which reacted with *o*-MeC_6H_4I (0.262 g, 1.2 mmol), affording 0.249 g of crude product (brown liquid) of which 0.169 g was subjected to column chromatography (silica gel, 10% Et_2O−petroleum ether, v/v, then pure Et_2O) to afford 0.113 g of pure **9** (pale yellow oil, 64% yield): IR 3068 (w), 3026 (w), 2979 (s), 2926 (m), 2878 (m), 1705 (vs), 1486 (m), 1463 (m), 1393 (vs), 1362 (s), 1255 (m), 1160 (vs), 1125 (s), 929 (m), 899 (m), 870 (m), 758 (m), 728 (s) cm^{-1}; ^1H NMR δ 1.15 (s, 6 H), 1.46 (s, 3 H), 1.58−1.81 (m, 1 H), 1.81−2.03 (m, 2 H), 2.32 (br s, 4 H), 3.38−3.78 (m, 2 H), 4.89−5.01 and 5.07−5.17 (2 m, 1 H, rotamers), 6.92−7.22 (m, 4 H); ^{13}C NMR δ 19.2, 23.1, 28.0 (28.5), 34.1, 47.1, 58.0, 79.0, 124.3, 125.8, 126.2, 129.9, 133.8, 143.2, 154.3; mass spectrum, *m/z* (intensity) CI 263 (11, $M^+ + 2$), 262 (65, $M^+ + 1$), 260 (4, $M^+ - 1$), 206 (100, $M^+ - C_4H_9$), 188 (13, $M^+ - C_4H_9O$), 162 (31). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.45; H, 8.91; N, 5.30.

***N*-(*tert*-Butoxycarbonyl)-2-(2-methylphenyl)piperidine (10).** General procedure A was employed. $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) and CuCN (9 mg, 0.10 mmol) were used as catalysts. *N*-Bocpiperidine (**2**, 0.185 g, 1 mmol) was converted into α-lithio amine **2-Li** which was reacted with *o*-methyliodobenzene (0.3301 g, 1.6 mmol) affording 0.2997 g of crude product (orange oil). Crude product (0.2747 g) was

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(39) Li, S. J.; Jiang, Y.; Mi, A.; Yang, G. *Synth. Commun.* **1992**, *22*, 1497.

subjected to preparative TLC (silica gel, 10% Et_2O−petroleum ether, v/v, $R_f = 0.49$), and 0.166 g of pure **10** (pale yellow oil) was obtained in 65% yield: IR 3101 (w), 3060 (w), 2971 (s), 2936 (s), 2870 (s), 1705 (vs), 1681 (vs), 1646 (m), 1479 (s), 1450 (s), 1402 (s), 1360 (s), 1277 (s), 1242 (s), 1182 (s), 1152 (s), 736 (m), 718 (w) cm^{-1}; ^1H NMR δ 1.27 (s, 9 H), 1.46−1.68 (m, 3 H), 1.68−2.00 (m, 3 H), 2.32 (s, 3 H), 3.11−3.42 (m, 1 H), 4.04 and 4.08 (2 br s, 1 H), 5.22 (t, $J = 5.54$ Hz, 1 H), 7.02−7.32 (m, 4 H); ^{13}C NMR δ 18.7, 19.2, 24.4, 28.1, 28.4, 41.2, 52.6, 79.2, 125.3, 125.6, 126.2, 130.6, 134.8, 142.5, 155.6; mass spectrum, *m/z* (intensity) CI 275 (5, M^+), 220 (93), 202 (14, $M^+ - C_4H_9O$), 128 (100, $M^+ - C_4H_9OH - C_6H_4CH_3$), 57 (22, C_4H_9). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.18; H, 9.09. Found: C, 74.08; H, 9.18.

***N*-(*tert*-Butoxycarbonyl)-2-(4-methylphenyl)pyrrolidine (11).** General procedure A was employed. $PdCl_2(PPh_3)_2$ (35 mg, 5 mol %) and CuCN (9 mg, 10 mol %) were used as catalysts in a 1 mmol scale reaction. *p*-Iodotoluene (0.262 g, 1.2 mmol) was used. Crude product (0.248 g), (a brown liquid), was obtained, of which 0.168 g was purified by column chromatography (silica gel, 10% Et_2O−petroleum ether, v/v) to afford 0.1190 g (67.3% yield) of pure **10** (pale yellow oil). When the product was placed in a freezer for approximately 2 weeks, it became colorless crystals: mp 62.7−64.2 °C; IR 3061 (w), 3025 (w), 2968 (s), 2874 (m), 1700 (vs), 1677 (vs), 1512 (m), 1459 (m), 1394 (vs), 1359 (s), 1158 (vs), 1123 (s), 822 (m), 775 (w), 740 (w) cm^{-1}; ^1H NMR δ 1.20 (s, 6 H), 1.46 (s, 3 H), 1.72−1.98 (m, 3 H), 2.30 (br s, 4 H), 3.61 (br s, 2 H), 4.73 and 4.91 (br s, 1 H, rotamer), 7.00−7.14 (m, 4 H); ^{13}C NMR δ 20.9 (20.3), 23.0, 28.1 (28.7), 35.8 (34.7), 46.9, 60.9 (60.0), 79.1, 125.3, 128.6, 135.8, 141.9, 154.6 (rotomers); mass spectrum, *m/z* (intensity) CI 263 (5, $M^+ + 2$), 262 (29, $M^+ + 1$), 260 (3, $M^+ - 1$), 206 (100), 188 (11, $M^+ - C_4H_9O$), 160 (32, $M^+ - C_4H_9 - CO_2$). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.44; H, 8.91; N, 5.21.

***N*-(*tert*-Butoxycarbonyl)-2-(4-methylphenyl)piperidine (12).** General procedure A was employed. $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) and CuCN (9 mg, 0.10 mmol) were used as catalysts. *N*-Bocpiperidine (**2**, 0.185 g, 1 mmol) was converted into α-lithio amine **2-Li** which was mixed with *p*-methyliodobenzene (0.262 g, 1.2 mmol)/catalyst mixture, affording 0.337 g of crude product (golden oil). Crude product (0.307 g) was subjected to preparative TLC (silica gel, 15% Et_2O−petroleum ether, v/v, $R_f = 0.26$), and 0.178 g of pure **12** was obtained as a colorless oil (71% yield): IR 3089 (w), 3060 (w), 3012 (w), 2977 (m), 2941 (s), 2870 (m), 1699 (vs), 1521 (m), 1485 (m), 1461 (m), 1420 (vs), 1372 (s), 1277 (s), 1248 (s), 1182 (s), 1164 (vs), 1040 (s), 879(m), 825 (m), 778 (w) cm^{-1}; ^1H NMR δ 1.46 (s, 9 H), 1.31−1.69 (m, 4 H), 1.69−1.94 (m, 1 H), 2.08−2.25 (m, 1 H), 2.26 (s, 3 H), 2.61−2.83 (m, 1 H), 4.04 and 4.06 (2 br s, 1 H, rotomers), 5.39 (br s, 1 H), 7.00−7.28 (m, 4 H); ^{13}C NMR δ 19.2, 20.8, 25.4, 27.9, 28.3, 39.9, 52.9, 79.3, 126.3, 129.1, 135.7, 137.1, 155.5; mass spectrum, *m/z* (intensity) CI 277 (4, $M^+ + 2$), 276 (32, $M^+ + 1$), 274 (3, $M^+ - 1$), 220 (100), 176 (57), 57 (11). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.18; H, 9.09; N, 5.09. Found: C, 73.93; H, 9.02; N, 4.96.

***N*-(*tert*-Butoxycarbonyl)-2-(1-naphthyl)pyrrolidine (13).** General procedure B was employed. $PdCl_2$ (9 mg, 0.05 mmol), bppf (27.7 mg, 0.05 mmol), CuCN (9 mg, 0.10 mmol), and K (2 mg, 0.05 mmol) were used to generate the catalyst. *N*-Bocpyrrolidine (**1**, 0.171 g, 1 mmol) was converted into α-lithio amine **1-Li** which reacted with 1-iodonaphthalene (0.381 g, 1.5 mmol) at −78 °C to room temperature for 13 h, affording 0.508 g of crude product (dark-yellow oil). Pure **13** was obtained in 39% yield as white/colorless crystals after preparative TLC (silica gel, 20 cm × 20 cm × 0.2 cm, 10% Et_2O−petroleum ether, v/v, $R_f = 0.20$): mp 126.1−127.6 °C; IR 3068 (w), 3052 (w), 2978 (m), 2882 (w), 1686 (vs), 1404 (vs), 1175 (s), 1132 (m), 909 (vs), 745 (vs) cm^{-1}; ^1H NMR δ 1.10 (s, 6 H), 1.46 (s, 3 H), 1.64−1.99 (m, 3 H), 2.25−2.55 (m, 1 H), 3.39−3.86 (m, 2 H), 5.60 and 5.75 (2 d, $J = 6.56$ Hz, $J = 7.94$ Hz, 1 H, rotamer), 7.11−8.06 (m, 7 H); ^{13}C NMR δ 22.9 (23.4), 28.0 (28.5), 34.3 (33.2), 46.8 (47.2), 58.1, 79.1, 121.7 (121.3), 122.9 (123.2), 125.2 (125.1), 125.6, 127.0, 128.7, 130.2, 133.7 (134.0), 138.7, 139.8, 154.5; mass spectrum, *m/z* (intensity) EI 297 (6, M^+), 241 (41, $M^+ - C_4H_8$), 240 (27, $M^+ - C_4H_9$), 196 (100, $M^+ - C_4H_9 - CO_2$), 168 (30), 127 (10, $C_{10}H_7$), 57 (54, C_4H_9). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.77; H, 7.74; N, 4.71. Found: C, 76.70; H, 7.80; N, 4.70.

***N*-(*tert*-Butoxycarbonyl)-2-(1-naphthyl)piperidine (14).** General procedure B was employed. (−)-Sparteine (0.23 mL, 1 mmol) was used in THF as solvent. $PdCl_2$ (9 mg, 0.05 mmol), CuCN (9 mg, 0.10 mmol), $SbPh_3$ (70.6 mg, 0.10 mmol), and K (2 mg, 0.05 mmol) were used to generate the catalyst mixture. The lithio amine **2-Li** was generated (1 mmol) and was mixed with 1-iodonaphthalene (0.381 g, 1.5 mmol)/catalyst mixture, affording 0.684 g of crude product (pink oil). Preparative TLC (silica gel, 10% Et_2O−petroleum ether, v/v, $R_f = 0.13$) afforded 0.1308 g of pure **14** (colorless oil, 42% yield): IR 3056 (w), 2977 (m), 2941 (m), 2862 (w), 1685 (vs), 1157 (m) cm^{-1}; ^1H NMR δ 1.25 (s, 9 H), 1.39−1.92 (m, 5 H), 1.92−2.25 (m, 2 H), 3.08−3.36 (m, 1 H), 3.90-4.21 (m, 1 H), 5.94 (t, $J = 4.45$ Hz, 1 H), 7.03−8.17 (m, 6 H); ^{13}C NMR δ 19.4, 24.7, 28.2, 29.4, 41.7, 52.1, 79.5, 123.2, 123.5, 124.9, 125.3, 125.8, 127.3, 128.8, 130.9, 134.0, 139.3, 155.7; mass spectrum, *m/z* (intensity) EI 312 (1.4, $M^+ + 1$), 311 (6, M^+), 255 (85, $M^+ - C_4H_8$), 210 (100, $M^+ - C_4H_9 - CO_2$), 194 (21), 154 (17), 127 (13, $C_{10}H_7$), 57 (38, C_4H_9). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.17; H, 8.04. Found: C, 77.02; H, 8.14.

2-[*N*-(*tert*-Butoxycarbonyl)-2-pyrrolidinyl]thiophene (15). General procedure B was employed. $PdCl_2$ (9 mg, 0.05 mmol), CuCN (9 mg, 0.10 mmol), $AsPh_3$ (61.5 mg, 0.10 mmol), and K (2 mg, 0.05 mmol) were used to generate the catalysts. *N*-Bocpyrrolidine (**1**, 0.171 g, 1 mmol) was converted into α-lithio amine **1-Li** which was mixed with α-iodothiophene (0.231 g, 1.1 mmol)/catalysts and stirred at −78 °C to room temperature for 18 h, affording 0.499 g of crude product (brown cake). Purification by preparative TLC (silica gel, 20 cm × 20 cm × 0.2 cm, 10% Et_2O−petroleum ether, v/v) gave pure **15** (yellow oil) in 36% yield: IR 3068 (w), 2978 (s), 2935 (m), 2877 (m), 1696 (vs), 1398 (vs), 1170 (s), 1111 (m), 702 (m) cm^{-1}; ^1H NMR δ 1.37 (br s, 9 H), 1.81−2.14 (m, 3 H), 2.14−2.42 (m, 1 H), 3.19−3.78 (m, 2 H), 5.13 (br s, 1 H), 6.72−7.00 (m, 2 H), 7.13 (d, $J = 6.26$ Hz, 1 H); ^{13}C NMR δ 23.3, 28.3, 35.0, 46.2, 56.7, 79.5, 123.0, 123.2, 126.4, 149.0, 154.4; mass spectrum *m/z* (intensity) EI 197 (99, $M^+ - C_4H_8$), 180 (19, $M^+ - C_4H_9O$), 152 (74, $M^+ - C_4H_9 - CO_2$), 57 (100, C_4H_9).

2-[*N*-(*tert*-Butoxycarbonyl)-2-piperidinyl]thiophene (16). General procedure B was employed. *N*-Bocpiperidine (**2**, 0.185 g, 1 mmol) was converted into lithio amine **2-Li** (TMEDA, 0.33 mL, 2.2 mmol was used). $PdCl_2$ (9 mg, 0.05 mmol), $SbPh_3$ (0.706 mg, 0.10 mmol), CuCN (10 mg, 0.11 mmol), and K (2 mg, 0.05 mmol) were used to generate the catalyst. 2-Iodothiophene (0.231 g, 1.1 mmol) was reacted with the lithio amine and afforded 0.315 g of crude product (brown cake), which was purified by preparative TLC (silica gel, 10% Et_2O−petroleum ether, v/v, $R_f = 0.47$) to afford 0.1121 g (42.0% yield) of **16** (pale yellow oil). The product was further purified by bulb-to-bulb distillation to afford a colorless oil: bp 110−125 °C (0.05−0.10 mmHg); IR 2969 (w), 2938 (m), 2865 (w), 1695 (vs), 1457 (m), 1415 (m), 1368 (m), 1274 (m), 1165 (m) cm^{-1}; ^1H NMR δ 1.49, (s, 9 H), 1.42−1.78 (m, 4 H), 1.78−2.01 (m, 1 H), 2.18 (d, $J = 13.87$ Hz, 1 H), 2.64−2.94 (dt, $J_1 = 2.88$ Hz, $J_2 = 13.04$ Hz, 1 H), 3.99 and 4.04 (2 br s, 1 H), 5.59 (br s,1 H), 6.82 (d, $J = 2.44$ Hz, 1 H), 6.95 (t, $J = 3.60$ Hz, 1 H), 7.20 (d, $J = 5.03$ Hz, 1 H); ^{13}C NMR δ 19.5, 25.3, 28.4, 29.4, 39.7, 50.7, 79.8, 124.1, 124.2, 126.7, 145.4, 154.9; mass spectrum, *m/z* (intensity) EI 211 (100, $M^+ - C_4H_8$), 194 (12, $M^+ - C_4H_9O$), 166 (58), 97 (14), 57 (47, C_4H_9). Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.92; H, 7.87. Found: C, 63.12; H, 8.04.

***N*-(*tert*-Butoxycarbonyl)-2-(1-hexenyl)pyrrolidine (17).** General procedure B was employed. *N*-Bocpyrrolidine (**1**, 0.171 g, 1.0 mmol) was converted into lithio amine **1-Li**. $PdCl_2$ (9 mg, 0.05 mmol), $SbPh_3$ (70.6 mg, 0.10 mmol), K (2 mg, 0.05 mmol), and CuCN (9 mg, 0.10 mmol) were used to generate the catalyst system. 1-Iodohexene (0.315 g, 1.5 mmol) was reacted with the lithio amine under the influence of the catalyst, affording 0.382 g of crude product (brown liquid), which was purified by column chromatography (silica gel, 10% Et_2O−petroleum ether, v/v, $R_f = 0.28$), and gave 0.0879 g (35% yield) of **17** (yellow oil) and 0.0675 g (36% yield) of *N*-Boc-2-hydroxypyrrolidine. Product **17** was further purified by bulb-

to-bulb distillation to afford a colorless oil: bp 105−115 °C (0.05−0.01 mmHg): IR 2961 (s), 2932 (s), 2873 (m), 1701 (vs), 1480 (m), 1455 (m), 1397 (vs), 1366 (s), 1174 (s), 1115 (m), 967 (w), 879 (w), 775 (w) cm^{-1}; ^1H NMR δ 0.88 (t, J = 6.9 Hz, 3 H), 1.19−1.54 (m, 5 H), 1.43 (s, 9 H), 1.54−2.10 (m, 5 H), 3.77 (br s, 2 H), 4.08−4.41 (m. 1 H), 5.22−5.58 (m, 2 H); ^{13}C NMR δ 13.8, 22.0, 22.8 (br), 28.4, 31.4, 31.7, 32.4 (br), 46.0 (br), 58.5, 78.7, 130.2 (2C), 154.6 (br); mass spectrum, *m*/*z* (intensity) EI 198 (3.6), 197 (25, $M^+ - C_4H_8$), 196 (15, $M^+ - C_4H_9$), 180 (17, $M^+ - C_4H_9O$), 152 (6, $M^+ - C_4H_9 - CO_2$). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.15; H, 10.67. Found: C, 70.88; H, 10.60.

***N*-(*tert*-Butoxycarbonyl)-2-(hex-1-enyl)piperidine (18).** General procedure B was employed. *N*-Bocpiperidine (**2**, 0.185 g, 1 mmol) was converted into lithio amine **2-Li** (TMEDA, 0.33 mL, 2.2 mmol was used). $PdCl_2$ (9 mg, 0.05 mmol), CuCN (9 mg, 0.10 mmol), $SbPh_3$ (0.706 mg, 0.10 mmol), and K (2 mg, 0.05 mmol) were used to generate the catalyst system. 1-Iodohexene (0.42 g, 2 mmol) was reacted with the lithio amine and gave 0.400 g of crude product (reddish oil), which was subjected to column chromatography (silica gel, 10% Et_2O−petroleum ether, v/v, R_f = 0.38), and gave 0.0461 g (17% yield) of pure **18** (colorless oil): bp 65−70 °C (0.01−0.05 mmHg); IR 3014 (w), 2939 (s), 2865 (m), 1701 (vs), 1679 (shoulder), 1426 (s), 1369 (m), 1277 (m), 1243 (m), 1169 (m), 1138 (s), 1020 (w), 876 (w), 762 (w) cm^{-1}; ^1H NMR δ 0.74−0.88 (m, 3 H), 1.44−1.77 (m, 10 H), 1.38 (s, 9 H), 1.86−2.17 (m, 1 H), 2.75 (t, J = 12.82 Hz, 1 H), 3.24−3.34 (m, 1 H), 3.85 (d, J = 12.17 Hz, 1 H), 4.66 (br s, 1 H), 5.22−5.53 (m, 2 H); ^{13}C NMR δ 13.9, 19.5, 22.1, 25.6, 28.5, 29.4, 31.5, 32.1, 39.6, 51.9, 79.1, 128.1, 131.9, 155.4; mass spectrum, *m*/*z* (intensity) EI 211 (20, $M^+ - C_4H_8$), 194 (17, $M^+ - C_4H_9O$), 166 (21, $M^+ - C_4H_9 - CO_2$), 154 (69), 141 (100), 57 (57, C_4H_9). Anal. Calcd for $C_{16}H_{29}NO_2$: C, 71.91; H, 10.86; N, 5.24. Found: C, 72.07; H, 11.03; N, 5.09.

***N*-(*tert*-Butoxycarbonyl)-2-(2-hexenyl)pyrrolidine (19).** General procedure B was employed using 2-iodo-1-hexene (0.415 g, 1.9 mmol). The crude material (0.452 g, brown liquid) was purified by column chromatography (silica gel, 10% Et_2O−petroleum ether, v/v, R_f = 0.26), and 0.0675 g (36% yield) of *N*-Boc-2-hydroxypyrrolidine along with 0.0263 g (colorless oil, 10% yield) of pure **19** was obtained: bp 100−115 °C (0.05−0.01 mmHg); IR 2965 (s), 2934 (s), 2879 (m), 1701 (vs), 1389 (vs), 1366 (s), 1178 (s), 1124 (s), 898 (w), 770 (w) cm^{-1}; ^1H NMR δ 0.91 (t, J = 7.16 Hz, 3 H), 1.17−1.64 (m, 4 H), 1.41 (s, 9 H), 1.64−2.39 (m, 6 H), 3.30−3.55 (br s, 2 H), 4.19 and 4.27 (2 br s, 1 H, rotamer), 4.71 (br s, 1 H), 4.75 (br s, 1 H); ^{13}C NMR δ 13.9, 22.6, 22.8 (23.2), 28.4, 30.2, 31.4, 32.7, 46.5 (46.8), 61.3, 78.9, 107.2, 150.2 (149.6), 154.6; mass spectrum, *m*/*z* (intensity) EI 253 (0.5, M^+), 197 (13, $M^+ - C_4H_8$), 180 (13, $M^+ - C_4H_9O$), 154 (18), 114 (100), 83 (1). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.15; H, 10.67. Found: C, 70.87; H, 10.69.

***N*-(*tert*-Butoxycarbonyl)-2-(1-hexynyl)pyrrolidine (21).** General procedure B was employed. *N*-Bocpyrrolidine (**1**, 0.171 g, 1.0 mmol) was used to generate the lithio amine [0.35 mL (ca. 1.5 mmol) of (−)-sparteine was used]. $PdCl_2$ (9 mg, 0.05 mmol), $SbPh_3$ (70.6 mg, 0.10 mmol), K (2 mg, 0.05 mmol), and CuCN (9 mg, 0.10 mmol) were used to generate the catalyst system. 1-Iodohexyne (0.367 g, ca. 1.6 mmol) was used as coupling substrate. The crude material (0.749 g, dark brown oil) was purified by column chromatography (silica gel, 10% Et_2O−petroleum ether, v/v, R_f = 0.33) and gave 0.0863 g (yellow oil, 34% yield) of **21**. The product was further purified by bulb-to-bulb distillation to give a colorless oil: bp 125 °C (0.05 mmHg); IR 2982 (m), 2962 (m), 2933 (m), 2875 (w), 1687 (vs), 1407 (s), 1375 (m), 1174 (m), 1116 (w) cm^{-1}; ^1H NMR δ 0.61−1.11 (m, 3 H), 1.41 (br s, 14 H), 1.69−2.06 (m, 3 H), 2.10 (t, J = 6.74 Hz, 2 H), 3.24 (br s, 1 H), 3.38 (br s, 1 H), 4.35 (br s, 1 H); ^{13}C NMR δ 13.5 (14.0), 18.2, 21.7, 23.7, 28.4 (28.5), 30.8, 33.9, 45.4, 48.2, 79.2, 80.5, 81.7, 154.1; mass spectrum, *m*/*z* (intensity) EI 195 (6, $M^+ - C_4H_8$), 178 (12), 153 (99), 81 (17), 57 (100).

***N*-(*tert*-Butoxycarbonyl)-2-hydroxypyrrolidine.** *N*-Boc-2-hydroxypyrrolidine was obtained in two ways: (1) The reduction of *N*-Boc-2-pyrrolidinone by DIBALH (2 equiv) at −78 °C gave an almost quantitative yield of *N*-(*tert*-butoxycarbonyl)-2-hydroxypyrrolidine; (2) The coupling reaction of 1- or 2-iodo-1-hexene with lithio amine **1-Li** (general procedure B) gave 36% yield of *N*-(*tert*-butoxycarbonyl)-2-hydroxypyrrolidine: IR 3448 (br, w), 2973 (s), 2934 (s), 2879 (m), 1704 (vs), 1397 (vs) cm^{-1}; ^1H NMR δ 1.47 (s, 9 H), 1.66−2.76 (m, 4 H), 2.92−3.42 (m, 1 H), 3.42−3.66 (m, 1 H), 3.66−4.18 (m, 1 H), 5.39 and 5.48 (2 br s, 1 H, rotamer); ^{13}C NMR δ 22.6 (21.9), 28.3, 32.7 (33.4), 45.8 (45.6), 79.9 (80.2), 81.5 (81.3), 155.0 (153, rotamers); mass spectrum, *m*/*z* (intensity) EI 169 (8, $M^+ - H_2O$), 113 (39), 96 (28), 68 (41), 57 (100, C_4H_9).

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