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Conjugate Addition Reactions of *N*-Carbamoyl-4-pyridones and 2,3-Dihydropyridones with Grignard Reagents in the Absence of Cu(I) Salts

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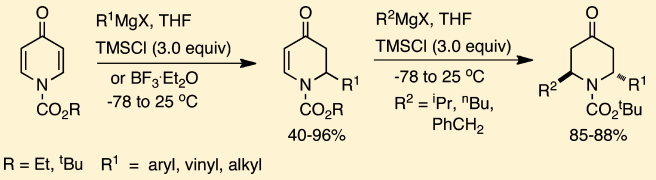
Supporting Information

ABSTRACT: *N*-Boc- and *N*-ethoxycarbonyl-4-pyridones and the resulting 2,3-dihydropyridones undergo 1,4-addition reactions with Grignard reagents in the presence of chlorotrimethylsilane (TMSCl) or $BF_3{\cdot}Et_2O$ in excellent yields. Copper catalysis is not required, and mechanistic considerations suggest that the reaction is proceeding by a conjugate addition pathway rather than by a pathway involving 1,2-addition to an intermediate pyridinium ion. TMSCl-mediated conjugate addition of Grignard reagents to 2-substituted-2,3-dihydropyridones gives the *trans*-2,6-disubstitued piperidinones stereoselectively, while cuprate reagents give either the *trans* or *cis* diastereomers or mixtures.



INTRODUCTION

Piperidines and their annulated derivatives are an extremely important class of medicinal compounds[1,2] reflected in the examination of over 12 000 discrete piperidine entities in clinical or preclinical studies over a 10-year period.[1b] Numerous synthetic strategies for the synthesis of piperidine derivatives have been developed.[3,4] Although most of these strategies rely extensively on manipulation of the chiral pool for appropriate starting materials[3b] or use of chiral auxiliaries,[3d] these protocols have been developed into effective methods that can be done on large scales and provide considerable versatility for the synthesis of a wide variety of *N*-heterocycles. Asymmetric synthetic routes to piperidines[3] generally revolve around four strategic approaches:[3a] (A) ring formation via alkylation of a nitrogen center with an acyclic precursor containing pre-established stereogenic centers; (B) asymmetric generation of stereocenters and substitution patterns on an existing six-membered nitrogen heterocycle; (C) ring expansion of pyrrolidine or furan derivatives; and more recently, (D) ring closing-metathesis on dialkyl substituted nitrogen derivatives where each alkyl group contains an appropriately positioned alkene functional group. Recent reports involving 2,3-dihydro-4-pyridones[4] are particularly attractive for piperidine syntheses via conjugate addition reactions.[5−7] Much of this work involves the use of dialkylzinc reagents in conjunction with copper catalysts, and these reagents remain limited in reactivity and general applicability.[5,7a,c] Recent developments in copper-catalyzed asymmetric Grignard conjugate additions promise greater reactivity and versatility[6,7b] as do the rhodium-catalyzed 1,4-additions of arylboroxines.[4b]

Regioselective 1,2-addition of Grignard reagents to pyridinium salts is also a well established synthetic strategy for the preparation of *N*-heterocycles containing the piperidine motif (Figure 1A).[8,9] In pursuit of a catalytic asymmetric approach to substituted piperidines or piperidinones, we reported the conjugate addition reactions of organocuprates, and of organozincate and organolithium reagents to *N*-carbamoyl-4-

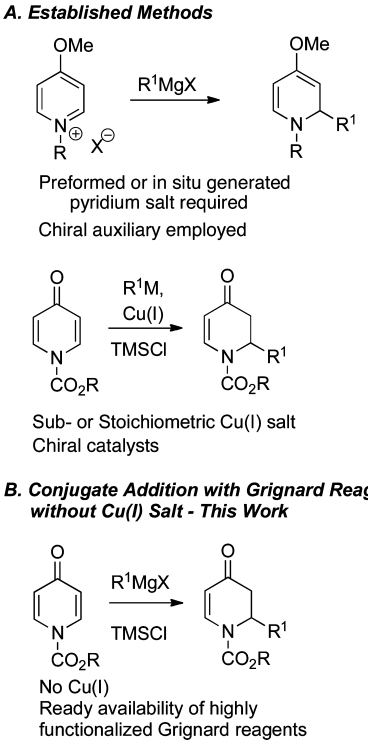


Figure 1. Synthesis of substituted-2,3-dihydropyridones.

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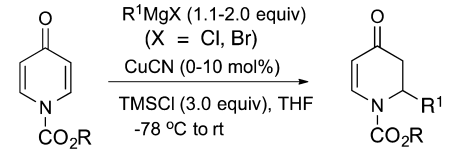
pyridones in the presence of catalytic or substoichiometric amounts of copper(I) salts (Figure 1A).[10] Subsequently, we examined the use of Grignard reagents with copper catalysis in pursuit of catalytic asymmetric conjugate additions to 4-pyridones. Chlorotrimethylsilane (TMSCl) accelerates copper mediated conjugate addition reactions in THF,[11] and after our initial report, we discovered that Grignard reagents in the presence of TMSCl undergo a formal 1,4-addition reaction to *N*-carbamoyl-4-pyridones in the absence of Cu(I) salts. The conjugate addition of a dithianyllithium[12a] reagent to a *N*-carbamoyl-4-quinolone and an *N*-carbamoylallyllithium reagent[12b] to a 4-pyridone represent two very limited examples of copper-free conjugate additions to these systems and do not demonstrate a generality of the reaction. Since the pioneering observation by Barbier[13a] and later detailed studies by Victor Grignard,[13b] the Grignard reagent has become ubiquitious in carbon−carbon bond forming reactions and offers advantages over the more basic and nucleophilic organolithium reagents. The use of highly functionalized Grignard reagents readily available from the corresponding halocompounds via halogen metal exhange reactions allows for an expansive application of this chemistry.[14]

RESULTS

Initially, we started our investigation with *n*-BuMgCl and *tert*-butyl carbamate **1** sequentially reducing the amount of added CuCN catalyst. The reaction afforded the 1,4-adduct in good chemical yields (Table 1, entries 1−2) with either 10.0 or 1.0 mol % of CuCN in the presence of trimethylsilyl chloride (TMSCl). No 1,2-addition product was observed. Surprisingly, an even higher chemical yield of the 1,4-adduct was obtained when the CuCN catalyst was eliminated from the reaction mixture (entry 3). In a control experiment, elimination of both the CuCN catalyst and the TMSCl additive afforded a low yield of the 1,4-adduct (entry 4). Alkyl Grignard reagents also added to the ethyl carbamate **2** in the presence (entry 5) and absence of CuCN (entry 6), although the yields were slightly lower than those obtained with the *tert*-butylcarbamate **1**. Although aryl Grignard reagents gave excellent yields of 1,4-addition products in the presence of CuCN (entries 7 and 9) and reduced yields in its absence (entry 8) with ethylcarbamate **2**, the heteroaryl cuprates gave good yields of conjugate addition products without the use of CuCN (entries 10 and 11).

Given the sometimes lower yields obtained with ethyl carbamate **2**, the scope of the addition of Grignard reagents to 4-pyridones in the absence of CuCN was explored with *N*-*tert*-butoxycarbonyl-4-pyridone **1** (Table 2).

Table 1. Reactions of R^1 MgCl with *N*-Carbamoyl-4-Pyridones with or without Catalytic Amounts of CuCN



1 R = ^{t}Bu
2 R = Et

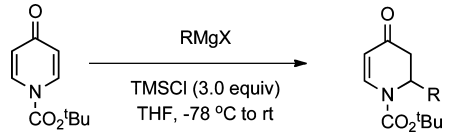
a R^1 = ^{n}Bu **b** R = ^{i}Pr
c R^1 = 2-$MeOC_6H_4$
d R^1 = 2-MeC_6H_4
e R^1 = 2-thienyl **f** R^1 = 2-furyl

3 R = ^{t}Bu
4 R = Et

entry	R^1	CuCN[a,b] (mol %)	product	%[c] yield
1	**1**	10	**3a**	79
2	**1**	1	**3a**	85
3	**1**	0	**3a**	90
4	**1**	0	**3a**	<5[d]
5	**2**	10	**4a**	76
6	**2**	0	**4b**	60
7	**2**	10	**4c**	71
8	**2**	0	**4c**	46
9	**2**	10	**4d**	72
10	**2**	0	**4e**	78
11	**2**	0	**4f**	75

[a]All the reactions were run in THF using 1.1−2.0 equiv of R^1 MgX (X = Cl, Br). TMSCl (3.0 equiv) was added as an additive. After the addition of starting 4-pyridone (**1** or **2**) at −78 °C, the reaction was stirred overnight and allowed to warm up to room temperature. [b]CuCN was added to a flask charged with argon as a solid, and dry THF was added followed by addition of R^1 MgCl at −78 °C. [c]Yields are based on isolated product purified by column chromatography. [d]No TMSCl was added.

Table 2. Reaction of Grignard Reagents with *N*-*tert*-Butoxycarbonyl-4-pyridone 1 in the Absence of CuCN



1 **3b-q**

entry	R (RMgX)[a]	RMgX (equiv)	**3**	%[b] yield
1	Me	1.2	**3g**	40
2	Et	1.2	**3h**	89
3	Et	1.2	**3h**	83[c]
4	^{i}Pr	1.1	**3b**	86
5	$PhCH_2$	2.0	**3i**	81
6	Ph	1.1	**3j**	85
7	2-$MeOC_6H_4$	1.2	**3c**	86
8	2-MeC_6H_4	1.2	**3d**	95
9	4-$Me_2NC_6H_4$	2.0	**3k**	96
10	2-$ClCH_2C_6H_4$	1.0	**3l**	86
11	1-naphthyl	2.0	**3m**	79
12	2-thienyl	2.0	**3e**	83
13	2-furyl	2.0	**3f**	85
14	2-(1-Me)pyrrolyl	2.0	**3n**	70
15	5-(1-Me)indolyl	1.0	**3o**	86
16	vinyl	1.2	**3p**	75
17	(*E*) 1-hexenyl	1.2	**3q**	82

[a]Reactions were run without the addition of CuCN. All the reactions were performed in the presence of 3.0 equiv of TMSCl. After the addition of starting 4-pyridone **1** and TMSCl (3.0 equiv) in THF at −78 °C, the reaction was allowed to warmed to room temperature and stirred overnight. All the reactions were quenched at room temperature. [b]Yields are based on isolated products purified by column chromatography. [c]The reaction was run in a 1:1 mixture of THF and *t*-BuOMe.

Alkyl Grignard reagents such as methyl, ethyl, isopropyl, and benzyl all readily added to *N*-*tert*-butoxycarbonyl (*N*-Boc)-4-pyridone (**1**) to afford the 1,4-conjugate adduct in modest to excellent chemical yields (Table 2, entries 1−5, 40−89%). With the employment of a 1:1 mixture of THF and *t*-BuOMe, ethylmagnesium chloride gave a slightly lower chemical yield than in pure THF (Table 2, entry 3 vs 2, 83 vs 89%). Aryl and heteroaryl Grignard reagents also added to *N*-Boc-4-pyridone

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(**1**) affording **3c,d,j–m** (79–96%) and **3e,f,n,o** (70–86%), respectively, with good to excellent yields (Table 2, entries 6–11 and 12–15, respectively) illustrating a compatibility with additional heteroatom functionality in the Grignard reagent. The utilization of vinyl Grignard reagents also proved successful (entries 16 and 17), affording the 1,4-adducts in comparable yields.

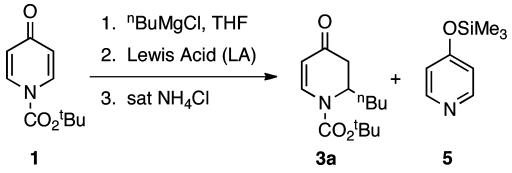
The procedure failed with alkynyl Grignard reagents and with Grignard reagents derived from *N*-methylimidazole, 2-bromonitrobenzene, and 1,3-dimethyl-5-iodouracil. The Grignard reagent derived from *N*-methylimidazole was successfully added to benzaldehyde (71%). Ketone and ester enolates also failed to undergo conjugate addition reactions. Attempts to extend the protocol to α,β-unsaturated amides was also unsuccessful.

A brief examination of Lewis Acids revealed that trimethylsilyl triflate (TMSOTf), *tert*-butyldimethylsilyl chloride (TBDMSCl), $TiCl_4$ and $Ti(O^iPr)_4$ failed to promote the addition reaction, while both TMSCl (Tables 2 and 3) and $BF_3\cdot Et_2O$ were effective (Table 3). The reaction was slow at −23 °C (entries 1–3), gave lower yields of **3a** when conducted at room temperature (Table 3, entries 5–6 vs Table 1, entry 3) with 2.0–3.0 equiv of TMSCl, and failed with 1 equiv of TMSCl (entry 4). When the reaction was carried out at room temperature, **3a** was formed in lower yields in toluene (entry 7) and chloroform (entry 8) than in THF (entries 6) but gave slightly higher yields in CH_2Cl_2 (entry 9). A significant amount of *N*-Boc cleavage product **5** was isolated from reactions run at room temperature confirming the competitive rate of the carbamate cleavage pathway at higher temperatures. $BF_3\cdot Et_2O$ was as effective as TMSCl under the standard conditions (i.e., THF, −78 to 25 °C, 12 h, entries 10–12). In contrast to TMSCl, 1 equiv of $BF_3\cdot Et_2O$ proved effective (entry 12), albeit in lower yields than when 2 equiv were employed.

Silanes other than TMSCl gave either cleavage of the carbamate functionality (e.g., TMSOTf) or recovered starting material (e.g., ^{t}BuMe$_2$SiCl) (Table 4). The cleavage pathway was slow with 2.0 equiv of TMSCl (entries 1–6), moderate with 4.0 equiv of TMSCl (entries 7–8), very slow with ^{t}BuMe$_2$SiCl (entries 9–15), and rapid with TMSOTf (entry 16). In NMR control experiments, the time-dependent observation of the carbamate cleavage product at 25 °C was a function of TMSCl concentration (entries 1–8). Cleavage products were confirmed by the presence of isobutylene (i.e., **7**: ^{13}C NMR[15a,b] δ 142.4, 110.5, 24.1; ^{1}H NMR[15c]) and ^{t}BuCl (**8a**: ^{13}C NMR δ 33.9, 66.7).[15d] The corresponding ^{t}BuOTf **8b** was not observed.

When the reaction of **1** with ^{n}BuMgCl and TMSCl (3.0 equiv) was monitored by NMR spectroscopy (25 °C, $CDCl_3$:THF, 4:1) species A was observed, which was slowly converted into B. The solution became cloudy after 45 min and displayed a suspension after 2 h, although the Grignard reagent absorption signal [i.e., δ −0.45 (t, 2H), $-CH_2-MgCl$] disappeared after 5 min. Addition of ^{n}Bu$_4$NF (1.0 equiv) converted the suspension into a clear solution. NMR analysis and comparison with known compounds revealed that B was 4-silyloxypyridine **5** resulting from carbamate cleavage, and product isolation from the mixture revealed the presence of **3a** (7%) and **1** (7%) as minor components along with carbamate cleavage products. When the $CDCl_3$ was filtered through basic aluminia to remove adventitious DCl before sample preparation, starting material and a new species consistent with the expected silyl enol ether **9** [^{13}C NMR δ

Table 3. Reaction of 4-Pyridone 1 with ^{n}BuMgCl and Lewis Acids

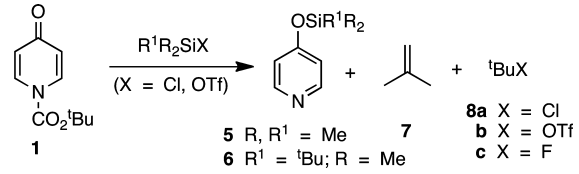


1 **3a** **5**

entry[a]	Lewis Acid	LA (equiv)	T (°C), t (h)	**3a**, % yield[b]	**1**:**3a**[c] or (% **5**)[b]
1	TMSCl	2.0	−23, 1	48	55:45
2	TMSCl	2.0	−23, 2	53	45:55
3	TMSCl	2.0	−23, 3	61	30:70
4	TMSCl	1.0	A[d]	trace	–
5	TMSCl	3.0	25, 2	57	
6	TMSCl	3.0	25, 3	68	
7	TMSCl	3.0	25, 3	47[e]	(41)
8[f]	TMSCl	3.0	25, 3	55[g]	(37)
9[f]	TMSCl	3.0	25, 3	73[h]	(13)
10	$BF_3.Et_2O$	2.0	A[d]	82	
11[f]	$BF_3.Et_2O$	2.0	A[d]	70	
12	$BF_3.Et_2O$	1.0	A[d]	57	

[a]The reaction was run using 2 equiv of ^{n}BuMgCl unless otherwise noted. [b]Yields are based upon isolated products purified by column chromatography. [c]Determined by NMR integration ratios of the olefin absorptions. [d]A = −78 to 25 °C, 12 h. [e]The reaction was conducted in $PhCH_3$. [f]^{n}BuMgCl (1.0–1.2 equiv). [g]The reaction was done in $CHCl_3$. [h]The reaction was done in CH_2Cl_2.

Table 4. NMR Investigations of 4-Pyridone–Lewis Acid Mixtures



1

entry	R[1], R, X	LA (equiv)	t (h)	NMR ratio **1**:**5**(**6**):**7**:**8**[b,c]
1	Me[a], Cl	2.0	0.08	no rxn
2	Me[a], Cl	2.0	0.33	94.5:5.5:3.7:1.8
3	Me[a], Cl	2.0	0.66	91:9:6:3
4	Me[a], Cl	2.0	1.0	87.3:20.5:13.7:6.8
5	Me[a], Cl	2.0	2.0	74.1:24.9:16.6:8.3
6	Me[a], Cl	2.0	3.0	76:24:14:19
7	Me[a], Cl	4.0	0.08	56.3:43.7:29.1:14.6
8	Me[a], Cl	4.0	18	0:100:66:33
9	^{t}Bu, Me, Cl	1.0	0.08	no rxn
10	^{t}Bu, Me, Cl	1.0	0.33	no rxn
11	^{t}Bu, Me, Cl	1.0	0.66	no rxn
12	^{t}Bu, Me, Cl	2.0	0.08	no rxn
13	^{t}Bu, Me, Cl	2.0	0.66	no rxn
14	^{t}Bu, Me, Cl	2.0	15	73:(27):14:13
15	^{t}Bu, Me, Cl	2.0	92	53:(47):22:25
16	Me, OTf	1.0	0.08	0:100:78:22

[a]R[1] = R. [b]The **7**:**8** ratios are determined relative to **5** or **6**. [c]The ratios were calculated from ^{1}H NMR absorption peaks. Reactions were run at room temperature.

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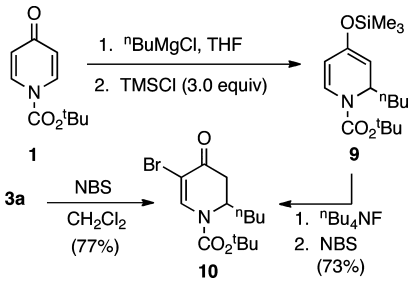
(calcd. value[16]): 162.5 (155.4), 151.0 (153.1) 122.5 (121.5) 114.3 (111.0), 98.4 (109.2), 43.7 (49.1)] were observed (Scheme 1). Control samples of **1** with and without added

Scheme 1. Attempted Trapping of Enol Ether 9

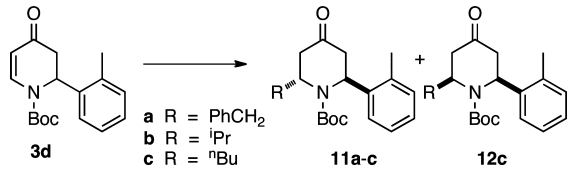


TMSCl showed no discernible difference in the chemical shifts of the absorption peaks, and the chemical yields of product in these NMR experiments mirrored those obtained in control experiments with untreated $CHCl_3$ (7%) and $CHCl_3$ treated with neutral alumina to remove HCl (50%).

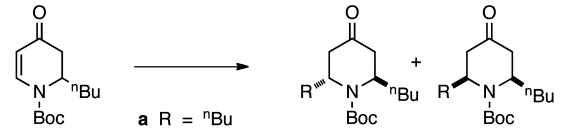
Efforts to effect reaction of the putative silyl enol ether proved unsuccessful. Reaction of **1** with ^{n}BuMgCl and TMSCl followed by sequential addition of ^{n}Bu$_4$NF and allyl bromide gave only the addition product **3a** (64%). Treatment of the reaction mixture of **1**, TMSCl, and ^{n}BuMgCl with ^{n}Bu$_4$NF and NBS gave *N*-Boc-5-bromo-2-butyl-2,3-dihydro-4-pyridone (i.e., **10**, 73% yield) involving bromination of the encarbamate moiety and not the putative silyl enol ether. The 5-bromo-4-pyridone derivative could also be prepared by treatment of **3a** with NBS in 77% yield (Scheme 1) as previously reported.[18a] All attempts to convert **3a** into the silyl enol ether [e.g., Et_3N, TMSCl, DMF, 80 °C, or (i) NaH (THF or CH_2Cl_2), (ii) TMSCl] yielded only starting material upon careful workup designed to avoid silyl enol ether hydrolysis.[17]

This new protocol affords 1,4-adducts of 4-pyridones[8a,b,18,20] that can be utilized in further synthetic applications. Previous studies have reported that Grignard reagents undergo conjugate addition to 2,3-dihydropyridinones in very low yields in the absence of Cu(I) salts.[19] In five experiments, we observed TMSCl-promoted conjugate addition of Grignard reagents to *N*-Boc-2,3-dihydropyridones in yields comparable to those observed for the *N*-Boc-4-pyridones (Scheme 2). For example, the facile addition of $PhCH_2MgBr$, ^{i}PrMgBr or ^{n}BuMgCl to 2-substituted-2,3-dihydro-*N*-Boc-4-pyridone **3d** afforded the 1,4-adducts **11a−c** as single diastereomers, while addition of ^{i}PrMgBr or ^{n}BuMgCl to dihydropyridone **3a** also gave 2,6-disubstituted tetrahydro-4-pyridones **13a,b**, respectively, as single diastereomers in good yields (Scheme 2, 85−89%). The stereochemistry in these bis-conjugate addition products could not be unambiguously assigned by literature precedent[19,20] or by simple analysis of NMR coupling constants. NOESY experiments on **11** and **12** did show NOE effects for the two methine protons adjacent to the *N*-atom and the methylene protons adjacent to the ketone but did not allow unambiguous stereochemical assignments. Alkylcuprate additions to 2-aryl-2,3-dihydro-4-pyridones were reported to afford the *cis*-2,6-disubstitution products,[18h,20a] while utilization of arylcuprates on similar substrates gave *trans*-2,6-disubstituted products.[19] In our hands, utilization of a literature protocol [i.e., ^{n}BuMgCl (2.0 equiv), CuI (2.0 equiv), $BF_3{\cdot}Et_2O$ (1.0 equiv)][20a] employing an alkyl copper reagent and a Lewis

Scheme 2. Preparation of 2,6-Disubstituted-4-Piperidinones via Conjugate Addition of Organometallic Reagents to Dihydropyridones



	11a-c	12c
$PhCH_2MgBr$, TMSCl, THF	89%	-
^{i}PrMgBr, TMSCl, THF	85%	-
^{n}BuMgCl, TMSCl, THF	88%	-
^{n}BuMgCl, CuI, $BF_3{\cdot}Et_2O$, Et_2O	49%	33%
^{n}Bu$_2$CuLi, SMe_2, Et_2O	88%	-



	13a-b	14a
^{n}BuMgCl, TMSCl, THF	89%	-
^{i}PrMgBr, TMSCl, THF	88%	-
^{n}Bu$_2$CuLi, SMe_2, Et_2O	-	86%

acid converted **3d** into a 60:40 mixture of diastereomers (i.e., **11c** + **12c**, Scheme 2) with the major diastereomer identical to the single diastereomer obtained from the RMgCl/TMSCl procedure. However, reaction of **3a** with ^{n}Bu$_2$CuLi gave a single diastereomer that was different than that obtained upon reaction of **3a** with ^{n}BuMgCl/TMSCl, and on the basis of literature precedent, the former was assigned as the *cis*-diastereomer **14a**.[20] Reaction of **3d** with ^{n}Bu$_2$CuLi in THF resulted in 1,4-conjugate reduction to afford the 2-aryl tetrahydropyridone in 76% yield.

In an attempt to obtain crystals for X-ray analysis, **11c** was converted into a series of derivatives. The 3,5-dinitrophenyl hydrazone gave crystals too small for X-ray analysis, while the oxime gave an inseparable mixture of syn and anti diastereomers. *N*-Boc deprotection of **11c** and conversion of the free amine to piperidinium salts with CF_3COOH, HCl, or picric acid failed to yield crystals as did conversion of the amine to the *n*-benzyl amine, methane sulfonamide, or *N*-chloro amine derivatives. Crystals suitable for X-ray analysis were obtained for tetrahydropyridone **11a** and the *trans* stereochemistry was thus confirmed.

Since attempted NOESY experiments on **11a−c** were ambiguous, dihydropyridones **11c**, **13a,b**, **12c**, and **14a** were reduced to the corresponding alcohols **15−19**, respectively, while **11b** was reduced to piperidinol **23**.[18h] Although dihydropyridones **13a** (δ 4.09) and **14a** (δ 4.95) displayed a single broad singlet for the two methine protons adjacent to the *N*-Boc group and one set of ^{13}C-signals for both ^{n}Bu groups due to potential symmetry (e.g., **14a** with rotation about the amide bond)[19] or conformational equilibration (e.g., **13a**), alcohol **16** displayed two methine proton absorptions (δ 4.01, 4.10) adjacent to the *N*-Boc group, while **19** displayed only one (δ 4.14), confirming the *trans* stereochemistry in **16** and the *cis* arrangement of substituents in **19** (Scheme 3). These chemical shift arguments were confirmed by NOESY experiments, which showed a single correlation for the carbinol and *N*-Boc methine

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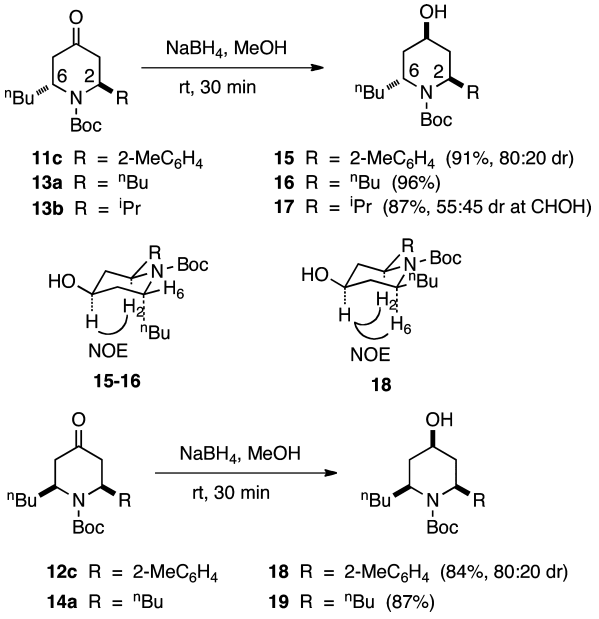
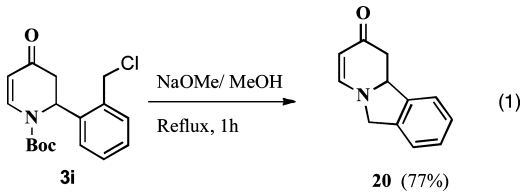
Scheme 3. Determination of Stereochemistry in 2,6-Disubstituted-4-Piperidinones



protons in the *trans* isomers **15** and **16** and two correlations for the *cis* isomer **18**. Reduction of **11b** afforded the alcohol syn to the aryl group as the major diastereomer (86%, 85:15 dr), which showed a NOESY correlation between the carbinol proton and the benzylic methine proton confirming the *trans*-2,6-stereochemistry. Reduction of **13b** gave a 55:45 mixture of diastereomers (87%) implicating the *trans*-2,6-stereochemistry, which could not be confirmed by NOESY experiments on the mixture of alcohols.

Refluxing of **3j** with NaOMe in MeOH furnished the tricyclic compound **20** in 77% yield illustrating the synthetic versatility available in these conversions of *N*-Boc-4-pyridone **1** to 2-substituted-2,3-dihydro-4-pyridinones (eq 1).

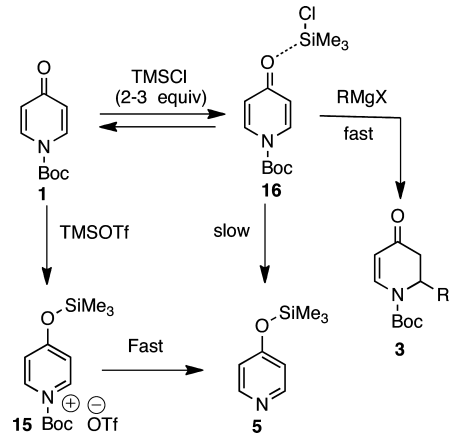


DISCUSSION

The addition of Grignard reagents to 4-pyridones **1** and **2** in the presence of TMSCl could in principle be viewed as either a 1,4-conjugate addition reaction to the enone π-system or as a 1,2-nucleophilic addition to a pyridinium intermediate. Although organocopper reagents are ubiquitious in organometal mediated conjugate addition reactions, Grignard[21] and organolithium[22] reagents do play a limited role in conjugate additions[23] to nitroalkenes,[21a] cyclopentadienones,[21b] *N*-enoylsultams,[21c,d] α-silylenones,[21e] enamides,[21f,22a] enoic acids,[21f] ennitriles,[21g,h] ynnitriles,[21i] indolylidenmalonates,[21j] and enamidomalonates.[21k]

The failure of TBDMSCl and TMSOTf to promote the addition of Grignard reagents to 4-pyridones **1** and **2** and their differential ability to promote carbamate cleavage suggests that a pyridinium ion is not an intermediate along the reaction coordinate. An alternative mechanistic scenario (Scheme 4) involves formation of a TMSCl-pyridone complex **16** that

Scheme 4. Mechanistic Implications for TMSCl-Promoted Addition of Grignard Reagents to *N*-Boc-4-pyridones



activates the 4-pyridone toward Grignard addition but does not fully form a pyridinium ion (i.e., **15**) intermediate. Once formed, this complex can undergo rapid addition of the Grignard reagent and a slow noncompetitive cleavage of the carbamate moiety. This behavior is reminiscent of a phenol-TMSCl complex that cleaves carbamates and does not generate HCl in situ[24] and of the use of TMSCl to accelerate cuprate conjugate addition reactions.[11c,25] Data from several studies on TMSCl, TMSI, and HMPA-TMSCl promoted acceleration of cuprate conjugate addition reactions in THF, support arguments involving stabilization of the transition state for reductive elimination from a Cu(III) intermediate with weak silylating agents (i.e., TMSCl)[25a] and direct silylation of an enone-Cu complex with strong silylating reagents [e.g, HMPA-TMSCl (i.e., $Me_3SiOPN[(Me)_2]_3^+$ Cl^-), TMSOTf, and TMSI] rather than cuprate attack on an enone-TMSCl complex.[25] Although pyridones **1** and **2** are vinylogous amides that could be more prone to form a complex with TMSCl than simple enones, we were unable to unambiguously observe such a complex (i.e., **16**) by NMR spectroscopy, which could be due to low concentration of **16** or rapid equilibrium between the complexed and uncomplexed species. Alternatively, invoking a concerted but nonsimultanous push−pull mechanism accommodates the relative rates of carbamate cleavage with reagent silylating ability but involves a significantly less likely termolecular activated complex.

The issue of 1,4- vs 1,2-addition is then largely a matter of semantics since formation of a TMSCl-pyridone complex before or during the Grignard addition enhances the electrophilic character of the enone β-carbon atom, which will also have a resonance contributor involving the carbamate *N*-lone pair. Although we were unable to definitively identify this complex in the NMR studies, the need for 2−3 equiv of TMSCl in order to obtain good yields of conjugate adducts is suggestive of formation of such a complex in a bimolecular or termolecular process. Partitioning between carbamate cleavage and Grignard addition can be subtlely influenced by reaction conditions (e.g., solvent and temperature).

The assignment of stereochemistry in *N*-Boc-2,6-disubstituted-4-piperidinones is fraught with difficulty revolving around conformational dynamics in the six-membered ring, which is

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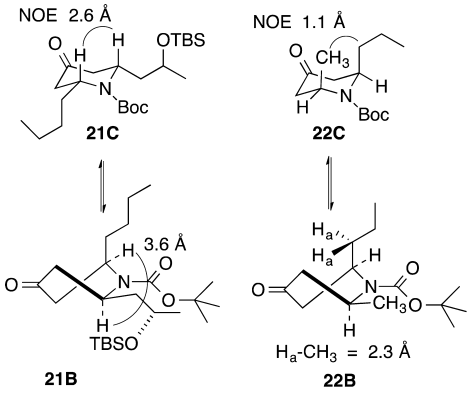
illustrated by literature assignments involving NOESY experiments. For piperidinone **21**, an NOE was reported for the two methine protons, and a chair conformation (i.e., **21C**) with the two alkyl substituents in an equatorial orientation was invoked,[18c] while piperidinone **22** displayed NOE between the methyl and the 1′-CH_2-group of the *n*-propyl substitutent and a chair conformation (i.e., **22C**) with the two alkyl groups in an axial orientation was invoked.[18g] There is ample literature precedent suggesting that both *N*-acyl *cis*[26]- and *trans*[19]-2,6-disubstituted piperidinones preferentially adopt a boat or twist boat conformation rather than chair conformations involving either 1,3-diaxial interactions or $A^{1,3}$-strain between the equatorial substituents and the amide functionality. For the NOE correlations reported (Scheme 5), it seems far more likely

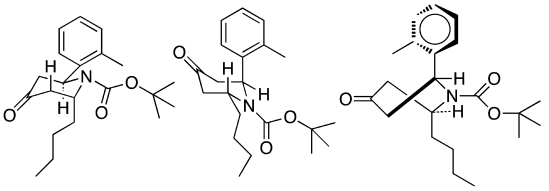
Scheme 5. Reported NOEs in *N*-Boc-2,6-Disubstituted Piperidinones[18c,g]



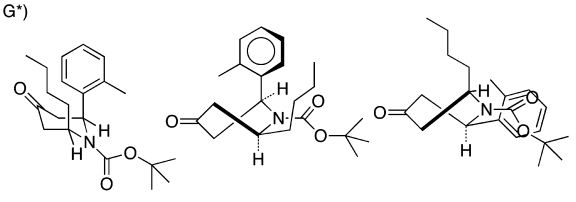
that these interactions are arising from similar boat or twist boat conformations (e.g., **21B** and **22B**) or are resulting from conformational dynamic averaging of NOE accessible conformations.[27,28]

A computational sampling of a small region of conformational space for several *N*-Boc-2,6-disubstituted-4-piperidinones and a 4-piperidinol was examined. Although the semiempirical calculations AM1 and PM3 gave inconsistent ordering of conformational stability, both *ab initio* calculations [(i.e., Hartree−Fock (HF, 6-31G*) and Density Functional Theory (DFT, B3LYP, 6-31G*)] generally gave consistent relative stability ordering for various chair and twist boat conformations (Chart 1). The *trans*-2-tolyl derivative **11c** was calculated to be most stable in the chair conformation with an axial aryl substituent, while the twist boat and chair conformations in the *cis* isomer **12c** with an axial aryl substitutent were each predicted to be more stable by HF and DFT calculations, respectively, although the energy differences in the HF calculation are insignificant. Hartree−Fock calculations predicted the twist boat conformation of the *trans*-2-isopropyl derivative to be more stable than the chair, and both ab initio calculations predicted the twist boat comformation of the *trans*-2-arylpiperidinol to be more stable than the axial 2-aryl chair conformer. The 1,4-twist conformations shown in Chart 1 are also in equilibrium with 2,5-twist and 3,6-twist boat conformations.[27a] These conformational transformations via pseudorotation about the ring atoms lead to a large number of conformational minima, some of which will be capable of displaying NOE (i.e., generally internuculear distances ≤3.5 Å) effects.[29]

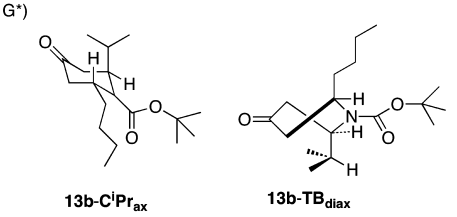
Chart 1. Relative Conformational Energies (i.e., Δ*E* Internal Energy) in kcal/mol[a]



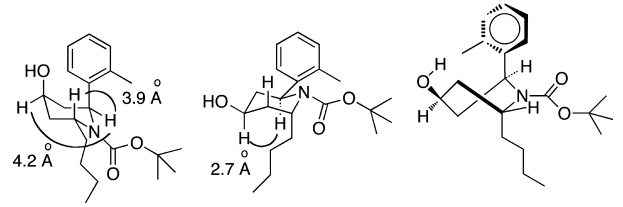
	11c-CR_{ax}	11c-CAr_{ax}	11c-TB_{diax}
AM1	0.00	-2.08	-3.00
PM3	-0.59	-0.96	0.00
HF (6-31G*)	0.00	-10.29	-3.33
DFT (B3LYP, 6-31G*)	0.00	- 8.16	-6.97



	12c-C_{diax}	12c-$TBAr_{ax}$	12c-TBR_{ax}
HF (6-31G*)	-2.89	-3.07	0.00
DFT (B3LYP, 6-31G*)	-5.96	-2.51	0.00



	13b-C^iPr_{ax}	13b-TB_{diax}
AM1	0.00	-1.32
HF (6-31G*)	0.00	-3.50



	15-CAr_{ax}	15-CR_{ax}	15-TB_{diax}
AM1	-0.64	-0.42	0.00
PM3	-3.68	-2.20	0.00
HF (6-31G*)	-4.52	0.00	-7.59
DFT (B3LYP, 6-31G*)	-3.45	0.00	-6.53

[a]C = chair, TB = twist boat, ax = axial, diax = diaxial.

The reaction of 2-substituted-2,3-dihydropyridones with Grignard reagents in the presence of TMSCl always leads to the *trans*-2,6-disubstituted piperidinones, while the conjugate addition of cuprate reagents leads to mixtures of *cis* and *trans* diastereomers where either isomer may predominate (Table 5). Formation of the *trans*-piperidinones in the Grignard conjugate addition reactions plausibly arise from an enone-TMSCl complex where the Lewis acid is not associated with the Grignard reagent, which attacks from the least sterically hindered enone π-face opposite the axial substituent (i.e., R^1). By contrast, cuprate conjugate addition generally requires coordination of the metal cation (e.g., Li^+) to the enone carbonyl[30] and given the dihedral angles for these half chair conformations[31] would favor attack of the cuprate reagent upon the π-face of the carbonyl shielded by the axial substituent R^1.

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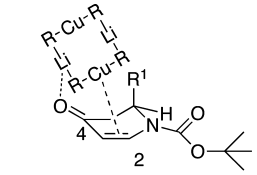
Table 5. Stereoselectivity in Conjugate Additions to 2,3-Dihydropyridones 3a, 3d, 3j, 24, and 25



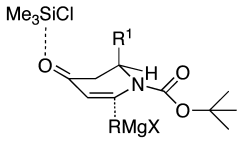
Dihedral angle: C5-C4-C3-C2

3a R^1 = ^{n}Bu: 10.4 °

3j R^1 = Ph: 7.8 °

3d R^1 = 2-MeC_6H_4: 13.3 °

24 R^1 = 3,4-$(MeO)_2C_6H_3$: 9.7 °



trans-product in all cases

25 R^1 = $CH_2CH{=}CH_2$: 9.1 °

R^1, R: Cu reagent and reaction cond	*cis:trans* (R^1, R)	[ref]
R^1 = 3,4-$(MeO)_2C_6H_4$; R = $Cl(CH_2)_4$: $R_2CuMgCl$ (?), THF	3:1	20a
RCu or RCuBrMgBr/$BF_3{\cdot}Et_2O$, THF	4.7:1	20a
R^1 = Ph; R = Me: MeCu or MeCuBrMgBr/$BF_3{\cdot}Et_2O$, THF	5:1	18h
R^1 = 2-MeC_6H_4; R = ^{n}Bu: ^{n}BuCu or ^{n}BuCuIMgX/$BF_3{\cdot}Et_2O$, THF	1:1.5[a]	
$^n Bu_2CuLi$, Me_2S, Et_2O	1:99[a]	
R^1 = R = Ph: R_2CuMgX, THF	1:20	19
R^1 = $CH_2CH{=}CH_2$; R = $CH_2{=}CH_2$: MeCuRM [M = Li or MgX], THF:Et_2O (3:1)	20:1	20b
R^1 = $CH_2CH{=}CH_2$; R = $CH_2{=}CH(CH_3)$: MeCuRM [M = Li or MgX], THF:Et_2O (3:1)	9:1	20b
R^1 = R = ^{n}Bu: $^n Bu_2CuLi$, Me_2S, Et_2O	99:1[a]	

[a]This work.

No simple pattern emerges from the data presented in Table 5 suggesting that multiple factors determine the stereochemical outcome. These multiple factors may include the steric hindrance of R^1 (i.e., A-values), the steric hindrance of the cuprate reagent (e.g., homodimer in Et_2O, heterodimer in THF, mixed cuprate reagents such as RCuMeLi or RCuBrMgBr)[30] including the transferable ligand, the cuprate counterion (e.g., Li^+, MgX^+), the C5−C4−C3−C2 dihedral angle in the substrate influencing the orientation of the carbonyl functional group, and the conformation preference of the specifically substituted 2,3-dihydropyridone.

The formation of *cis*-substituted derivatives has been rationalized by the more stable 2-substituted-2,3-dihydropyridone axial conformer undergoing axial attack by the cuprate reagent,[20a] while the *trans*-substituted derivatives are rationalized by cuprate axial attack on a half-boat confomer postulated to occur for 2,3-dihydropyridones containing a bulky 2-substitutent[19] (e.g., aryl). Since 2-aryl-2,3-dihydropyridones are reported to undergo cuprate-mediated conjugate addition to form both *cis*-[18h,20] and *trans*-substituted[19] 2,6-tetrahydropyridones, the stereochemical outcome of the conjugate addition most likely results from a complex interplay of multiple factors. AM1 semiempirical calculations employing MacSpartan confirm that the axial conformer for both **3a** and **3j** is more stable than the equatorial conformer by 2.0−2.6 kcal/mol.[20a] Additionally, both have roughly the same conformation of the pyridone ring, which is closer to a chair conformation than to a half-boat. The supposition of a half-boat conformation was predicated on an X-ray structure,[19] which need not mirror solution conformations. The *cis*/*trans*-stereochemical outcome of the conjugate addition reactions seems to reflect the steric hindrance of both the 2-substitutent on the 2,3-dihydropyridone and the ligand on the organometallic reagent. Thus, as argued by Comins[20a] the more stable axial conformer generally prefers to undergo axial attack by the organometallic reagent leading to the *cis*-diastereomer, but as our work and that of Hamblett and co-workers[19] shows, this stereoelectronic preference can be circumvented by the cumulative steric hindrance of the 2-substitutent on the 2,3-dihydropyridone and the organometallic ligand to afford the *trans*-diastereomer. This perspective also accounts for the range of *cis*/*trans*-diastereomers observed as a function of the cuprate reagent[20a] and presumably solvent reflecting the reacting cuprate structure and composition.[30]

Reduction of the 2,6-disubstituted piperidinones is also intriguing, giving a 4:1 diastereomeric ratio for **11c** and a 1:1 ratio for **13b**. The higher diastereoselectivity obtained for reduction of **11c** can be rationalized by the larger A-value for the phenyl substitutent in either the boat or chair conformation while the lack of stereoselectivity in the reduction of **13b** reflects the comparable A-values for the ^{n}Bu and ^{i}Pr-substituents. These diastereomeric ratios are also consistent with calculations indicating a preference for the chair conformation for **11c** and a twist boat conformation for **13b** (Chart 1).

■ SUMMARY

In summary, we have successfully developed conjugate addition reactions of Grignard reagents with *N*-carbamoyl-4-pyridones in the presence of TMSCl without using Cu(I) salts. This reaction was shown to be compatible with alkyl, aryl, benzyl, vinyl 1-naphthyl and highly functionalized heterocycle containing Grignard reagents. The synthetic utilities of the 1,4-adducts provided by this new Grignard reagent conjugate addition protocol was demonstrated. This methodology provides a direct route to the highly functionalized and synthetically important 2-substituted-2,3-dihydropyridones,[4b,8a,b,18−20] which can be utilized for the synthesis of piperidones, piperidines, indolizidines, and quinolizidines and provides opportunities for development of catalytic enantioselective 1,4-additions to 4-pyridones using Grignard reagents.

■ EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded as $CDCl_3$ or C_6D_6 solutions on a 500 MHz NMR instrument. The ^{1}H NMR chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS, δ = 0.00)/$CHCl_3$ (δ = 7.28) or C_6H_6 (δ = 7.16) as internal standard. The ^{13}C NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to the $CDCl_3$ signal (triplet, centerline δ = 77.0 ppm) or C_6D_6 signal (multiplet, centerline δ = 128.4 ppm). Infrared (IR) spectra were recorded as neat samples (liquid films on NaCl plates). Gas chromatography−mass spectrometry measurements were performed on a GC coupled to a quadrupole detector at 70 eV. Analytical thin layer chromatography (TLC) was performed on silica gel plates, 200 μ mesh with F_{254} indicator. Visualization was accomplished by UV light (254 nm), and/or a 10% ethanol solution of phosphomolybdic acid. Flash column chromatography was performed with 200−400 μ silica. The yields are of materials isolated by column chromatography.

Anhydrous tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. TMSCl was distilled from CaH_2 under a positive N_2 atmosphere. *n*-BuLi (2.5 M in hexane) was commercially available and titrated using sec-butyl alcohol and 1,10-phenanthroline monohydrate in THF. *n*-BuMgCl (1.6 M in THF), EtMgCl (1. 0 M in THF), MeMgCl (3.0 M in diethyl ether), *i*-PrMgBr (2.0 M in diethyl ether), and PhMgCl (2.80 M in diethyl ether) were commercially available and titrated using menthol and 1,10-

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phenanthroline monohydrate in THF.[32] All glassware was flame-dried under a high vacuum and purged with argon and then cooled under a dry nitrogen atmosphere. Low temperature baths (as low as −78 °C) were prepared using thermoflasks with dry ice-isopropyl alcohol slush bath mixtures. All reactions were conducted under a positive, dry argon atmosphere in anhydrous solvents in flasks fitted with a rubber septum.

HRMS data on compounds **3e**, **3f**, **3k**−**n**, **3q**, **4d**, **11b**, **12c**, **13a**, **16**, **19**, and **20** were analyzed by Q-TOF detector (hybrid quadrupole time-of-flight MS), while compounds **4b**−**c**, **4e**, **4f**, **10**, **11c**, **13b**, **14a**, **15**, **17**−**18** and **23** were analyzed by TOF MS. Compounds **1**, **2**, **3a**, **3b**, **3d**, **3g**−**j**, **3p**, and **4a** have been fully characterized and reported.[1b,10,38,39]

Method A: Synthesis of Grignard Reagents from Heteroaryl Compounds. The heteroaryl Grignard reagents were prepared from a slight modification of a literature procedure.[33] To the heteroaryl compound (2.0 mmol) in THF (3.0 mL) at 0 °C under argon was added *n*-BuLi (0.80 mL, 2.50 M in hexane, 2.00 mmol) dropwise. Then the reaction mixture was warmed to room temperature and stirred for 2 h at this temperature. The reaction mixture was transferred to flame-dried $MgBr_2$ (368 mg, 2.0 mmol) in THF (5.0 mL) at 0 °C via cannula under argon, stirred for 30 min at this temperature and used for further reactions using General Procedure A.

Method B: Synthesis of Grignard Reagents from Aryl Halides. Aryl Grignard reagents that were not available commercially were synthesized in situ by using a modified literature procedure[34] from the corresponding aryl halides as described below. To magnesium (192 mg) in THF (5.0 mL) under argon was added a catalytic amount of iodide (15 mg). Then a solution of aryl halide (2.00 mmol in 5.0 mL THF) was added dropwise. During addition, the reaction mixture was heated at 50 °C for 10 min. After the addition was complete, the reaction mixture was stirred for an additional 30 min at room temperature and used for the conjugate addition reactions using General Procedure A.

Method C: Synthesis of Grignard Reagent via Halogen Metal Exchange. The halogen metal exchange reaction of the vinyl iodide was performed by using the literature procedure.[35] To *i*-PrMgCl (1.20 mL, 2.0 M in diethyl ether, 2.4 mmol) in THF (3.0 mL) at 0 °C was added *n*-BuLi (1.92 mL, 2.5 M in hexane, 4.8 mmol) under argon, and the mixture was stirred for 10 min. Iodo compound (2.0 mmol) was added, and the mixture was stirred for 1 h at 0 °C and then used for further reactions following General Procedure A.

General Procedure A: Reaction of Grignard Reagents with *N*-Carbamoyl-4-pyridones in the Presence of TMSCl. To the cooled −78 °C solution of Grignard reagent (1−2 equiv) was added the starting *N*-carbamoyl-4-pyridone (**1** or **2**) [1.0 mmol mixed with TMSCl (3.0 equiv) in THF (3.0 mL)] dropwise. The reaction mixture was allowed to warm to room temperature overnight with stirring. Then the reaction mixture was diluted with dichloromethane (5.0 mL), quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with dichloromethane (3 × 10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 1−3% MeOH in CH_2Cl_2, v/v) to give pure compounds.

General Procedure B: Reaction of Organocuprate Reagents with *N*-Boc-2-alkyl-2,3-dihydropyridone. The organocuprate reagents used for the reaction were prepared by the reaction of either RLi (2.0 equiv), CuCN (1.0 equiv) and LiCl (2.0 equiv) or the reaction of RMgX (1.0 equiv) with CuI (1.0 equiv). In the first method, to the mixture of LiCl (2.0 equiv), CuCN (1.0 equiv) and Me_2S (2.0 equiv) under argon in diethyl ether was added *n*-BuLi (2.0 equiv) at −78 °C, and the reaction mixture warmed up to −30 °C over 30 min. In the second method, CuI (1.0 equiv) was mixed with RMgX (1.0 equiv) in THF under argon at −60 °C, and the resulting mixture was warmed to −30 °C over 30 min following slight modification of Comin's procedure.[20a] The reaction mixture was cooled to −78 °C, boron trifluoride etherate (0.5 equiv) was added, and the resulting mixture was stirred for 10 min before *N*-carbamoyl-4-pyridone (1.0 equiv in 2.0 mL diethyl ether) was added over 10 min at −78 °C. The reaction mixture was warmed to room temperature overnight with continuous stirring. Then the reaction mixture was diluted with dichloromethane (5.0 mL), quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with dichloromethane (3 × 10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 1−3% MeOH in CH_2Cl_2, v/v) to give pure compounds.

General Procedure C: Preparation of *N*-Carbamoyl-4-pyridones (1−2). *N*-Carbamoyl-4-pyridones (**1** and **2**) used for the reactions were prepared using a modified literature procedure.[36] To the solution of 4-hydroxypyridine (1.90 g, 20.0 mmol) in ^{t}BuOH (20.0 mL) was added sodium hydride (624 mg, 26.0 mmol) under argon, and the reaction mixture was heated in hot water bath (∼50 °C) until the mixture turned to a slurry. Then the appropriate chloroformate (26.0 mmol) in ^{t}BuOH (7.0 mL) was added dropwise. The reaction mixture was cooled to room temperature and stirred for 12 h at that temperature. The reaction mixture was quenched with water (20.0 mL) with caution, acidified to pH = 7 with 10% HCl, and the aqueous portion was extracted with ether (3 × 15.0 mL). The ether layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated by a vacuum to give crude product. Purification by flash chromatography (1−3% MeOH in CH_2Cl_2, v/v) afforded *N*-carbamoyl-4-pyridones **1**−**2**.

Preparation of *N*-*tert*-Butoxycarbonyl-4-pyridone (1). Employing General Procedure C and using, *tert*-butoxycarbonyl anhydride (5.67 g, 26.0 mmol), 4-hydroxypyridine (1.90 g, 20.0 mmol) gave **1** after purification by flash column chromatography (silica gel, 1−3% MeOH:CH_2Cl_2, v/v) as a white solid in good yields (73%). ^{1}H NMR and ^{13}C NMR data are identical to a literature report.[12b]

Preparation of *N*-Ethoxycarbonyl-4-pyridone (2). Employing General Procedure C and using ethyl chloroformate (2.82 g, 26.0 mmol) 4-hydroxypyridine (1.90g, 20.0 mmol) gave **2** after purification by flash column chromatography (silica gel, 1−3% MeOH:CH_2Cl_2, v/v) as white solid in good yields (79%). ^{1}H NMR and ^{13}C NMR data were identical to a literature report.[37]

***N*-Boc-2-(2-methoxyphenyl)-2,3-dihydro-4-pyridone (3c).** Employing Method B, General Procedure A and using 2-bromoanisole (374 mg, 2.00 mmol), magnesium (192 mg, 8.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave white crystalline solid **3c** (260 mg, 86%): mp 112.8−114.9 °C; IR (neat) 2975 (w), 2838 (w), 1721 (s), 1667 (s), 1602 (s), 1489 (m), 1457 (m), 1421 (m), 1316 (s), 1243 (m), 1150 (s), 1027 (m), 853 (m), 752 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (br s, 9H), 2.79 (d, J = 16.9 Hz, 1H), 3.06 (dd, J = 8.2, 16.5 Hz, 1H), 3.85 (s, 3H), 5.36 (d, J = 8.2 Hz, 1H), 5.94 (d, J = 7.8 Hz, 1H), 6.81−6.90 (m, 2H), 6.98 (d, J = 7.3 Hz, 1H), 7.20−7.26 (m, 1H), 8.11 (d, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 40.6, 51.5, 55.3, 83.4, 106.5, 110.8, 120.5, 125.1, 126.5, 128.9, 143.7, 151.4, 156.1, 191.9; mass spectrum *m*/*z* (relative intensity) EI 303 (M^+, 0.01), 223 (0.04), 203 (100), 187 (6), 172 (16), 160 (16), 134 (38), 119 (97), 105 (9), 91 (85), 77 (19), 65 (21), 51 (11). Elemental analysis, found: C, 67.22; H, 7.18; N, 4.52%. Calculated for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62%.

***N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone (3d).**[38] Employing Method B, General Procedure A and using 2-bromotoluene (342 mg, 2.0 mmol), magnesium (192 mg, 8.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave white amorphous solid **3d** (273 mg, 95%): mp 117.1−119.5 °C; IR (neat) 3077 (w), 2974 (m), 2929 (w), 1724 (s), 1667 (s), 1605 (s), 1458 (w), 1417 (m), 1368 (m), 1319 (s), 1258 (m), 1213 (m), 1148 (s), 1009 (w), 976 (w), 923 (w), 853 (w), 756 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 9 H), 2.28 (s, 3 H), 2.48 (d, J = 16.5 Hz, 1H), 3.07 (dd, J = 8.7, 16.4 Hz, 1H), 5.33 (d, J = 8.7 Hz, 1 H), 5.67 (d, J = 8.7 Hz, 1H), 6.96−7.12 (m, 4H), 8.08 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 27.9, 40.8, 53.3, 83.7, 106.3, 123.9, 126.6, 127.8, 131.2, 133.8, 137.7, 144.3, 151.4, 191.8; mass spectrum *m*/*z*

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(relative intensity) EI 287 (M^+, 0.02), 239 (0.10), 207 (0.42), 187 (56), 172 (6), 158 (7), 144 (29), 130 (100), 117 (100), 96 (51), 70 (36), 51 (13).

***N*-Boc-2-(2-thienyl)-2,3-dihydro-4-pyridone (3e).** Employing Method A, General Procedure A and using thiophene (168 mg, 2.0 mmol), *n*-BuLi (0.80 mL, 2.50 M in hexane, 2.0 mmol), $MgBr_2$ (368 mg, 2.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave colorless oil **3e** (232 mg, 83%): IR (neat) 2977 (m), 2925 (w), 1723 (s), 1663 (s), 1599 (s), 1418 (m), 1366 (m), 1328 (s), 1260 (m), 1215 (m), 1151 (s), 1004 (m), 850 (m), 763 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53 (br s, 9 H), 2.84 (d, J = 16.9 Hz, 1 H), 3.07 (dd, J = 6.8, 16.4 Hz, 1H), 5.32 (d, J = 8.2 Hz, 1H), 5.84 (br s, 1H), 6.86 (dd, J = 3.6, 5.0 Hz, 1H), 6.92 (dd, J = 0.9, 3.6 Hz, 1H), 7.18 (d, J = 5.0 Hz, 1H), 7.70 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 41.5, 51.7, 84.2, 106.9, 125.5, 126.0, 126.5, 141.3, 141.8, 151.1, 192.4; mass spectrum m/z (relative intensity) EI 279 (M^+, 0.05), 239 (0.06), 195 (0.5), 179 (36), 162 (18), 151 (20), 136 (4), 110 (100), 84 (10), 66 (17), 51 (50); HRMS (ESI) calculated for $[C_{14}H_{17}NO_3S]^+$ 279.09292, found 279.09328.

***N*-Boc-2-(2-furyl)-2,3-dihydro-4-pyridone (3f).** Employing Method A, General Procedure A and using furan (136 mg, 2.0 mmol), *n*-BuLi (0.80 mL, 2.50 M in hexane, 2.0 mmol), $MgBr_2$ (368 mg, 2.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave colorless oil **3f** (224 mg, 85%): IR (neat) 2977 (w), 2925 (w), 1723 (s), 1667 (s), 1595 (s), 1430 (w), 1370 (m), 1317 (s), 1260 (m), 1219 (m), 1151 (s), 1008 (m), 853 (w), 760 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.54 (s, 9H), 2.80 (d, J = 16.5 Hz, 1 H), 2.99 (dd, J = 6.9, 16.9 Hz, 1H), 5.29 (d, J = 9.6 Hz, 1H), 5.70 (br s, 1H), 6.17 (d, J = 2.7 Hz, 1H), 6.27 (d, J = 1.4 Hz, 1H), 7.31 (s, 1H), 7.72 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 39.0, 50.1, 83.9, 106.7, 108.0, 110.3, 141.9, 142.6, 151.2, 151.3, 192.3; mass spectrum m/z (relative intensity) EI 263 (M^+, 0.88), 239 (0.05), 231 (0.05), 218 (0.08), 207 (25), 190 (2), 163 (28), 135 (17), 106 (10), 94 (76), 81 (5), 57 (100); HRMS (ESI) calculated for $[C_{14}H_{18}NO_4]^+$ 264.1236, found 264.1233.

***N*-Boc-2-(4-*N*,*N*-dimethylaminophenyl)-2,3-dihydro-4-pyridone (3k).** Employing Method B, General Procedure A and using *N*,*N*-dimethyl-4-bromoaniline (400 mg, 2.0 mmol), magnesium (192 mg, 8.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave white amorphous powder **3k** (302 mg, 96%): mp 115.9−117.3 °C; IR (neat) 2976 (w), 2360 (b), 1722 (s), 1656 (s), 1603 (s), 1330 (b), 1221 (s), 1151(s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.78 (d, J = 16.4 Hz, 1H), 2.94 (s, 6H), 3.09 (dd, J = 7.3, 16.5 Hz, 1H), 5.34 (d, J = 8.2 Hz, 1H), 5.61(d, J = 6.9 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 40.5, 41.6, 54.9, 83.4, 106.7, 112.6, 126.9, 127.1, 142.7, 149.8, 151.5, 192.9; mass spectrum m/z (relative intensity) EI 317 (M^+ +1, 3.6), 316 (M^+, 18), 260 (30), 216 (41), 147 (100), 146 (37), 134 (20), 91 (5), 77 (11), 57 (32); HRMS (ESI) calculated for $[C_{18}H_{24}N_2O_3]^+$ 316.17870, found, 316.17786.

***N*-Boc-2-(2-chloromethylphenyl)-2,3-dihydro-4-pyridone (3l).** Employing Method C, General Procedure A and using *i*-PrMgBr (0.6 mL, 1.2 mmol, 2.0 M in diethyl ether), *n*-BuLi (0.96 mL, 2.4 mmol, 2.50 M in hexane), 2-iodo-(1-chloromethyl) benzene (253 mg, 1.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave yellow viscous oil **3l** (278 mg, 86%): IR (neat) 2976 (w), 1725 (s), 1668 (s), 1609 (s), 1370 (s), 1319 (b), 1217 (s), 1150 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (br s, 9H), 2.71 (d, J = 16.5 Hz, 1H), 3.31 (dd, J = 8.7, 16.5 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.83 (d, J = 11.9, 1H), 5.40 (d, J = 8.7 Hz, 1H), 5.84 (d, J = 8.75 Hz, 1H), 7.22−7.32 (m, 4H), 8.09 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 41.9, 43.6, 52.3, 84.0, 106.1, 125.2, 128.4, 129.7, 131.2, 133.5, 139.5, 144.2, 151.2, 191.5; mass spectrum m/z (relative intensity) EI 322 (M^+, 2.11), 308 (2), 294 (2), 192 (11), 190 (27), 165 (21), 164 (83), 149 (100), 134 (6), 121 (14), 104 (8), 91 (9), 77 (9), 65 (8), 51 (8); HRMS (ESI) calculated for $[C_{17}H_{21}NO_3Cl]^+$ 322.1210, found 322.1205.

***N*-Boc-2-(1-napthanyl)-2,3-dihydro-4-pyridone (3m).** Employing Method B, General Procedure A and using 1-napthanyl bromide (414 mg, 2.0 mmol), magnesium (192 mg, 8.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave white amorphous solid **3m** (256 mg, 79%): mp 126.5−128.3 °C; IR (neat) 2977 (w), 1727 (s), 1670 (s), 1312 (b), 1149 (b), 857 (b), 773 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (br s, 9H), 2.87 (d, J = 16.5 Hz, 1H), 3.30 (dd, J = 8.7, 16.5 Hz, 1H), 5.43 (d, J = 8.7 Hz, 1H), 6.44 (d, J = 8.2 Hz, 1H), 7.27−7.92 (m, 7H), 8.25 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 41.3, 53.0, 83.7, 106.1, 121.6, 121.9, 125.1, 125.7, 126.6, 128.5, 129.4, 133.9, 134.4, 143.9, 151.3, 191.6; mass spectrum m/z, (relative intensity) EI 323 (0.01, M^+), 289 (9), 288 (39), 230 (14), 229 (70), 198 (58), 197 (32), 181 (47), 170 (34), 157 (97), 165 (27), 159 (15), 158 (15), 157(97), 155 (39), 154 (32), 141 (19), 132 (17), 129 (97), 128 (63), 127 (38), 117 (19), 91 (60), 90 (24), 75 (100), 73 (68), 58 (7); HRMS (ESI) calculated for $[C_{20}H_{22}NO_3]^+$ 324.1600, found 324.1606.

***N*-Boc-2-(2-(1-methyl)-pyrrolyl)-2,3-dihydro-4-pyridone (3n).** Employing Method A, General Procedure A and using *N*-methylpyrrole (162 mg, 2.0 mmol), *n*-BuLi (0.80 mL, 2.0 mmol, 2.50 M in hexane,), $MgBr_2$ (368 mg, 2.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave yellow viscous oil **3n** (193 mg, 70%): IR (neat) 2973 (m), 2925 (m), 1720 (s), 1667 (s), 1599 (s), 1366 (m), 1321 (s), 1215 (m), 1151 (s), 1008 (m), 853 (w), 714 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 2.68 (dd, J = 1.3, 17.8 Hz, 1 H), 3.08 (dd, J = 7.3, 16.5 Hz, 1 H), 3.66 (s, 3 H), 5.41 (dd, J = 0.9, 7.3 Hz, 1 H), 5.73 (d, J = 6.8 Hz, 1 H), 5.99 (dd, J = 2.7, 3.2 Hz, 1 H), 6.05 (d, J = 2.3 Hz, 1 H), 6.54 (s, 1 H), 7.77 (d, J = 8.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 34.3, 41.7, 48.7, 83.7, 107.1, 107.2, 107.9, 123.0, 129.7, 142.5, 151.1, 192.6; mass spectrum m/z (relative intensity) EI 276 (M^+, 1), 261 (0.15), 246 (1), 232 (3), 219 (1), 203 (5), 185 (1), 176 (22), 159 (65), 148 (12), 131 (8), 118 (4), 107 (100), 94 (16), 81 (15), 56 (21); HRMS (ESI) calculated for $[C_{15}H_{20}N_2O_3]^+$ 276.14740, found 276.14772.

***N*-Boc-2-(5-(1-methyl)-indole)-2,3-dihydro-4-pyridone (3o).** Employing Method C, General Procedure A and using *i*-PrMgBr (0.6 mL, 1.2 mmol, 2.0 M in diethyl ether), *n*-BuLi (0.96 mL, 2.50 M in hexane, 2.4 mmol), 5-iodo-*N*-methyl indole (257 mg, 1.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave white amorphous solid **3o** (286 mg, 88%): mp 127.4−129.1 °C; IR (neat) 2977 (w), 1722 (s), 1668 (s), 1604 (s), 1332 (m), 1153 (s), 762 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.87 (d, J = 16.9 Hz, 1H), 3.20 (dd, J = 7.3, 16.5 Hz, 1H), 3.78 (s, 3H), 5.38 (d, J = 8.7 Hz, 1H), 5.79 (d, J = 7.3 Hz, 1H), 6.43 (d, J = 3.2 Hz, 1H), 7.05 (d, J = 3.2 Hz, 1H) 7.13 (dd, J = 1.3, 8.7 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 7.47 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 32.9, 42.4, 56.1, 83.5, 101.3, 107, 109.6, 118.3, 120.0, 128.5, 129.5, 130.1, 136.3, 143.1, 151.7, 192.9; mass spectrum m/z (relative intensity) EI 327 (0.01, M^+), 227 (12), 226 (75), 225 (24), 209 (32), 198 (10), 197 (13), 183 (10), 181 (15), 157 (100), 156 (26), 144 (8), 131(16), 115 (18), 103 (5), 96 (10), 77 (9), 63 (4). Elemental analysis, found: C, 69.87; H, 6.90; N, 8.38%. Calculated for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58%.

***N*-Boc-2-ethenyl-2,3-dihydro-4-pyridone (3p).**[39] Using General Procedure A and vinyl magnesium bromide (1.2 mL, 1.0 M in THF, 1.20 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave yellow oil **3p** (166 mg, 75%): IR (neat) 2980 (w), 2354 (b), 1723 (s),

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1670 (s), 1420 (w), 1335 (w), 1156 (s), 766 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 9H), 2.52 (d, J = 16.5 Hz, 1H), 2.91 (dd, J = 7.3, 16.5 Hz, 1H), 4.05 (br s, 1H), 5.13 (dd, J = 1.3, 16.9 Hz), 5.21 (dd, J = 0.9, 10.5 Hz, 1H), 5.28 (d, J = 8.2 Hz, 1H), 5.79 (ddd, J = 1.4, 6.4,11.9 Hz, 1H), 7.78 (d, J = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 39.8, 54.4, 83.5, 106.4, 117.0, 133.0, 142.1, 151.1, 192.4; mass spectrum m/z (relative intensity), EI 223 (3.2, M^+), 167 (10), 123 (15), 106 (3), 96 (23), 95 (15), 80 (9), 68 (9), 57 (100), 54 (16).

***N*-Boc-2-(1-hexenyl)-2,3-dihydro-4-pyridone (3q).** Employing Method C, General Procedure A and using *i*-PrMgBr (1.20 mL, 2.4 mmol, 2.0 M in diethyl ether), *n*-BuLi (1.92 mL, 4.8 mmol, 2.50 M in hexane), 1-iodohexene (420 mg, 2.0 mmol), *N*-(*tert*-butoxycarbonyl)-4-pyridone **1** (195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave yellow viscous oil **3q** (226 mg, 82%): IR (neat) 2979 (w), 2354 (b), 1722 (s), 1672 (s), 1335 (b), 1155 (b), 861 (s), 766 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.22−1.34 (m, 4H), 1.53 (s, 9H), 1.99 (q, J = 6.8 Hz, 2H), 2.47 (d, J = 16.0 Hz, 1H), 2.88 (dd, J = 6.8, 16.5 Hz, 1H), 4.98 (br s, 1H), 5.27 (d, J = 8.2 Hz, 1H), 5.45 (dd, J = 5.9, 15.1 Hz, 1H), 5.55−5.61 (m, 1H), 7.76 (d, J = 7.7 Hz,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.0, 27.9, 31.0, 31.7, 40.5, 54.3, 83.2, 106.2, 124.5, 134.0, 142.1, 151.2, 192.9; mass spectrum m/z (relative intensity) EI 279 (0.2, M^+), 224 (2), 223 (3), 206 (2), 179 (10), 178 (5), 136 (23), 122 (16), 108 (7), 96 (26), 95 (8), 94 (19), 83 (8), 81 (15), 80 (18), 70 (11), 57 (100), 54 (25); HRMS (ESI) calculated for $[C_{16}H_{25}NO_3]^+$ 279.18345, found 279.18300.

***N*-Ethoxycarbonyl-2-(1-methylethyl)-2,3-dihydro-4-pyridone (4b).** Employing General Procedure A and using *i*-PrMgBr (0.55 mL, 2.0 M in Et_2O, 1.1 mmol), *N*-ethoxycarbonyl-4-pyridone **2** (167 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave colorless oil **4b** (127 mg, 60%): IR (neat) 2962 (m), 2923 (m), 2871 (w), 2851 (w), 1723 (s), 1664 (s), 1601 (s), 1466 (m), 1421 (m), 1369 (m), 1324 (s), 1258 (s), 1223 (m), 1192 (s), 1164 (m), 1084 (m), 993 (m), 765 (m) cm^{-1}; ^1H NMR δ 0.83 (d, J = 6.90 Hz, 3H), 0.87 (d, J = 6.85 Hz, 3 H), 1.28 (t, J = 7.35 Hz, 3H), 2.00−2.11 (m, 1 H), 2.54 (d, J = 16.95 Hz, 1H), 2.70 (dd, J = 6.90, 16.45 Hz, 1H), 4.19−4.29 (m, 2H), 5.24 (d, J = 6.40 Hz, 1H), 7.76 (d, J = 6.40 Hz, 1H); ^{13}C NMR δ 14.4, 19.0, 19.6, 29.0, 29.8, 38.3, 58.7, 63.4, 107.6, 142.2, 153.2, 193.6; mass spectrum m/z (relative intensity) EI 211 (M^+, 25), 196 (0.06), 183 (0.83), 168 (69), 140 (16), 124 (1), 96 (100), 78 (12), 68 (20), 56 (10); HRMS (ESI) calculated for $[C_{11}H_{18}NO_3]^+$ 212.1287, found 212.1295.

***N*-Ethoxycarbonyl-2-(2-methoxyphenyl)-2,3-dihydro-4-pyridone (4c).** Employing Method B, General Procedure A and using 2-bromoanisole (374 mg, 2.0 mmol), magnesium (192 mg, 8.0 mmol), *N*-ethoxycarbonyl-4-pyridone **2** (167 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave yellow viscous oil **4c** (195 mg, 71%). Without addition of CuCN, lower chemical yield was observed (46 vs 71%): IR (neat) 2979 (w), 2925 (w), 2841 (w), 1725 (s), 1670 (s), 1605 (s), 1489 (m), 1461 (m), 1410 (m), 1367 (m), 1302 (s), 1243 (m), 1200 (s), 1106 (m), 1027 (m), 752 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (br s, 3H), 2.81 (d, J = 16.5 Hz, 1H), 3.03 (dd, J = 8.2, 16.5 Hz, 1H), 3.83 (s, 3H), 4.21 (q, J = 6.8 Hz, 2H), 5.36 (d, J = 8.7 Hz, 1H), 5.95 (d, J = 7.3 Hz, 1H), 6.78−6.90 (m, 2H), 6.95 (d, J = 7.3 Hz, 1H), 7.17−7.24 (m, 1H), 8.11 (d, J = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 40.6, 51.8, 55.3, 63.6, 107.4, 110.9, 120.5, 125.3, 125.9, 129.0, 135.3, 143.3, 156.1, 192.8; mass spectrum m/z (relative, intensity) EI 276 (11, M^++1), 275 (59, M^+), 274 (M-1, 29), 258 (0.57), 244 (12), 232 (5), 216 (6), 202 (100), 187 (14), 168 (17), 160 (8), 144 (6), 134 (42), 119 (93), 108 (11), 91 (60), 77 (15), 65 (13), 51 (6); HRMS (ESI) calculated for $[C_{15}H_{18}NO_4]^+$ 276.1236, found 276.1225.

***N*-Ethoxycarbonyl-2-(2-methylphenyl)-2,3-dihydro-4-pyridone (4d).** Employing Method B, General Procedure A and using 2-bromotoluene (342 mg, 2.0 mmol), magnesium (192 mg, 8.0 mmol), *N*-ethoxycarbonyl-4-pyridone **2** (167 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave yellow viscous oil **4d** (186 mg, 72%): IR (neat) 3081 (w), 2974 (m), 2929 (w), 1728 (s), 1671 (s), 1605 (s), 1462 (w), 1422 (m), 1368 (m), 1303 (s), 1254 (m), 1209 (m), 1168 (m), 1107 (m), 1021 (m), 976 (w), 919 (w), 764 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, J = 6.9 Hz, 3H), 2.29 (s, 3H), 2.49 (d, J = 16.0 Hz, 1H), 3.08 (dd, J = 8.7, 16.5 Hz, 1 H), 4.12 (q, J = 6.8 Hz, 2 H), 5.36 (d, J = 8.7 Hz, 1 H), 5.75 (d, J = 8.2 Hz, 1H), 6.98−7.05 (m, 1H), 7.05−7.12 (m, 3H), 8.09 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 19.1, 40.9, 53.2, 63.7, 107.0, 124.1, 126.6, 128.0, 131.3, 134.0, 137.4, 143.8, 152.7, 191.7; mass spectrum m/z (relative, intensity) EI 259 (M^+, 22), 244 (3), 230 (1), 216 (5), 202 (100), 186 (19), 168 (30), 158 (17), 144 (16), 130 (27), 117 (96), 105 (18), 96 (47), 91 (29), 77 (8), 65 (10), 51 (5); HRMS (ESI) calculated for $[C_{15}H_{18}NO_3]^+$ 260.1287, found 260.1276.

***N*-Ethoxycarbonyl-2-(2-thienyl)-2,3-dihydro-4-pyridone (4e).** Employing Method A, General Procedure A and using thiophene (168 mg, 2.0 mmol), *n*-BuLi (0.80 mL, 2.50 M in hexane, 2.0 mmol), $MgBr_2$ (368 mg, 2.0 mmol), *N*-ethoxycarbonyl-4-pyridone **2** (167 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave colorless oil **4e** (195 mg, 78%): IR (neat) 3082 (w), 2970 (w), 2917 (w), 2846 (w), 1723 (s), 1659 (s), 1595 (s), 1422 (w), 1366 (m), 1290 (m), 1260 (m), 1087 (w), 1012 (w), 756 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, J = 6.9 Hz, 3 H), 2.87 (d, J = 16.5 Hz, 1H), 3.10 (dd, J = 6.8, 16.9 Hz, 1H), 4.27−4.40 (m, 2H), 5.39 (d, J = 8.2 Hz, 1H), 5.92 (d, J = 4.1 Hz, 1H), 6.89 (dd, J = 3.6, 5.0 Hz, 1H), 6.95 (s, 1H), 7.19 (d, J = 5.0 Hz, 1H), 7.74 (d, J = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 41.7, 52.0, 64.0, 107.7, 125.6, 126.2, 126.6, 141.0, 141.4, 152.5, 192.1; mass spectrum m/z (relative intensity) EI 252 (M^++1, 9), 251 (M^+, 59), 234 (2), 223 (13), 208 (5), 195 (2), 178 (28), 162 (11), 150 (8), 134 (9), 110 (100), 97 (31), 84 (11), 66 (16), 51 (31); HRMS (ESI) calculated for $[C_{12}H_{14}NO_3S]^+$ 252.0694, found 252.0689.

***N*-Ethoxycarbonyl-2-(2-furyl)-2,3-dihydro-4-pyridone (4f).** Employing Method A, General Procedure A and using furan (136 mg, 2.0 mmol), *n*-BuLi (0.80 mL, 2.50 M in hexane, 2.0 mmol), $MgBr_2$ (368 mg, 2.0 mmol) *N*-ethoxycarbonyl-4-pyridone **2** (167 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave yellow viscous oil **4f** (176 mg, 75%): IR (neat) 3117 (w), 2981 (w), 2928 (w), 1727 (s), 1667 (s), 1603 (s), 1426 (m), 1373 (m), 1313 (s), 1264 (m), 1219 (s), 1173 (m), 1106 (w), 1012 (m), 763 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.3 Hz, 3H), 2.82 (d, J = 16.5 Hz, 1H), 3.00 (dd, J = 6.9, 16.5 Hz, 1H), 4.27−4.39 (m, 2H), 5.33 (d, J = 8.2 Hz, 1H), 5.75 (s, 1H), 6.19 (d, J = 3.2 Hz, 1H), 6.27 (dd, J = 1.8, 3.2 Hz, 1H), 7.31 (d, J = 1.4 Hz, 1H), 7.74 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 39.0, 50.2, 63.8, 107.4, 108.3, 110.3, 141.3, 142.7, 151.0, 152.7, 192.1; mass spectrum m/z (relative intensity) EI 235 (M^+, 48), 218 (5), 207 (9), 193 (49), 162 (25), 146 (17), 134 (27), 120 (9), 106 (16), 94 (100), 81 (20), 66 (31), 53 (7); HRMS (ESI) calculated for $[C_{12}H_{14}NO_4]^+$ 236.0923, found 236.0913.

Synthesis of *N*-Boc-2-butyl 2,3-dihydro-5-bromo-4-pyridone (10). To the mixture of *N*-*tert*-butyl-carbamoyl-4-pyridone (**1**, 195 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) in THF under argon was added *n*-butyl magnesium chloride (0.75 mL, 1.6 M in THF, 1.2 mmol) dropwise at room temperature, and the resulting mixture was stirred for 3 h. After that tetra-*n*-butyl ammonium fluoride (*n*-Bu_4NF, 1.0 M solution in THF, 1.0 mmol) was added, and the reaction mixture was stirred for 10 min. Next, *N*-bromosuccinimide (356 mg, 2.0 mmol) was added, and the reaction mixture was stirred overnight. Then the reaction mixture was diluted with dichloromethane (5.0 mL), quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with dichloromethane (3 × 10.0 mL). The combined organic phase was washed with water (10.0 mL), brine (10.0 mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) to give a colorless oil (**10**, 243 mg, 73%). The use of a literature method[18a] (**3a** with NBS in CH_2Cl_2) gave 256 mg, 77% yield: IR (neat) 3105 (w), 2977 (w), 1733 (s), 1677 (s), 1401

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(m), 1363 (m), 1259 (m), 1210 (s), 1116 (w), 776 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 1.16−1.29 (m, 4H), 1.53 (s, 3H), 1.55−1.65 (m, 2H), 2.66 (d, J = 16.5 Hz, 1H), 2.86 (dd, J = 6.7, 16.5 Hz, 1H), 4.52 (br s, 1H), 8.08 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 22.2, 27.7, 27.8, 30.0, 39.4, 53.4, 84, 99.2, 142.5, 150.1, 185.8; mass spectrum m/z (relative intensity) EI 333 (M^+, 0.1), 331 (M^+ 0.1), 233 (28), 231 (29), 176 (98), 174 (100), 152 (32), 148 (12), 122 (8), 120 (8), 110 (14), 96 (70), 95 (69), 67 (68), 55 (12); HRMS (ESI) calculated for $[C_{14}H_{23}NO_3Br]^+$ 332.0861, found 332.0860.

***trans*-*N*-Boc-2-(2-methylphenyl)-6-phenylmethyl-4-piperidinone (11a).** Employing Method B, General Procedure A and using benzylbromide (342 mg, 2.0 mmol), magnesium (192 mg, 8.0 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **3d** (287 mg, 1.0 mmol) and TMSCl (326 mg, 3.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave colorless crystals (337 mg, 89%). The stereochemistry of this molecule was determined by X-ray crystallography: m.p. 109.3−111.4 °C; IR (neat) 3449 (br, s), 2975 (s), 2854 (s), 1668 (s), 1366 (s), 1167 (s), 702 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (br s, 9H), 2.31 (s, 3H), 2.54 (d, J = 17.5 Hz, 1H), 2.66−2.78 (m, 3H), 3.00 (dd, J = 8.2, 18.0 Hz, 1H), 3.38 (dd, J = 3.2, 13.0 Hz, 1H), 4.77 (br s, 1H), 5.61 (br s, 1H), 7.15−7.35 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 28.2, 41.2, 43.0, 43.1, 52.8, 53.5, 80.5, 124.2, 126.1, 126.8, 127.2, 128.7, 129.5, 131.2, 137.7, 154.7, 206.5; mass spectrum m/z (relative intensity) EI 379 (M^+, 0.1), 279 (2.0), 207 (3.0), 188 (60), 145 (100), 117 (23), 91 (25), 70 (15), 65 (8).

***trans*-*N*-Boc-2-(2-methylphenyl)-6-(1-methylethyl)-4-piperidinone (11b).** Employing Method B, General Procedure A and using *i*-PrMgBr (0.50 mL, 2.0 M in diethyl ether, 1.0 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **3d** (143 mg, 0.50 mmol) and TMSCl (163 mg, 1.5 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave pure **11b** (141 mg, 85%): IR (neat) 2966 (m), 2925 (m), 2872 (w), 1723 (m), 1690 (s), 1460 (w), 1362 (s), 1339 (m), 1249 (m), 1170 (s), 1110 (m), 1019 (w), 974 (w), 861 (w), 767 (w), 748 (w); ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.15 (br s, 9H), 1.79−1.89 (m, 1H), 2.24 (s, 3H), 2.53 (d, J = 17.4 Hz, 1H), 2.62 (dd, J = 2.3, 17.8 Hz, 1H), 2.78 (dd, J = 5.9, 18.3 Hz, 1H), 2.99 (dd, J = 7.8, 17.4 Hz, 1H), 4.20 (br s, 1H), 5.45 (d, J = 7.3 Hz, 1H), 7.02−7.09 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 19.4, 20.5, 28.1, 35.0, 42.1, 43.2, 52.9, 56.6, 80.2, 124.0, 126.2, 127.1, 131.1, 134.1, 142.0, 155.5, 207.4; mass spectrum m/z (relative intensity) EI 331 (M^+, 0.09), 288 (26), 258 (2), 232 (30), 214 (1), 188 (81), 174 (4), 145 (93), 117 (17), 91 (12), 70 (6), 57 (100); HRMS (ESI) calculated for $[C_{20}H_{29}NO_3]^+$ 331.21475, found 331.21528.

***trans*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone (11c).** Using General Procedure A and *n*-BuMgCl (0.63 mL, 1.6 M in THF, 1.0 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **3d** (143 mg, 0.50 mmol) and TMSCl (163 mg, 1.5 mmol) after purification by flash column chromatography (silica, 1−3% methanol:dichloromethane, v/v) gave colorless oil **11c** (154 mg, 89%). On the other hand, using General Procedure B and *n*-BuLi (0.80 mL, 2.5 M in THF, 2.0 mmol), CuCN (89 mg, 1.0 mmol), LiCl (85 mg, 2.0 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **3d** (143 mg, 0.50 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave colorless oil **11c** (152 mg, 88%), while the application of *n*-BuMgCl (0.63 mL, 1.6 M in THF, 1.0 mmol), CuI (191 g, 1.0 mmol), $BF_3{\cdot}OEt_2$ (0.5 mmol), *N*-Boc-2-(2-methylphenyl)-2,3-dihydro-4-pyridone **3d** (143 mg, 0.50 mmol) after purification by flash column chromatography (silica, 1−3% methanol:dichloromethane, v/v) gave colorless oil **11c** (85 mg, 49% and **12c** (56 mg, 32.5%). *trans*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone **11c**: IR (neat) 2960 (s), 2931 (s), 2861 (s), 1668 (s), 1367 (s), 1171 (s), 754 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 6.4 Hz, 3H), 1.28 (br s, 9H), 1.33−1.41 (m, 3H), 1.45−1.52 (m, 1H), 1.62 (br s, 1H), 1.90−1.99 (m, 1H), 2.31 (s, 3H), 2.65 (dd, J = 17.4, 33.9 Hz, 2H), 2.87 (dd, J = 6.0, 17.9 Hz, 1H), 3.07 (dd, J = 7.8, 17.4 Hz, 1H), 4.51 (br s, 1H), 5.55 (d, J = 6.9 Hz, 1H), 7.14 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 19.1, 22.5, 28.1, 28.9, 37.0, 42.4, 43.0, 51.3, 52.5, 80.1, 124.2, 126.1, 127.1, 131.1, 134.1, 141.3, 154.7, 206.9; mass spectrum m/z (relative intensity) EI, 345 (M^+, 0.1), 245 (13), 213 (10), 202 (30), 188 (88), 145 (100), 118 (13), 117 (76), 91 (51), 65 (15); HRMS (ESI) calculated for $[C_{21}H_{31}NO_3Na]^+$ 368.2202, found 368.2207. *cis*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone **12c**: IR (neat) 2972 (s), 29333 (s), 1664 (s), 1359 (s), 1172 (s), 1052 (s) 772 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 6.9 Hz, 3H), 1.17 (br s, 9H), 1.26−1.54 (m, 5H), 1.89 (br s, 1H), 2.34 (s, 3H), 2.58−2.75 (m, 4H), 4.61−4.67 (m, 1H), 5.31 (br s, 1H), 7.12−7.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 19.1, 22.4, 27.9, 29.1, 37.0, 43.5, 44.6, 51.7, 52.3, 80.4, 124.1, 126.6, 126.8, 130.5, 134.2, 142.9, 155.5, 208.1; mass spectrum m/z (relative intensity) EI 345 (M^+, 0.1), 274 (4), 245 (4), 213 (11), 210 (10), 188 (49), 146 (44), 145 (100), 117 (38), 115 (34), 91 (25), 65 (81); HRMS (ESI) calculated for $[C_{21}H_{32}NO_3]^+$ 346.2382, found 346.2377.

***trans*-*N*-Boc-2,6-butyl-4-piperidinone (13a).** Using General Procedure A and *n*-BuMgCl (0.63 mL, 1.6 M in THF, 1.0 mmol), *N*-Boc-2- butyl-2,3-dihydro-4-pyridone **3a** (127 mg, 0.50 mmol) and TMSCl (163 mg, 1.5 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave colorless oil **13a** (138 mg, 89%): IR (neat) 2961 (m), 2927 (s), 1723 (m), 1693 (s), 1464 (w), 1359 (s), 1249 (s), 1113 (s), 977 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 6H), 1.22−1.35 (m, 10H), 1.48 (s, 9H), 1.78 (br s, 2H), 2.52 (d, J = 17.9 Hz, 2H), 2.68 (dd, J = 6.0, 17.9 Hz, 2H), 4.10 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.4, 28.4, 28.9, 36.7, 41.5, 51.0, 79.8, 154.6, 208.4; mass spectrum m/z (relative intensity) EI 311 (M^+, 0.74), 270 (3), 254 (75), 238 (18), 199 (40), 198 (99), 156 (34), 155 (28), 154 (100), 112 (93), 96 (13), 83 (15), 69 (33), 57 (99); HRMS (ESI) calculated for $[C_{18}H_{34}NO_3]^+$ 312.2539, found 312.2550.

***trans*-*N*-Boc-2-(1-methylethyl)-6-butyl-4-piperidinone (13b).** Using General Procedure A and *i*-PrMgBr (0.50 mL, 2.0 M in diethyl ether, 1.0 mmol), *N*-Boc-2- butyl-2,3-dihydro-4-pyridone **3a** (127 mg, 0.50 mmol) and TMSCl (163 mg, 1.5 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave colorless oil **13b** (130 mg, 88%): IR (neat) 2961 (m), 2925 (m), 2867 (w), 1723 (m), 1691 (s), 1468 (w), 1367 (m), 1338 (m), 1252 (w), 1169 (m), 1101 (w), 1007 (w), 978 (w), 863 (w), 773 (w); ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.18−1.32 (m, 6H), 1.46 (s, 9H), 1.64−1.72 (m, 1H), 2.47 (dd, J = 2.7, 17.8 Hz, 1H), 2.56−2.60 (m, 2H), 2.62 (dd, J = 1.8, 6.4 Hz, 1H), 3.95 (br s, 1H), 4.00 (br s, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 14.1, 19.3, 20.3, 22.6, 28.5, 29.1, 34.8, 36.6, 41.8, 41.9, 51.8, 56.3, 80.0, 155.5, 209.0; mass spectrum m/z (relative intensity) EI 297 (M^+, 1), 296 (M^+ − 1, 6), 282 (1), 266 (3), 240 (53), 226 (13), 196 (39), 182 (14), 170 (2), 156 (6), 140 (29), 112 (28), 98 (6), 86 (7), 69 (20), 57 (100); HRMS (ESI) calculated for $[C_{17}H_{31}NO_3Na]^+$ 320.2202, found 320.2203.

***cis*-*N*-Boc-2,6-dibutyl-4-piperidinone (14a).** Employing General Procedure B and *n*-BuLi (0.80 mL, 2.5 M in THF, 2.0 mmol), CuCN (89 mg, 1.0 mmol), LiCl (85 mg, 2.0 mmol), *N*-Boc-2-butyl-2,3-dihydro-4-pyridone **3a** (127 mg, 1.0 mmol) after purification by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) gave colorless oil **14a** (135 mg, 86%): IR (neat) 2964 (m), 2923 (s), 1718 (m), 1689 (s), 1467 (w), 1361 (s), 1254 (s), 1110 (s), 976 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 3H), 1.26−1.37 (m, 4H), 1.43−1.48 (m, 1H), 1.49 (s, 9H), 1.61−1.67 (m, 1H), 2.35 (d, J = 14.7 Hz, 1H), 2.68 (dd, J = 7.8, 14.7 Hz, 1H), 4.57 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.4, 28.4, 29.1, 36.5, 43.7, 52.7, 80.1, 154.9, 209.0; mass spectrum m/z (relative intensity) EI 311 (M^+, 0.9), 270 (13), 254 (68), 238 (38), 199 (41), 198 (100), 156 (31), 155 (22), 154 (99), 112 (91), 96 (24), 83 (36), 69 (31), 57 (89); HRMS (ESI) calculated for $[C_{18}H_{33}NO_3Na]^+$ 334.2358, found 334.2355.

General Procedure D: Reduction of 2,6-Disubstituted 4-Piperidinones.[40] To the solution of 2,6-disubstituted 4-piperidinone (1.0 equiv) was added $NaBH_4$ (2.0 equiv) in methanol, and the resulting mixture was stirred for 30 min at room temperature. The reaction mixture was quenched with saturated ammonium chloride (5.0 mL) and extracted with diethyl ether (3 × 10.0 mL). The combined organic phase was washed with water (10.0 mL), brine

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(10.0 mL), dried over anhydrous magnesium sulfate, and filtered. The mixture was concentrated in vacuo and purified by flash column chromatography (silica, 20−25% ethyl acetate:petroleum ether, v/v).

***trans*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinol (15).** Employing General Procedure D and using *trans*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone (70 mg, 0.2 mmol, **11c**) and $NaBH_4$ (15 mg, 0.4 mmol) after purification by flash column chromatography (silica, 20−25% ethyl acetate:petroleum ether, v/v) gave colorless oil **15** along with other minor isomer (63 mg, 91%, 75:25 dr at CHOH): IR (neat) 3402 (br s), 2961 (s), 2926 (s), 2857 (s), 1655 (s), 1543 (s), 1366 (s), 1172 (s), 1066 (s), 792 (s); Major, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 6.0 Hz, 3H), 1.02 (s, 9H), 1.16−1.33 (m, 5H), 1.50−1.69 (m, 4H), 2.14−2.23 (m, 2H), 2.26 (s, 3H), 3.94−3.99 (m, 1H), 4.35 (br s, 1H), 4.64 (dd, J = 4.2, 9.2 Hz, 1H), 7.01−7.21 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 19.4, 22.6, 27.8, 28.1, 29.3, 32.3, 35.6, 40.8, 51.8, 53.6, 64.2, 79.6, 125.1, 126.1, 130.4, 133.8, 143.3, 156.1; mass spectrum m/z (relative intensity) EI 347 (M^+, 0.1), 220 (27) 205 (100), 189 (4), 177 (11), 145 (12), 105 (8), 57 (26); Minor, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, J = 7.3 Hz, 3H), 1.00 (s, 9H), 1.78−1.85 (m, 1H), 1.98−2.03 (m, 1H), 2.24 (s, 3H), 3.81 (s, 1H), 3.94−3.99 (m, 1H), 5.23 (s, 1H), 7.01−7.21 (m, 4H), other hydrogens were imbedded underneath major isomer hydrogens; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 19.2, 22.5, 28.1, 29.1, 29.7, 35.4, 35.9, 36.5, 52.8, 63.4, 79.4, 125.2, 125.5, 126.5, 130.8, 135.1, 143.5, 155.4; HRMS (ESI) calculated for $[C_{21}H_{33}NO_3Na]^+$ 370.2358, found 370.2360.

***trans*-*N*-Boc-2,6-dibutyl-4-piperidinol (16).** Employing General Procedure D and using *trans*-*N*-Boc-2,6-dibutyl-4-piperidinone (78 mg, 0.25 mmol, **13a**) and $NaBH_4$ (19 mg, 0.5 mmol) after purification by flash column chromatography (silica, 20−25% ethyl acetate:petroleum ether, v/v) gave colorless oil **16** (75 mg, 96%): IR (neat) 3447 (br, s), 2941 (s), 2909 (s), 2830 (s), 1681 (s), 1666 (s), 1423 (s), 1233 (s), 1069 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 6.4 Hz, 3H), 0.92 (t, J = 6.9 Hz, 3H), 1.25−1.36 (m, 9H), 1.46 (s, 9H), 1.60−1.71 (m, 4H), 1.89−1.95 (m, 1H), 1.99−2.06 (m, 3H), 3.41−3.51 (m, 1H), 4.09 (br s, 1H), 4.07−4.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2-carbons), 22.5, 22.6, 28.5, 29.0, 29.4, 32.6, 34.9, 35.3, 36.4, 51.5, 51.7, 64.7, 79.2, 155.4; mass spectrum m/z (relative intensity) EI 313 (M^+, 0.07), 256 (35), 240 (38), 213 (7), 200 (98), 156 (100), 138 (57), 112 (31), 95 (18), 69 (33), 57 (93); HRMS (ESI) calculated for $[C_{18}H_{36}NO_3]^+$ 314.2695, found 314.2686.

***trans*-*N*-Boc-2-(1-methylethyl)-6-butyl-4-piperidinol (17).** Employing General Procedure D and using *trans*-*N*-Boc-2-(1-methylethyl)-6-butyl-4-piperidinone (70 mg, 0.2 mmol, **13b**) and $NaBH_4$ (15 mg, 0.4 mmol) after purification by flash column chromatography (silica, 20−25% ethyl acetate:petroleum ether, v/v) gave colorless oil **17** (52 mg, 87%, 1:1 dr at CHOH): IR (neat) 3412 (br s), 2975 (s), 2931 (s), 1664 (s), 1539 (s), 1359 (s), 1163 (s), 1075 (s), ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88−0.96 (m, 18H), 1.21−1.39 (m, 8H), 1.46 (s, 18H), 1.47−1.59 (m, 6H), 1.75−1.83 (m, 3H), 1.90−1.96 (m, 3H), 1.99−2.06 (m, 3H), 2.28−2.35 (m, 1H), 2.98−3.07 (m, 1H), 3.17−3.23 (m, 1H), 3.62−3.68 (m, 1H), 3.91−4.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.4 (2-carbons), 19.8, 20.1, 20.5, 20.8, 22.5, 22.6, 22.7, 28.5 (2-carbons), 28.9 (2-carbons), 29.5, 30.9, 34.2, 35.1, 35.6, 36.6, 38.3, 52.2, 52.3, 58.5, 59.2, 66.0 (2-carbons), 79.3 (2-carbons), 156.3, 156.4; mass spectrum m/z (relative intensity), major EI 299 (M^+, 0.01), 256 (21), 226 (6), 201 (22), 200 (100), 186 (11), 157 (11), 156 (90), 142 (12), 138 (29), 112 (32), 111 (12), 98 (11), 57 (99), 41 (36); HRMS (ESI) calculated for $[C_{17}H_{33}NO_3Na]^+$ 322.2358, found 322.2367.

***cis*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinol (18).** Employing General Procedure D and using *cis*-*N*-Boc-2-(2-methylphenyl)-6-butyl-4-piperidinone (35 mg, 0.1 mmol, **12c**) and $NaBH_4$ (8 mg, 0.2 mmol) after purification by flash column chromatography (silica, 20−25% ethyl acetate:petroleum ether, v/v) gave colorless oil **18** (29 mg, 84%): IR (neat) 3448 (br s), 2961 (s), 2930 (s), 2859 (s), 1687 (s), 1366 (s), 1171 (s), 1071 (s), 782 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 3H), 1.12 (s, 9H), 1.26 (br s, 1H), 1.40−1.47 (m, 4H), 1.65−1.78 (m, 3H), 2.02−2.08 (m, 1H), 2.16−2.25 (m, 1H), 2.36 (s, 3H), 2.37−2.44 (m, 1H), 4.07−4.13 (m, 1H), 4.22−4.28 (m, 1H), 4.89 (dd, J = 5.1, 12.5 Hz, 1H), 7.12−7.34 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 19.0, 22.7, 28.0, 29.3, 37.0, 38.3, 39.6, 51.7, 53.8, 65.6, 79.5, 124.4, 126.1, 126.3, 130.2, 133.6, 144.4, 155.8; mass spectrum m/z (relative intensity) EI 347 (M^+, 0.7), 220 (33) 205 (100), 189 (14), 177 (17), 145 (9), 105 (12), 57 (34); HRMS (ESI) calculated for $[C_{21}H_{34}NO_3]^+$ 348.2539, found 348.2531.

***cis*-*N*-Boc-2,6-dibutyl-4-piperidinol (19).** Employing General Procedure D and using *cis*-*N*-Boc-2,6-dibutyl-4-piperidinone (78 mg, 0.25 mmol, **14a**) and $NaBH_4$ (19 mg, 0.5 mmol) after purification by flash column chromatography (silica, 20−25% ethyl acetate:petroleum ether, v/v) gave colorless oil **19** (68 mg, 87%): IR (neat) 3433 (br, s), 2931 (s), 2869 (s), 1687 (s), 1662 (s), 1409 (s), 1365 (s), 1175 (s), 1095 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 6.9 Hz, 6H), 1.26−1.34 (m, 8H), 1.46 (s, 9H), 1.49−1.60 (m, 4H), 1.71−1.79 (m, 3H), 2.14 (m, 2H), 3.89−3.93 (m, 1H), 4.11−4.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 28.5, 29.0, 36.1, 38.1, 50.3, 65.8, 79.2, 155.4; mass spectrum m/z (relative intensity) EI 313 (M^+, 0.08), 256 (25), 240 (5), 200 (100), 156 (99), 138 (26), 112 (54), 95 (8), 69 (25), 57 (98); HRMS (ESI) calculated for $[C_{18}H_{36}NO_3]^+$ 314.2695, found 314.2703.

1,10b-Dihydropyrido[2,1,*α*]isoindole-2-one (20). The cyclization of compound **3l** to tricyclic compound **20** was carried out using literature procedure.[41] To the solution of *N*-Boc-2-(2′chloromethylphenyl)-2,3-dihydro-4-pyridone **3l** (161 mg, 0.5 mmol) in methanol (5.0 mL) was added sodium metal (48 mg, 2.0 mmol), and the mixture was heated to reflux for 1 h. The mixture was concentrated in vacuo and purified by flash column chromatography (silica, 1−3% MeOH:CH_2Cl_2, v/v) to give white pure solid **20** (71 mg, 77%): mp 134.7−136.1 °C; IR (neat) 2961 (m), 2944 (s), 1715 (m), 1464 (w), 1363 (s), 1241 (s), 1170 (s), 1010 (m), 934 (w), 737 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (t, J = 16.5 Hz, 1H), 2.81 (dd, J = 5.0, 17.0 Hz, 1H), 4. 85 (dd, J = 14.0, 34.5 Hz, 2H), 5.11 (d, J = 7.0 Hz, 1H), 5.22 (dd, J = 4.5, 16.0 Hz, 1H), 7.25−7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.8, 54.5, 62.7, 98.7, 122.1, 122.9, 128.3 (2-carbons), 136.6, 139.6, 149.6, 191.3; mass spectrum m/z (relative intensity) EI 186 (M^++1, 14.34), 185 (M^+, 100), 168 (17), 157 (15), 156 (52), 142 (8), 130 (17), 129 (20), 115 (34), 91 (9), 77 (11), 65 (6), 51 (8); HRMS (ESI) calculated for $[C_{12}H_{11}NO]^+$ 185.08407, found 185.08450.

***trans*-*N*-Boc-2-(2-methylphenyl)-6-(1-methylethyl)-4-piperidinol (23).** Employing General Procedure D and using *trans*-*N*-Boc-2-(2-methylphenyl)-6-(1-methylethyl)-4-piperidinone (70 mg, 0.2 mmol, **11b**) and $NaBH_4$ (15 mg, 0.4 mmol) after purification by flash column chromatography (silica, 20−25% ethyl acetate:petroleum ether, v/v) gave colorless oil **23** along with other minor isomer (62 mg, 93%): IR (neat) 3431 (br s), 2955 (s), 2933 (s), 2872 (s), 1643 (s), 1371(s), 1273 (s), 1166 (s), 752 (s); Major, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (dd, J = 6.4, 8.3 Hz, 6H), 1.10 (s, 9H), 1.23 (br s, 1H), 1.74−2.07 (m, 3H), 2.29−2.35 (m, 1H), 2.35 (s, 3H), 2.39−2.42 (m, 1H), 4.02−4.11 (m, 1H), 4.14−4.18 (m, 1H), 4.81 (dd, J = 5.1, 11.9 Hz, 1H), 7.11−7.30 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5, 20.0, 20.9, 27.8, 31.4, 35.2, 39.2, 52.0, 58.2, 64.3, 79.3, 125.4, 126.0, 126.3, 130.6, 134.2, 142.9, 156.3. Minor, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (dd, J = 6.9, 21.5 Hz, 6H), 1.12 (s, 9H), 1.26 (s, 1H), 1.42−1.48 (m, 2H), 2.34 (s, 3H), 3.48−3.52 (m, 1H), 4.02−4.11 (m, 1H), 5.32 (br s, 1H), 7.11−7.30 (m, 4H); other hydrogens were imbedded underneath the major isomer hydrogens); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2 (2-carbons), 20.4, 28.1, 29.6, 33.0, 34.8, 53.6, 57.6, 63.6, 79.8, 125.2, 125.5, 126.5, 130.8, 134.1, 142.8, 155.7; mass spectrum m/z (relative intensity) EI 333 (M^+, 0.02), 207 (3), 190 (100), 172 (10), 147 (57), 129 (21), 117 (16), 105 (8), 91 (16); HRMS (ESI) calculated for $[C_{20}H_{31}NO_3Na]^+$ 356.2202, found 356.2202.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for **3c−f**, **3k−q**, **4b−f**, **10**, **11a−c**, **12c**, **13a,b**, **14a**, **15−20**, **23**, ab initio minimized geometries for twist-boat conformations **11c-TB$_{diax}$**, **12c-TBAr$_{ax}$**, **12c-TBR$_{ax}$**,

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and **15-TB$_{diax}$** and coordinates of all stationary points are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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