Asymmetric Catalysis

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# Catalytic Enantioselective Addition of Dialkylzinc Reagents to *N*-Acylpyridinium Salts**

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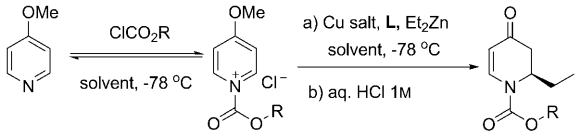
Chiral, substituted piperidinones are key units in medicinal chemistry and highly versatile intermediates in organic synthesis.[1] A number of synthetic methodologies have been developed to access these useful heterocyclic compounds.[2] An important strategy for their construction is the direct asymmetric addition of nucleophiles to *N*-acylpyridinium salts. Although significant progress has been achieved in this area,[3] most studies have focused on the use of chiral pyridine substrates. Only two examples have been described for the catalytic enantioselective nucleophilic addition to *N*-acylpyridinium salts (using TMSCN[4] and alkynes[5] as nucleophiles). To the best of our knowledge, there have been no reports on a catalytic enantioselective addition of organometallic reagents to *N*-acylpyridinium salts. Herein, we disclose the first highly enantioselective addition of dialkylzinc reagents to *N*-acylpyridinium salts using copper/phosphoramidite catalysts.

As summarized in Table 1, we initially studied the reaction of 4-methoxypyridine with various chloroformates, solvents, copper salts, and phosphoramidites (Figure 1). A typical procedure consists of the reaction of 4-methoxypyridine with the corresponding chloroformate (1 equiv) at −78 °C for 30 minutes and subsequent addition of a solution of freshly prepared catalyst, derived from the appropriate copper salt and (*S*,*R*,*R*)-**L1**, and then addition of $Et_2Zn$.

Under these conditions, using $Cu(OTf)_2$, (*S*,*R*,*R*)-**L1**, and benzyl chloroformate, several solvents were tested (Table 1, entries 1–4). The reaction in THF gave the desired product with 34% *ee* (Table 1, entry 4), and the screening of different chloroformates (Table 1, entries 5–7) did not provide better enantioselectivities. The use of phosphoramidite ligand (*S*,*R*)-**L2**, which gives excellent results in the 1,4-addition of dialkylzinc reagents to N-protected 2,3-dehydro-4-piperidones,[6] led to an increase in the *ee* value to 59% (Table 1, entry 8). We also studied the effect of the copper salt upon the reaction, but lower enantioselectivities compared to those obtained using $Cu(OTf)_2$ were achieved in all the cases (Table 1, entries 9–12). The screening of more than 40 different phosphoramidite ligands[7] concluded with ligand (*S*)-**L3** being the most suitable in terms of enantioselectivity (74% *ee*), despite the relatively low yield (Table 1, entry 13). To improve the yield, the reaction was carried out at −45 °C; however, a similar yield and lower enantioselectivity (41% *ee*) were obtained (Table 1, entry 14).

***Table 1:*** Screening of copper salts, solvents, chloroformates, and ligands for the addition of $Et_2Zn$ to *N*-acylpyridinium salts.[a]

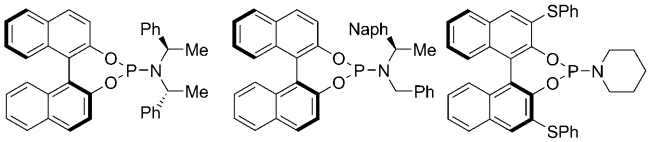



**1a** R = Bn
**1b** R = Me
**1c** R = Et
**1d** R = Ph

**2a** R = Bn
**2b** R = Me
**2c** R = Et
**2d** R = Ph

| Entry | R | Ligand | Solvent | Cu salt | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | Bn | **L1** | toluene | $Cu(OTf)_2$ | 30 | 8 |
| 2 | Bn | **L1** | $CH_2Cl_2$ | $Cu(OTf)_2$ | 30 | 12 |
| 3 | Bn | **L1** | $Et_2O$ | $Cu(OTf)_2$ | 26 | 5 |
| 4 | Bn | **L1** | THF | $Cu(OTf)_2$ | 26 | 34 |
| 5 | Me | **L1** | THF | $Cu(OTf)_2$ | 25 | 5 |
| 6 | Et | **L1** | THF | $Cu(OTf)_2$ | 18 | 10 |
| 7 | Ph | **L1** | THF | $Cu(OTf)_2$ | 25 | 0 |
| 8 | Bn | **L2** | THF | $Cu(OTf)_2$ | n.d. | 59 |
| 9 | Bn | **L2** | THF | CuI | n.d. | 46 |
| 10 | Bn | **L2** | THF | $CuBr{\cdot}SMe_2$ | n.d. | 40 |
| 11 | Bn | **L2** | THF | CuTC[d] | n.d. | 55 |
| 12 | Bn | **L2** | THF | CuCN | n.d. | 29 |
| 13 | Bn | **L3** | THF | $Cu(OTf)_2$ | 26 | 74 |
| 14[e] | Bn | **L3** | THF | $Cu(OTf)_2$ | 20 | 41 |

[a] Reaction conditions: 4-Methoxypyridine (1 equiv, 0.12 M), $ClCO_2Bn$ (1 equiv), $Cu(OTf)_2$ (5 mol%), **L** (10 mol%), $R_2Zn$ (2 equiv). [b] Overall yield of isolated product from 4-methoxypyridine. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralpak AS). [d] CuTC = Copper(I) thiophene-2-carboxylate. [e] Reaction was carried out at −45 °C. Bn = benzyl, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl, n.d. = not determined.




(*S*,*R*,*R*)-**L1** (*S*,*R*)-**L2** (*S*)-**L3**

***Figure 1.*** Phosphoramidite ligands used in this study.

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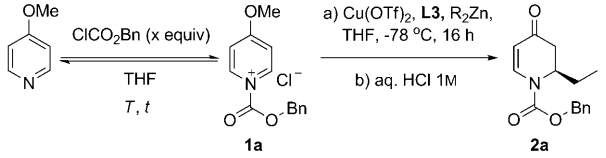
To check if the low yield was a result of problems in the formation of the *N*-acylpyridinium salt **1**, we increased the temperature to room temperature for the preparation of the salt **1** . Much to our delight, under these reaction conditions, the yield increased to 37% and the enantioselectivity increased significantly to reach 89% *ee* (Table 2, entry 1).

***Table 2:*** Optimization of the addition of $Et_2Zn$ to *N*-acylpyridinium salts.[a]




| Entry | Equiv of $ClCO_2Bn$ | *T* [°C] | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | 1.2 | RT | 0.5 | 37 | 89 |
| 2 | 2 | RT | 0.5 | 37 | 90 |
| 3 | 2 | RT | 4 | 34 | 81 |
| 4[d] | 2 | RT | 4 | 0 | – |
| 5[e] | 1.2 | – | | 16 | 66 |
| 6 | 4 | 0 | 0.5 | 45 | 89 |
| **7**[f] | **4** | **0** | **0.5** | **69** | **95** |

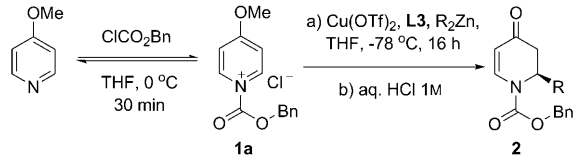
[a] Reaction conditions: 4-Methoxypyridine (1 equiv, 0.12 M), $ClCO_2Bn$ (*x* equiv), $Cu(OTf)_2$ (5 mol%), **L3** (10 mol%), $R_2Zn$ (2.5 equiv). [b] Overall yield of product isolated from 4-methoxypyridine. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralpak AS). [d] Slow addition of $Et_2Zn$. [e] $ClCO_2Bn$ was added after $Et_2Zn$. [f] **1a** was added dropwise to the reaction mixture.

The use of two equivalents of benzyl chloroformate provided similar results (Table 2, entry 2), but a longer reaction time for the formation of the salt **1a** gave a lower yield and enantioselectivity, perhaps because of the instability of the salt (Table 2, entry 3). Other experimental modifications, such as the slow addition of $Et_2Zn$ to the reaction mixture (Table 2, entry 4) or the addition of benzyl chloroformate as the final reagent (Table 2, entry 5), gave no conversion and lower enantioselectivity and yield, respectively.

In the reaction of 4-methoxypyridine with 1.2 equivalents of benzyl chloroformate in THF, a white solid was formed (we assumed this to be the salt **1a**); nevertheless, the $^1H$ NMR analysis of the reaction mixture showed the presence of approximately 50% of remaining 4-methoxypyridine. To shift the equilibrium towards the formation of the salt, we tried different additives ($AgNO_3$, $AgBF_4$, $NaBPh_4$, $MgBr_2{\cdot}OEt_2$, etc.); however, lower yields and enantioselectivities were obtained in all cases. In view of the stability of the salt **1a**, we decided to continue our studies using a reaction temperature of 0 °C. When forming **1a** at 0 °C with a larger excess of benzyl chloroformate (4 equiv), a higher yield (45%) and the same enantioselectivity (89% *ee*) were obtained (Table 2, entry 6). Finally, we observed that if we inverted the order of addition of the reagents, adding a solution of the preformed salt **1a** (prepared at 0 °C by mixing 4-methoxypyridine with 4 equivalents of benzyl chloroformate in THF and stirring 30 min) dropwise into the reaction mixture comprising the catalyst and $Et_2Zn$ at −78 °C, the desired product was obtained with good yield (69%) and excellent enantioselectivity (95% *ee*) (Table 2, entry 7).

To prove the synthetic utility of the method, different dialkylzinc reagents were tested. Noncommercial dialkylzinc reagents were prepared by using the new methodology introduced by Côté and Charette.[8] The addition of $nBu_2Zn$ and $(PhCH_2CH_2)_2Zn$ gave the corresponding 2,3-dihydro-4-pyridones **2e**,**f** with good yields and excellent enantioselectivities (Table 3, entries 2 and 3). In the case of the bulky

***Table 3:*** Addition of $R_2Zn$ to *N*-acylpyridinium salts.[a]

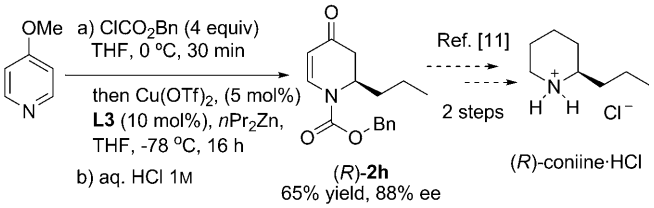



| Entry | R | Product[b] | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|
| 1 | Et | **2a** | 69 | 95 (−) |
| 2 | Bu | **2e** | 63 | 93 (−) |
| 3 | $CH_2CH_2Ph$ | **2f** | 50 | 97 (−) |
| 4 | *i*Pr | **2g** | 65 | 56 (−) |

[a] Reaction conditions: 4-Methoxypyridine (1 equiv, 0.08 M), $ClCO_2Bn$ (4 equiv), $Cu(OTf)_2$ (5 mol%), **L3** (10 mol%), $R_2Zn$ (2.5 equiv). [b] Absolute configuration was deduced by analogy to the literature data for **2h** (see reference [11]). [c] Overall yield of isolated product from 4-methoxypyridine. [d] Determined by HPLC analysis on a chiral stationary phase. The sign in parentheses indicates the sign of the optical rotation (see the Supporting Information for further details).

*i*$Pr_2Zn$, the enantioselectivity of the product **2g** was lower (Table 3, entry 4), which was not entirely unexpected in view of previous work.[9] The less reactive $Me_2Zn$ did not provide the desired product at −78 °C or −55 °C, and starting material was recovered.[10]

To additionally demonstrate the synthetic potential of this new methodology, the formal synthesis of the alkaloid (−)-coniine is presented (Scheme 1). The addition of the non-




***Scheme 1.*** Formal synthesis of (*R*)-coniine.

commercially available reagent $nPr_2Zn$ provided **2h** with good yield and high enantioselectivity. In the previous reported synthesis of (*R*)-coniine, described by Comins and co-workers, five steps are necessary to provide the intermediate **2h**.[11]

In conclusion, we have developed the first catalytic enantioselective addition of dialkylzinc reagents to *N*-acylpyridinium salts with good yields and excellent enantioselec-

tivities using a copper/phosphoramidite complex as the catalyst. The versatility of the method to make advanced chiral heterocyclic building blocks in a single step from 4-methoxypyridine is illustrated in the formal synthesis of the alkaloid (*R*)-coniine. Currently, efforts are directed towards expanding the scope of this new asymmetric transformation regarding the addition of functionalized dialkylzinc reagents.

## Experimental Section

Benzyl chloroformate (1 mmol) was added to a solution of 4-methoxypyridine (0.25 mmol) in THF (1 mL) at 0 °C, and stirred for 30 min at the same temperature (solution A). A solution of the catalyst, freshly prepared at room temperature from $Cu(OTf)_2$ (0.0125 mmol, 5 mol%) and (*S*)-**L3** (0.025 mmol, 10 mol%) in THF (1 mL), was cooled down to −78 °C and the corresponding dialkylzinc reagent (2.5 equiv) was added. Subsequently, solution A was added dropwise to the reagent mixture (to collect all the salt **1a** in the syringe, the flask was washed twice with 2 portions of THF (0.5 mL) each). The resulting mixture was stirred for 16 h at −78 °C, quenched with aq. HCl (1M), and stirred for 10 min at room temperature. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by distillation and subsequent by flash chromatography on silica gel (EtOAc/*n*-hexane 1:3) (see the Supporting Information for further details).

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**Keywords:** asymmetric catalysis · copper · heterocycles · nucleophilic addition · phosphane ligands

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[10] The reaction with $Me_2Zn$ at −20 °C gave the desired product in 34% yield and 26% *ee*. In addition, preliminary experiments with $Ph_2Zn$ did not provide the corresponding piperidone probably because of solubility issues.

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