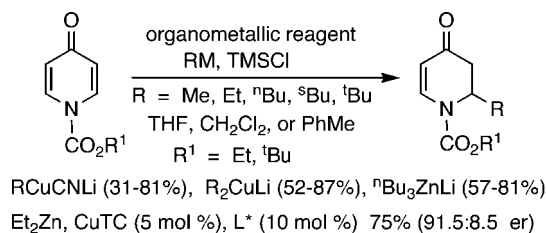# JOC*Article*

# Conjugate Addition Reactions of *N*-Carbamoyl-4-Pyridones with Organometallic Reagents

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$R = Me, Et, {}^nBu, {}^sBu, {}^tBu$
THF, $CH_2Cl_2$, or PhMe
$R^1 = Et, {}^tBu$

RCuCNLi (31-81%), $R_2$CuLi (52-87%), ${}^nBu_3$ZnLi (57-81%)
$Et_2$Zn, CuTC (5 mol %), L* (10 mol %)  75% (91.5:8.5  er)

*N*-Carbamoyl-4-pyridones undergo conjugate addition reactions with organocuprates and organozincates to afford 2-substituted-2,3-dihydro-4-pyridones providing a direct synthetic approach to substituted piperidines and piperidones. Good to excellent yields of conjugate adducts are achieved with lithium dialkylcuprates, alkylcyanocuprates, RLi/CuCN (0.3 equiv), and trialkylzincates with copper catalysis. Copper catalysis in the conjugate addition of Grignard reagents affords modest yields of conjugate adducts. An enantioenriched phosphoramidite ligand promotes the copper catalyzed conjugate addition of $Et_2$Zn to a *N*-carbamoyl-4-pyridone with an er of 91.5:8.5.

## Introduction

The piperidine ring is an important structural feature in many medicinal compounds and naturally occurring alkaloids.[1] This motif includes both simple and annulated piperidines [e.g., indolizidines (1-azabicyclo[4.3.0]nonanes) and quinolizidines (1-azabicyclo (4.4.0)decanes], and 12 000 piperidine derivatives were reported in clinical trials[2a] in a 10 year period. Numerous asymmetric[2b] synthetic routes have been developed,[3,4] which generally revolve around four strategic approaches:[3a] (1) ring formation via alkylation of a nitrogen center with an acyclic precursor containing pre-established stereogenic centers; (2) asymmetric generation of stereocenters and substitution patterns on an existing six-membered nitrogen heterocycle; (3) ring

expansion of pyrrolidine or furan derivatives, and more recently; (4) ring closing-metathesis on dialkyl substituted nitrogen derivatives where each alkyl group contains an appropriately positioned alkene functional group.

Although each of the above strategies relies extensively on manipulation of the chiral pool for appropriate starting materials[3b] or use of chiral auxiliaries,[3d,4] 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. In pursuit of a catalytic asymmetric approach to substituted piperidines or piperidinones, we were intrigued by the possibility of effecting organocuprate conjugate addition reactions on 4-pyridones (eq 1). Surprisingly, we could find no examples of this reaction in the literature.

Although organometallic mediated conjugate addition of alkyl or aryl ligands to 4-pyridones (i.e., **1**) could provide a rapid entry to the highly versatile 2,3-dihydropyridones[4] (e.g., **2/3**), the addition of an allyllithium[5a] reagent to a 4-pyridone and a dithianyllithium[5b] reagent to a *N*-cabamoyl-4-quinolone appear to be the only reported examples of such a reaction.[5] While

(1) (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680. (b) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681.
(2) (a) Stinson, S. C. *C&EN* **2001**, *79* (20), 45–57. (b) Thayer, A. M. *C&EN* **2007**, *85* (32), 11–19.
(3) For reviews on piperidine and piperidone synthesis see: (a) Cossy, J. *Chem. Rec.* **2005**, *5*, 70–80, and references cited therein. (b) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159–2191. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (d) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030. (e) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (f) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813. (g) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633–640.
(4) For reviews see: (a) Joseph, S.; Comins, D. L. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 870–880. (b) Comins, D. L. *J. Hetero. Chem.* **1999**, *36*, 1491–1500.

(5) (a) Lim, S. H.; Curtis, Michael, D.; Beak, P. *Org. Lett.* **2001**, *3*, 711–714. (b) Alvarez, M.; Ajana, W.; Lopez-Calahorra, F.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 917–919. (c) Albaneze-Walker, J.; Rossen, K.; Volante, R. P.; Reider, P. J. A conjugate reduction of a *N*-alkyl-4-pyridone has also been reported. *Tetrahedron Lett.* **1999**, *40*, 4917–4920.

copper[4b,6] and rhodium[7] mediated conjugate additions to 2,3-dihydropyridones are well established, the addition of nucleophiles to pyridinium salts[8a–c] is employed as a synthetic alternative to a 4-pyridone conjugate addition strategy. Similarly, addition of alkyllithium reagents to quinolinium salts generated by addition of $BF_3 \cdot Et_2O$ or trialkylsilyltriflates to *N*-cabamoyl-4-quinolones has also been reported.[8d,e] We now report that a variety of organometallic reagents do in fact undergo conjugate addition reactions with *N*-carbamoyl-4-pyridones to afford 2-substituted 2,3-dihydro-4-pyridones (eq 1).
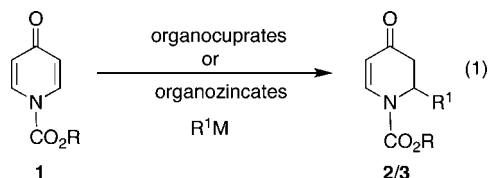
## Results and Discussion

Lithium diphenyl- and dialkylcuprates, as well as the corresponding cyanocuprate reagents, readily add to *N*-carbamoyl-4-pyridones (Table 1, entries 1–25) when the reaction is conducted in THF in the presence of trimethylsilylchloride (TMSCl). No conjugate addition occurs in the absence of TMSCl. Reaction of lithium dimethylcuprate with the ethyl-carbamate **1a** gave modest yields of the 1,4-adduct accompanied by formation of a pyridone dimer (entry 1), which was suppressed by utilization of the *tert*-butylcarbamate **1b** (entry 3). For the more reactive lithium dialkylcuprates (i.e., alkyl = $^n$Bu, $^s$Bu, $^t$Bu, entries 6 vs 8, 11 vs 13, and 16 vs 18) and lithium diphenylcuprate entry 21 vs 23) comparable yields were obtained with both carbamates **1a** and **1b**.

Similarly, various methylcuprates (entries 1–4) gave lower yields than the corresponding butyl (entries 6–9 and 11–19) and phenylcuprates (entries 21–24), reflecting the facility of ligand transfer and pyridone reactivity. Consistent with these reactivity patterns, the cyanocuprate reagents (i.e., RCuCNLi) generally gave lower yields than the Gilman reagents (i.e., $R_2CuLi$), which was significant for the methyl ligand (26–30%, entries 2 vs 1, 4 vs 3) and very modest (1–13%) to insignificant for the other ligands (entries 6–9, 11–19, and 21–24). Thus, for phenyl and alkyl groups larger than methyl, the conjugate addition reaction is insensitive to cuprate stoichiometry (i.e., $R_2CuLi$ vs RCuCNLi) and carbamate structure (i.e., **1a** vs **1b**).

In the interest of developing an asymmetric variation of the reaction, a series of procedures catalytic in copper were examined. Although CuCN (10 mol%) effectively catalyzed the conjugate addition of *n*-BuMgCl (entry 26) to **1b** in THF, established procedures for copper catalyzed asymmetric conjugate addition of Grignard reagents called for changes in solvent
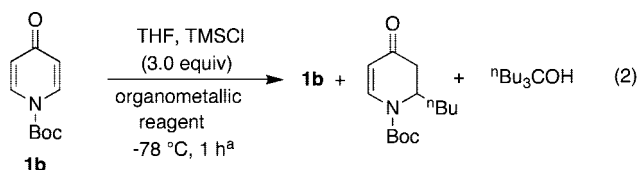
(6) (a) Sebesta, R.; Pizzuti, M.; Boersma, A. J.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2005**, 1711–1713. (b) Kranke, B.; Hebrault, D.; Schultz-Kukula, M.; Kunz, H. *Synlett* **2004**, 671–674. (c) Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151–1160.

(7) (a) Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2005**, 7, 2433–2435. (b) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, 126, 6240–6241. For rhodium catalyzed addition of arylzinc reagents to *N*-carbamoyl-4-quinolones see: (c) Shintani, R.; Yamagami, T.; Kimura, T.; Hayashi, T. *Org. Lett.* **2005**, 7, 5317–5319.

(8) For a review see: (a) Comins, D. L.; Joseph, S. P. *Adv. Nitrogen Heterocycles* **1996**, 2, 251–294. (b) Klegraf, E.; Follmann, M.; Schollmeyer, D.; Kunz, H. *Eur. J. Org. Chem.* **2004**, 3346–3360. (c) Focken, T.; Charette, A. B. *Org. Lett.* **2006**, 8, 2985–2988. (d) For addition of organometallic reagents to quinolinium salts see: Beifuss, U.; Ledderhose, S. *Synlett* **1997**, 3, 313–315. (e) Beifuss, U.; Feder, G.; Bes, T.; uson, I. *Synlett* **1998**, 649–651.

**TABLE 1. Reactions of *N*-(Carbamoyl)-4-Pyridones with Organocuprate Reagents**

| | 1a R = Et | a $R^1$ = Me | d $R^1$ = $^t$Bu | 2 R = Et |
| | 1b R = $^t$Bu | b $R^1$ = $^n$Bu | e $R^1$ = Ph | 3 R = $^t$Bu |
| | | c $R^1$ = $^s$Bu | f $R^1$ = Et | |

| entry | *N*-Boc | reagent[a] | Cpd no. | % yield[b] |
|---|---|---|---|---|
| 1 | **1a** | $Me_2CuLi$ | **2a** | 52–58[c] |
| 2 | **1a** | MeCuCNLi | **2a** | 36[c] |
| 3 | **1b** | $Me_2CuLi$ | **3a** | 69 |
| 4 | **1b** | MeCuCNLi | **3a** | 39 |
| 5 | **1b** | MeLi/CuCN (0.3 equiv) | **3a** | 62 |
| 6 | **1a** | $^nBu_2CuLi$ | **2b** | 83–85 |
| 7 | **1a** | $^n$BuCuCNLi | **2b** | 73–75 |
| 8 | **1b** | $^nBu_2CuLi$ | **3b** | 85–87 |
| 9 | **1b** | $^n$BuCuCNLi | **3b** | 77–80 |
| 10 | **1b** | $^n$BuLi/CuCN (0.3 equiv) | **3b** | 77[c] |
| 11 | **1a** | $^sBu_2CuLi$ | **2c** | 67–70 |
| 12 | **1a** | $^s$BuCuCNLi | **2c** | 76 |
| 13 | **1b** | $^sBu_2CuLi$ | **3c** | 71–75 |
| 14 | **1b** | $^s$BuCuCNLi | **3c** | 78 |
| 15 | **1b** | $^s$BuLi/CuCN | **3c** | 70 |
| 16 | **1a** | $^tBu_2CuLi$ | **2d** | 59–65 |
| 17 | **1a** | $^t$BuCuCNLi | **2d** | 56 |
| 18 | **1b** | $^tBu_2CuLi$ | **3d** | 66–70 |
| 19 | **1b** | $^t$BuCuCNLi | **3d** | 65 |
| 20 | **1b** | $^t$BuLi/CuCN (0.3 equiv) | **3d** | 62 |
| 21 | **1a** | $Ph_2CuLi$ | **2e** | 86 |
| 22 | **1a** | PhCuCNLi | **2e** | 73 |
| 23 | **1b** | $Ph_2CuLi$ | **3e** | 80–85 |
| 24 | **1b** | PhCuCNLi | **3e** | 81 |
| 25 | **1b** | PhLi/CuCN (0.3 equiv) | **3e** | 75 |
| 26 | **1b** | $^n$BuMgCl/CuCN (10 mol%) | **3b** | 79 |
| 27 | **1b** | EtMgBr/CuBrDMS[d,e] | **3f** | 39 |
| 28 | **1b** | EtMgBr/CuBrDMS[d,f] | **3f** | 52–57 |

[a] Reagent prepared by adding $R^1$Li to MX or $MX_2$ (M = Cu or Zn and X = CN and Br, respectively). TMSCl (3.0 equiv) was used unless noted. [b] Yields are based upon isolated products purified by column chromatography. [c] Pyridone dimer was formed (entry 1, 10%; entry 2, 24%; entry 10, 5%). [d] $^t$BuOMe was used as solvent. [e] 5 Mol% of CuBr·Me$_2$S was used. [f] No TMSCl was employed.

and copper(I) salt.[9] Reaction of **1b** with commercially available EtMgBr and catalytic quantities (5 mol %) of CuBr·SMe$_2$ gave a low yield (39%) of 1,4-adduct in the presence of TMSCl (entry 27) and a better yield in the absence of TMSCl (52–57%) (entry 28). These results are consistent with the observation that the accelerating effect of TMSCl on 1,4-conjugate additions for both stoichiometeric cuprates[10a,b] and procedures catalytic in copper[10c] is significantly greater in THF than in diethyl ether and that in the absence of TMSCl cuprate mediated 1,4-additions are faster in ether[10d] than in THF. Utilization of the TMSCl (2.0 equiv)/HMPA (2.0 equiv) combination[10c] gave no significant increase in chemical yield (42%). These results are

(9) (a) Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, 126, 12784–12785. (b) Lopez, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, 44, 2752–2756. (c) Harutyunyan, S. R.; Lopez, F.; Browne, W. R.; Correa, A.; Pena, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, 128, 9103–9118.

(10) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, 26, 6019–6022. (b) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, 27, 4029–4032. (c) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, 45, 349–362. (d) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, 43, 2443–2454.

potentially amenable to the development of asymmetric copper catalyzed conjugate addition of Grignard reagents to *N*-carbamoyl-4-pyridones.

Having achieved success in allylic substitution reactions with Grignard reagents and 0.3 equivalents[11] of CuCN, we examined this stoichiometry with alkyllithium reagents obtaining conjugate adducts **3a,b,d** (Table 1, entries 5, 10, and 20) in yields comparable to those obtained with the alkylcyanocuprate reagents RCuCNLi. When the amount of CuCN was reduced to 10 mol%, reaction of *n*BuLi and **1b** in the presence of TMSCl gave **3b** (21%), starting material **1b** (20%), and a tertiary alcohol, 1,1-di-*n*-butyl-1-pentanol (34%), arising from attack at the carbamate carbonyl (eq 2). In the absence of copper, the tertiary alcohol was formed in a 34% molar ratio (quantitative based upon one equivalent of *n*-BuLi as limiting reagent) after one hour at −78 °C. These results indicate that CuCN can be reduced to 0.3 equivalents of the alkyllithium stoichiometry without deleterious effect perhaps suggesting involvement of a cuprate species of stoichiometry $R_3CuLi_2$ or an aggregate such that free RLi is not present in solution. Although Ashby[12a,b] reported a similar species (i.e., $Me_3CuLi_2$) that chemoselectively afforded 1,4-addition over 1,2-addition to cyclohexenone, Lipshutz[12c] showed that when prepared in the absence of LiI in $Et_2O$ or in the presence of LiI in an $Et_2O$:THF solvent mixture $Me_3CuLi_2$ is not a discrete species and these solutions contain substantial amounts of free MeLi. Further NMR studies involving scalar coupling measurements also revealed that $Me_3CuLi_2$ consisted largely of $Me_2CuLi$ and MeLi in halide free THF solutions.[12d] Chemical reactions and Gilman tests also revealed that MeLi was present in $Et_2O$:THF solutions of $Me_2CuLi$ free of LiI, but was not present in solutions of $Me_2CuLi \cdot LiI$.[12c]
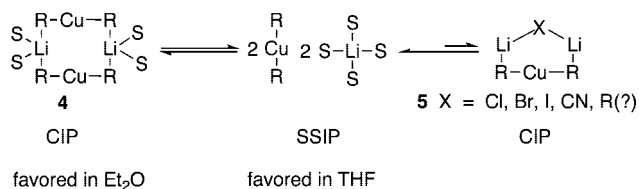
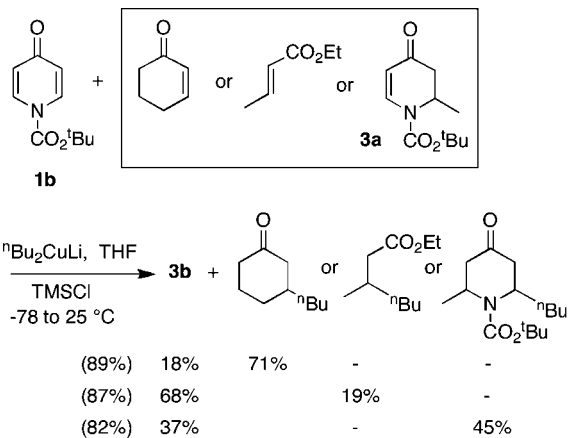<sup>a</sup> Unless otherwise noted. <sup>b</sup> <sup>1</sup>H NMR determined molar ratios. <sup>c</sup> isolated yields. <sup>d</sup> 1.5 Equivalents of <sup>n</sup>BuLi was used. <sup>e</sup>*Tert*-butyl pentanoate was formed (16%)<sup>b</sup>.

## SCHEME 1. *N*-Carbamoyl-4-Pyridone Competition Experiments

More recent structural studies[13a] of cuprate reagents [e.g., $R_2CuLi$ and $R_2CuLi \cdot LiX$ (X = Br, I, CN)] suggest a homodimeric structure **4** in $Et_2O$, and solvent separated ion pairs (SSIP) in THF that are in equilibrium with minor amounts of heterodimers **5** (X = Cl, Br, I, CN). All these studies suggest that THF solutions of $R_3CuLi_2$ stiochiometry should contain substantial amounts of RLi. As expected, a THF solution of *n*-$Bu_3CuLi_2$ gave a positive Gilman Test indicative of free *n*-BuLi. Reaction of this solution with **1b** at −78 C for one hour gave **1b**, dihydropyridone **3a**, and tertiary alcohol (55:35:10 ratio with CuCN and 60:30:10 with CuCN·2LiCl). Utilization of 10 mol% of CuCN or CuCN·2LiCl gave substantially greater amounts of the *tert*-alcohol. The cyano Gilman reagent prepared from either CuCN·2LiCl or CuCN gave only starting **1b** and product **3b** after one hour at −78 °C. In all cases, the addition of LiCl gave lower yields of conjugate adduct **3b**. These results suggest that the *n*-$Bu_3CuLi_2$ composition is not more reactive toward conjugate addition than the Gilman reagent, and that free *n*-BuLi is present in solution for the former composition. Product distribution then is determined by the relative rates of reaction between **1b** and *n*-BuLi, *n*-$Bu_2CuLi$ and **1b**, and the rate for regeneration of the Gilman reagent from *n*-BuCu and *n*-BuLi. At 30 mol% CuCN, the competitive rates favor conjugate addition, while with 10 mol% CuCN the relative rates favor addition of *n*-BuLi to the carbamate carbonyl. Thus, successful utilization of 30 mol% CuCN will be dependent upon the relative rate of RLi reaction with a particular substrate as originally observed by Ashby.[12b] Computational studies predict aggregate **5** (X = CN) to be only slightly more stable than the aggregate arising from exchange of CN and R perhaps accounting for the anomalous positive Gilman test displayed by the Lipshutz reagent.[13b] Nevertheless, it seems unlikely that a heterodimer **5** (X = *n*-Bu, for *n*-$Bu_3CuLi_2$) is playing any role in these conjugate addition reactions given the above experimental results.

In order to gauge the reactivity of **1b**, a series of competition experiments were carried out with 2-cyclohexenone, ethyl crotonate, and *N*-Boc-2-methyl-2,3-dihydro-4-pyridone (Scheme 1). These individual experiments revealed that **1b** is three times more reactive than ethyl crotonate and one-fourth as reactive as 2-cyclohexenone toward lithium di-*n*-butylcuprate and comparable in reactivity to dihydropyridone **3a** by a factor of 0.8.

**TABLE 2. Reactions of *N*-(Carbamoyl)-4-Pyridones with Organozinc Reagents with or without Copper Catalysis**



| | 1a R = Et | a R¹ = Me | 2 R = Et |
| | 1b R = ᵗBu | b R¹ = ⁿBu | 3 R = ᵗBu |
| | | f R¹ = Et | |

| entry | N-Boc | reagent[a] | Cpd no. | % yield[b] |
|---|---|---|---|---|
| 1 | 1a | ⁿBu₃ZnLi | 2b | 57 |
| 2 | 1b | ⁿBu₃ZnLi | 3b | 63 |
| 3 | 1b | ⁿBu₃ZnLi[c] | 3b | 78−81 |
| 4 | 1a | ⁿBuMe₂ZnLi/CuCN[d] | 2b | 78[e] |
| 5 | 1a | ⁿBu₃ZnLi/CuCN[d] | 2b | 81 |
| 6 | 1a | Bu₃ZnLi/CuCN[c,d] | 2b | 82 |
| 7 | 1b | Bu₃ZnLi/CuCN[c,d] | 3b | 83 |
| 8 | 1a | BuZnMe/CuCN[c,d] | 2b | 50 |
| 9 | 1b | ⁿBuZnBr/CuCN (1.0) | 3b | 70 |
| 10 | 1b | ⁿBuZnᵗBu₂Li/CuCN (1.0) | 3b | 40[f] |
| 11 | 1b | ⁿBuZnᵗBu₂Li/CuCN (0.1) | 3b | 38[f] |
| 12 | 1b | ⁿBuZnᵗBu₂Li/CuCN (0.1) | 3b | 40[f] |
| 13 | 1b | Et₂Zn (2.0)/CuCN·2LiCl (1.0) | 3f | 77 |
| 14 | 1a | Et₂Zn (2.0)/CuCN·2LiCl (1.0) | 2f | 65 |
| 15 | 1b | Et₂Zn (2.0)/CuCN·2LiCl (0.1) | 3f | 62 |
| 16 | 1b | Et₂Zn/Cu(OTf)₂ (5 mol%)/P(OME)₃ (−20 °C)[g] | 3f | 31−42 |
| 17 | 1b | Et₂Zn/Cu(OTf)₂, (5 mol%)/P(OME)₃ (25 °C)[g] | 3f | 53−58 |
| 18 | 1b | Et₂Zn/Cu(OTf)₂ (5 mol%)/P(OMe)₃ (−20 °C)[g,h] | 3f | 0 |

[a] Reagent prepared by adding R¹Li to ZnBr₂ in the absence or presence of CuCN unless noted. TMSCl (3.0 equiv) was used unless noted. [b] Yields are based upon isolated products purified by column chromatography. [c] Allyl bromide (1.0 equiv) was present during the conjugate addition reaction. [d] Catalytic amount of CuCN (0.1 equiv) was employed. [e] By-product 2a was formed in 18% yield. [f] Product 3d was also formed (31%, 31%, 21%, entries 10, 11, and 12 respectively). [g] Dichloromethane was used as solvent. [h] No TMSCl was employed.

We next turned our attention to the conjugate addition reactions of organozincate and organozinc reagents,[14] which are known to occur both with and without copper catalysis (Table 2). Lithium tri-*n*-butylzincate underwent conjugate addition to carbamates 1a−b in comparable and modest yields (entries 1−2). In an effort to achieve tandem conjugate addition-α-allylation, allyl bromide was added to the reaction mixture after the addition of the zincate reagent. Surprisingly, although α-allylation was not achieved, the chemical yields of the conjugate adduct were increased (entries 1−2 vs 3) to 78−81%. Higher chemical yields were obtained from the zincate reagents when 10 mol % of CuCN was employed (entries 4−7), although the mixed *n*-butyldimethylzincate/CuCN gave significant amounts of 2a via competitive methyl transfer (entry 4). The mixed dialkylzinc reagent ⁿBuZnMe with copper catalysis (entry 8) gave significantly lower yields, although the monoalkylzinc

reagent ⁿBuZnBr with stoichiometric amounts of CuCN gave good yields of conjugate adduct (entry 9). In the copper mediated reactions, the presence of allyl bromide did not enhance the chemical yield (entries 4−8), and did not effect allyation of the intermediate enolate. Mixed zincates containing *n*-Bu and *t*-Bu ligands transferred the *n*-Bu ligand with slightly greater efficiency (entries 10−12, 38−40% vs 21−31%, respectively).

Reaction of Et₂Zn in the presence of stoichiometric amounts of CuCN gave higher yields (entry 13) than the procedure catalytic in copper (entry 15). These procedures (entries 13−15) gave yields slightly lower than those obtained with the zincate reagents and catalytic amounts of CuCN (entries 4−7). Reaction of 1b with Et₂Zn in the presence of catalytic amounts of Cu(OTf)₂ and methylphosphite afforded the 1,4-adduct 3f in low yields at −20 °C (entry 16) and in modest yields at room temperature (entry 17). These reactions required TMSCl to effect the conjugate addition reaction (entry 18).

The phosphoramidite catalysts have proven to be very effective for the asymmetric conjugate addition of organozinc reagents[15] to cyclic enones and dihydropyridones.[6a] Although no conjugate addition was observed for 1b when literature protocols[6a] for 2,3-dihydro-4-pyridone were followed, very good yields and ers were obtained upon addition of TMSCl.

Thus, employing binapthol catalyst 6a and Cu(OTf)₂ a modest chemical yield and er (eq 3) was achieved for 3f upon addition of TMSCl. This crucial observation strongly suggests that TMSCl does not disrupt the Zn−Cu binuclear metal complex[15c] that imparts the facial selectivity, while effectively accelerating the conjugate addition reaction even in toluene. Both chemical yields and enantioselectivity could be improved by use of catalyst 6b. A very small improvement in yield and enantioselectivity was achieved utilizing copper 2-thienylcarboxylate (CuTC) under optimized conditions recently reported.[16] These results clearly illustrate the significantly greater degree of ligand accelerated catalysis (LAC) promoted by the phosphoramidite ligands, since in the absence of the ligand the reaction was limited to 30% conversion of starting material to conjugate adduct.
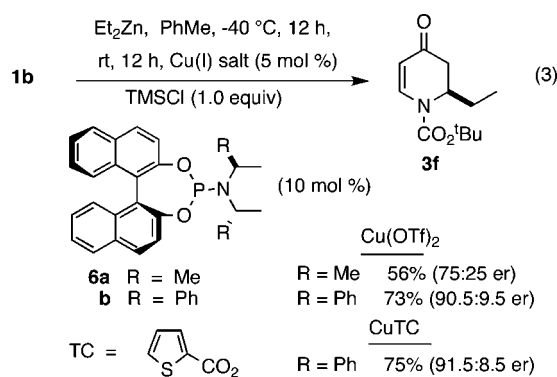


The sense of asymmetric induction was determined by hydrogenation of 3f to the known (*R*) tetrahydro-2-ethyl-4-pyridone.[6a]

(11) Dieter, R. K.; Guo, F. *Org. Lett.* **2008**, *10*, 2097−2090.
(12) (a) Ashby, E. C.; Watkins, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 5312−5317. (b) Ashby, E. C.; Lin, J. J.; Watkins, J. J. *J. Org. Chem.* **1977**, *42*, 1099−1102. (c) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197−3204. (d) Mobley, T. A.; Muller, F.; Berger, S. *J. Am. Chem. Soc.* **1998**, *120*, 1333−1334.
(13) For reviews see: (a) Gschwind, R. M. *Chem. Rev.* **2008**, *108*, 3029−3053. (b) Nakamura, E.; Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1−12.
(14) (a) Watson, R. A.; Kjonaas, R. A. *Tetrahedron Lett.* **1986**, *27*, 1437−1440. (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: Boca Raton, 1996; Chapter 4.

(15) (a) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865−2878. For reviews see: (b) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; Chapter 7, pp 224−258. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (d) Alexakis, A.; Backvall, J. E.; Krause, N.; Paimies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796−2823.
(16) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263.

The importance of annulated *N*-heterocycles prompted an examination of functionalized zinc cuprates (eq 4). Initial efforts to effect conjugate addition of the 3-(carboethoxy)propylzinc reagent **7** to **1b** proved unsuccessful. Treatment of **1b** with the mono alkylzinc iodide **7**, the 3-carboethoxypropyl(methyl)zinc, or the 3-carboethoxypropyl(dimethyl)zincate in the presence of CuCN and LiCl gave only recovered 4-pyridone. Treatment of EtOC(CH$_2$)$_3$ZnI with catalytic quantities of Me$_2$CuLi·LiCN, following the Lipshutz transmetalation protocol,[17] afford the 1,4-adduct in 49−53% yield along with **3a** (<5%).
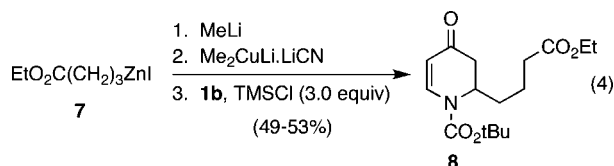


## Summary

In summary, *N*-carbamoyl-4-pyridones participate in conjugate addition reactions with a variety of organocopper and organozinc reagents. Procedures catalytic in copper can promote the conjugate addition reactions of Grignard, trialkylzincate, and dialkylzinc reagents with *N*-Boc protected 4-pyridones, and the catalytic process can be extended to functionalized alkylzinc halides. Utilization of an enantioenriched phosphoramidite ligand in the presence of TMSCl can promote the enantioselective conjugate addition of Et$_2$Zn to *N*-Boc-4-pyridone with very good enantiomeric excesses. This methodology provides a direct route to the synthetically important 2-substituted-2,3-dihydropyridones, which can be utilized for the synthesis of piperidones, piperidines, indolizidenes, and quinolizidenes.

## Experimental Section

**Conjugate Addition of Organolithium Reagents to *N*-Boc-4-Pyridone in the Presence of 30 mol% of CuCN.** To CuCN (0.39 mmol, 35 mg, 30 mol%) in THF (3.0 mL) at −78 °C under argon, was added PhLi (1.30 mmol, 0.72 mL, 1.80 M) and the mixture was stirred for 30 min. A solution of 4-pyridone **1b** (195 mg, 1.0 mmol), and TMSCl (325 mg, 3.0 mmol) in THF (3.0 mL) was then added in one addition. The reaction mixture was stirred overnight and allowed to warm up to room temperature. The reaction mixture was quenched with saturated aqueous NH$_4$Cl, extracted with Et$_2$O (3 × 10.0 mL), and the combined organic layers were dried over anhydrous MgSO$_4$, filtered and evaporated to afford the crude compound. Purification by flash column chromatography (MeOH/dichloromethane, 98:2, v/v) afforded pure 2-phenyl-2,3-dihydro-*N-tert*-butoxycarbonyl-4-pyridone (**3e**, 205 mg, 75%): IR (neat) 1723, 1663, 1603 cm$^{-1}$; $^1$H NMR δ 1.43 (s, 9 H), 2.76 (d, *J* = 16.50 Hz, 1 H), 3.12 (dd, *J* = 7.30, 16.50 Hz, 1 H), 5.33 (d, *J* = 8.20 Hz, 1 H), 5.63 (d, *J* = 6.40 Hz, 1 H), 7.14−7.32 (m, 5 H), 7.95 (d, *J* = 7.35 Hz, 1 H); $^{13}$C δ 28.0, 41.9, 55.8, 83.8, 107.1, 125.8, 127.9, 128.9, 139.0, 143.1, 151.5, 192.1; mass spectrum *m/z* (relative intensity) EI 273 (0.3, M$^+$), 173 (51), 145 (6), 104 (100), 91 (11), 78 (20), 51 (8).

**Conjugate Addition Reactions of Mixed Trialkylzincates [R$_1$(R$_2$)$_2$ZnLi/cat. CuCN] with *N*-Carbamoyl-4-Pyridones.** To a cold (0 °C) THF (4.0 mL) solution of ZnBr$_2$ (294 mg, 1.30 mmol) under argon was added a commercially available hexane solution of *n*-BuLi (1.30 mmol, 0.52 mL, 2.50 M) and MeLi (2.60 mmol, 1.63 mL, 1.60 M in diethyl ether). The mixture was stirred for 30 min at 0 °C and then cooled to −78 °C, followed by addition of

solid CuCN (12 mg, 0.1 equiv, 0.13 mmol) in one portion by opening the septem and adding the solid quickly. The reaction mixture was stirred for an additional 20 min at −78 °C and a mixture of *N*-Boc-4-pyridone **1b** (195 mg, 1.0 mmol) and TMSCl (325 mg, 3.0 mmol) in THF (3.0 mL)] were added dropwise as a THF solution at −78 °C. The reaction mixture was allowed to warm up to room temperature during overnight stirring. Then the reaction mixture was diluted with dichloromethane (5.0 mL), quenched with saturated aqueous NH$_4$Cl and extracted with dichloromethane (3 × 10.0 mL). The combined organic phase was dried over anhydrous MgSO$_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica gel, methanol:dichloromethane, 2:98, v/v) to give **3a** (38 mg, 18%) and 2-*n*-butyl-2,3-dihydro-*N-tert*-carbonyl-4-pyridone (**3b**, 197 mg, 78%): IR (neat) 1718, 1672, 1597 cm$^{-1}$; $^1$H NMR δ 0.90 (t, *J* = 7.20 Hz, 3 H), 1.18−1.36 (m, 4 H), 1.46−1.52 (m, 1 H), 1.55 (s, 9 H), 1.58−1.69 (m, 2 H), 2.44 (dd, *J* = 1.20, 16.50 Hz, 1 H), 2.80 (dd, *J* = 6.60, 16.50 Hz, 1 H), 4.46−4.60 (m, 1 H), 5.28 (d, *J* = 8.10 Hz, 1 H), 7.74 (d, *J* = 7.80 Hz, 1 H); $^{13}$C δ 13.9, 22.4, 28.0, 28.1, 30.0, 39.7, 52.9, 83.2, 106.0, 141.1, 151.3, 193.4; mass spectrum *m/z* (relative intensity) EI 253 (4, M$^+$), 197 (13), 153 (24), 140 (8), 96 (99), 57 (100). Anal. Calcd for C$_{14}$H$_{23}$NO$_3$: C, 66.37; H, 9.15. Found: C, 66.59; H, 9.27.

**Competition Experiments: Conjugate Addition Reactions of Lithium Dialkylcuprates (R$_2$CuLi, 1.0 equiv) with a 1:1 Mixture of *N*-Carbamoyl-4-pyridone and 2-Cyclohexenone, Ethyl Crotonate, or *N*-Boc-6-methyl-5,6-dihydro-4-Pyridone.** To a THF (3.0 mL) solution of CuCN (89 mg, 1.0 mmol, 1.0 equiv) and LiCl (85 mg, 2.00 equiv) under argon and cooled to −78 °C, was added commercially available *n*-BuLi (0.8 mL, 2.0 mmol, 2.5 M). The solution was stirred for an additional 45 min at −78 °C, followed by addition of a THF (3.0 mL) solution of *N*-Boc-4-pyridone (195 mg, 1.0 mmol), the other α,β-unsaturated carbonyl compound (1.0 mmol) and TMSCl (543 mg, 5.0 mmol) at −78 °C. 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$_4$Cl, and extracted with dichloromethane (3 × 10.0 mL). The combined organic phase was dried over anhydrous MgSO$_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica gel, 2% methanol: dichloromethane, v/v) to give **3b** and the 1,4-adduct of the corresponding α,β-unsaturated carbonyl compounds.

**Conjugate Addition of Diethylzinc to *N*-Boc-4-pyridone Employing a Chiral Phosphoramidite Ligand and Cu(OTf)$_2$.** A modification of Feringa's procedure[6a] was employed. A suspension of Cu(OTf)$_2$ (0.05 mmol) and phosphoramidite **4b** (54 mg, 0.10 mmol) in toluene (5.0 mL, freshly distilled) was stirred under argon at room temperature for 1 h. The starting 4-pyridone **1b** (195 mg, 1.00 mmol) and TMSCl (108 mg, 1.0 mmol) was added and the mixture was stirred at room temperature for 10 min. Then the reaction mixture was cooled to −40 °C and Et$_2$Zn (1.50 mmol, 1.36 mL, 1.10 M in tolune) was added dropwise over 10 min. The reaction mixture was stirred for 12 h at −40 °C, and warmed up to room temperature and stirred for an additional 12 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl solution and extracted with dichloromethane (3 × 10.0 mL). The combined organic phase was dried over anhydrous MgSO$_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica gel, methanol:dichloromethane, gradient, 0−2:100−98, v/v) to give pure **3f** (168 mg, 75%): IR (neat) 1724, 1670, 1598, cm$^{-1}$; $^1$H NMR δ 0.76 (t, *J* = 7.30 Hz, 3 H), 1.39 (s, 9 H), 1.42−1.60 (m, 2 H), 2.30 (d, *J* = 16.50 Hz, 1 H), 2.65 (dd, *J* = 6.85, 16.50 Hz, 1 H), 4.30 (s, 1 H), 5.12 (d, *J* = 7.80 Hz, 1 H), 7.59 (d, *J* = 7.80 Hz, 1 H); $^{13}$C δ 13.9, 22.4, 28.0, 28.1, 30.0, 39.7, 52.9, 83.2, 106.0, 141.1, 151.3, 193.4; mass spectrum *m/z* (relative intensity) EI 225 (13, M$^+$), 210 (0.53), 195 (0.05), 169 (44), 140 (15), 125 (20), 110 (7), 96 (95), 82 (5), 57 (100).

The enantiomeric excess was determined by chiral HPLC analysis on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenyl-carbamate) on silica gel] to be 81% ee (hexane/$^i$PrOH, 99:1 (v/v),

(17) Lipshutz, B. H.; Wood, M. R.; Tirado, R. *J. Am. Chem. Soc.* **1995**, *117*, 6126–6127.

flow rate = 0.352 mL/min, detection at $\lambda$ = 286. The (*R*)-enantiomer (major) eluted first with a retention time of 28.3 min followed by the (*S*)-enantiomer (minor) at 31.7 min.

**2-(4-Ethoxycarbonylbutyl)-2,3-dihydro-*N*-tert-butoxycarbonyl-4-pyridone (8).** Using a modification of Lipshutz's procedure,[17] 4-ethoxycarbonylbutylzinc bromide (1.20 mmol, 2.40 mL, 0.50 M in THF) was added to a cold (−78 °C) THF solvent (3.0 mL) under argon, whereupon MeLi (1.20 mmol, 0.75 mL of 1.60 M in diethyl ether) was added and the mixture was stirred for 45 min. At the same time dimethyl cuprate was prepared by adding MeLi (0.48 mmol, 0.30 mL of 1.60 M in diethyl ether) to CuCN (43 mg, 0.48 mmol) in THF (2.0 mL) in a separate flask at −78 °C and stirring for 45 min. The dimethyl cuprate solution was transferred via syringe into the flask containing the zinc reagent and the reaction mixture was stirred for 10 min at −78 °C. The cooling bath was then removed and *N*-Boc-4-pyridone **1b** [(195 mg, 1.0 mmol premixed with TMSCl (326 mg, 3.0 mmol) in THF (3.0 mL)] was added immediately in one addition. The reaction mixture was stirred overnight, diluted with dichloromethane (5.0 mL), quenched with saturated aqueous $NH_4Cl$, and extracted with dichloromethane (3 × 10.0 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and purified by flash column chromatography (silica gel, 2% methanol: dichloromethane, v/v) to give **8** (165 mg, 53%): IR (neat) 1722, 1670, 1601 cm$^{-1}$; $^{1}$H NMR $\delta$ 1.12 (t, *J* = 7.35 Hz, 3 H), 1.42 (s, 9 H), 1.44−1.52 (m, 1 H), 1.52−1.63 (m, 2H), 2.13−2.22 (m, 2H), 2.29 (d, *J* = 16.50 Hz, 1 H), 2.70 (dd, *J* = 6.90, 16.50 Hz, 1 H), 3.99 (q, *J* = 7.35 Hz, 2 H), 4.43 (s, 1 H), 5.15 (d, *J* = 6.45 Hz, 1 H), 7.61 (s, 1 H); $^{13}$C $\delta$ 14.3, 21.4, 28.1, 30.1, 33.9, 40.0, 52.7, 60.4, 83.6, 106.2, 142.2, 151.3, 173.0, 193.2; mass spectrum *m/z* (relative intensity) EI 311 (0.02, M$^{+}$), 281 (0.2), 224 (0.05), 210 (30), 182 (0.89), 166 (13), 136 (5), 124 (6), 110 (6), 96 (100), 68 (15), 55 (8). 2-Methyl-2,3-dihydro-*N*-Boc-4-pyridone **3a** (25 mg, 12%) was isolated as minor product.

**Supporting Information Available:** General experimental information, materials, general procuedures, data reduction, and $^{1}$H and $^{13}$C NMR spectra for **2a−f, 3(a,c,d)**, and 2-*n*-butyl-6-methyl-*N*-Boc-4-piperidinone. This material is available free of charge via the Internet at http://pubs.acs.org.

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