

## CONJUGATE ADDITIONS WITH CHIRAL LITHIUM (2-PYRIDYL)- [(S)-2-(1-DIMETHYLAMINOETHYL)PHENYL]CUPRATE

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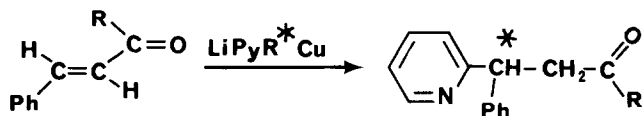
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### Summary

The cuprate ( $\text{LiPyR}^*\text{Cu}$ ) transfers its pyridyl group to 4-phenyl-3-buten-2-one at  $-60^\circ\text{C}$  in ether to give (+)-4-phenyl-4-(2-pyridyl)-2-butanone in good yield with some enantioselectivity (23% e.e.). Additions to ethyl 3-phenyl-propenoate and to 5-phenyl-2,2-dimethyl-4-penten-3-one give good yields but low inductions. Induction is also low on transfer of a phenyl group from  $\text{LiPhR}^*\text{Cu}$  to 4-(2-pyridyl)-buten-2-one.

Enantioselective reactions are at present the subject of considerable interest [1]. Much effort is being devoted achieving asymmetric induction in conjugate additions involving chiral organocuprates. For example, the use of chiral homocuprates  $\text{LiRR}^*\text{Cu}$  have been investigated, where  $\text{R}^*$  is the chiral 2-(1-dimethylamino-ethyl)phenyl group or a related group [2–5]. Most of these cuprates gave low asymmetric inductions, while chiral heterocuprates have given more promising results [6–9].

Recently we found that lithium di(pyridyl)cuprate readily transfers a 2-pyridyl group to enones and enoates and that the mixed lithium phenyl(2-pyridyl)cuprate selectively transfers the pyridyl group to the same substrates [10]. This indicated to us that the pyridyl nitrogen might play a role in the product-differentiating step, perhaps by metal coordination. Such an interaction could also be of importance in a stereo-differentiating step in asymmetric synthesis.



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TABLE 1

CONJUGATE ADDITION OF  $\text{LiPyR}^*\text{Cu}$  TO 4-PHENYL-3-BUTEN-2-ONE YIELDING 4-PHENYL-4-(2-PYRIDYL)-2-BUTANONE (Substrate/reagent ratio 1.2/1)

| Solvent              | Approx.<br>time (min) | Temp.<br>(°C) | Isol. yield<br>(%) | $[\alpha]_D^{23}$<br>(c 0.15, EtOAc)<br>(°) |
|----------------------|-----------------------|---------------|--------------------|---------------------------------------------|
| Ether <sup>a</sup>   | 5                     | 0             | 56                 | 14.2                                        |
| Ether <sup>a</sup>   | 5                     | -45           | 39                 | 44.6                                        |
| Ether <sup>b</sup>   | 20                    | -45           | 72                 | 84.8                                        |
| Ether <sup>b</sup>   | 250                   | -60           | 65                 | 87.9 <sup>c</sup>                           |
| THF <sup>b</sup>     | 400                   | -60           | 30                 | 80.6                                        |
| Toluene <sup>b</sup> | 5                     | -45           | 65                 | 16.7                                        |

<sup>a</sup> Ether-washed 2-pyridylcopper was used for preparation of cuprate. <sup>b</sup> THF- and ether-washed 2-pyridylcopper was used for preparation of cuprate. <sup>c</sup> Enantiomeric excess 23% as determined with NMR/ $\text{Eu}(\text{facam})_3$  utilising the methyl signals.

We have tested this idea with the mixed chiral lithium (2-pyridyl)[(*S*)-2-(1-dimethylaminoethyl)phenyl]cuprate reagent,  $\text{LiPyR}^*\text{Cu}$ , made from 2-pyridylcopper and (*S*)-2-(1-dimethylaminoethyl)phenyllithium. The efficiency of this reagent was somewhat dependent on the quality of the 2-pyridylcopper; the best results were obtained when the pyridylcopper was washed with a moderate amount of THF, which dissolved some dark-coloured impurities along with some pyridylcopper.

Conjugate addition was also tried with some standard substrates, viz. 4-phenyl-3-buten-2-one (at 0 and -45°C), ethyl 3-phenylpropenoate (at 0°C) and the more hindered 5-phenyl-2,2-dimethyl-4-penten-3-one (at 0 and -45°C). The additions were fast at 0°C for all the substrates and were accompanied by precipitation of 2-(1-dimethylaminoethyl)phenylcopper. Only addition to 4-phenyl-3-buten-2-one gave encouragingly high asymmetric inductions, and so this reaction was investigated in some detail. The asymmetric inductions and yields are summarised in Table 1. The highest enantiomeric excess (23%) was obtained from reaction in ether at -60°C. The e.e. was determined on the basis of the NMR spectrum of the product with added europium shift reagent.

As in similar cases [3], reaction in THF was slower than in ether, but without giving greater induction. Reaction in toluene was fast but gave lower induction.

For comparison, we also examined the addition of  $\text{LiPhR}^*\text{Cu}$  [3] to 4-(2-pyridyl)-3-buten-2-one [11]; we again obtained 4-phenyl-4-(2-pyridyl)-2-butanone, but in lower yield and low asymmetric induction.

## Discussion

The degree of asymmetric induction obtained when  $\text{LiPyR}^*\text{Cu}$  reacts with 4-phenyl-3-buten-2-one is thus considerably higher than when methyl or butyl groups are transferred with the same chiral auxiliary present in the cuprate. We are still far from preparatively useful inductions, but the new results are encouraging. The observations may be compared with the recent finding that  $\text{LiR}^*_2\text{Cu}$  adds the  $\text{R}^*$  group stereoselectively to the same substrate (among others) [12].

It seems probable that the pyridine nitrogen interacts with a metal atom (copper or lithium) in the stereo-differentiating step. This is consistent with the general principle that several points of interaction are necessary for stereo-differentiation [13].

On the other hand, the presence of a pyridyl group in the substrate 4-(2-pyridyl)-3-buten-2-one had no interesting effect on the addition of the chiral  $\text{LiPhR}^*\text{Cu}$ . The chemical yield was moderate and the asymmetric induction as low as that obtained in addition of  $\text{LiMeR}^*\text{Cu}$  to 4-phenyl-3-buten-2-one [5].

## Experimental

### General

All reactions were performed under nitrogen. Reagents were transferred with syringes. Ether and THF were distilled from sodium benzophenone ketyl. The products were distilled in a Büchi short-path Kugelrohr apparatus. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. NMR spectra were recorded on a Bruker 270 MHz instrument.

### Preparation of $\text{LiPyR}^*\text{Cu}$

A solution of copper(I) iodide (12 mmol, Fluka) and dibutyl sulfide (25 mmol) in ether (15 ml) was stirred at 0°C. A solution of 2-pyridyllithium (10 mmol) was prepared from 2-bromopyridine (11 mmol) in ether (10 ml) and butyllithium (10 mmol) at –70°C [14]; the mixture was stirred for 10 min and then added rapidly to the copper iodide solution, giving a yellowish precipitate of 2-pyridylcopper. The mixture was stirred for 10 min and was then centrifuged. The precipitate was washed at 0°C with ether (2 × 10 ml) or THF followed by ether (6 ml THF and 2 × 10 ml ether).

(*S*)-2-(1-dimethylaminoethyl)phenyllithium [3], prepared from (*S*)-(1-dimethylamino)ethylbenzene and butyllithium (ether, r.t., three days), was added to a slurry of the precipitate in ether (15 ml) at 0°C, until Gilman test I [15] was slightly positive. This cuprate reagent was used immediately.

### General procedure for conjugate additions

A solution of the substrate in ether (3 ml) was added dropwise to the reagent solution. The reagent substrate ratio was 1.2/1 for the enones and 2/1 for the enoate. The reaction mixture was hydrolysed with aqueous ammonium chloride/ammonia after precipitation of 2-(1-dimethylaminoethyl)phenylcopper when GLC analysis indicated complete reaction. The ethereal layer was extracted with 2 *M* HCl (3 × 15 ml). The aqueous extract was adjusted to pH 5.5 with aqueous ammonia and then extracted with ether (2 × 30 ml). The ethereal layer was dried and evaporated and the residue was distilled.

### 4-Phenyl-4-(2-pyridyl)-2-butanone

The product was distilled at 170°C/100 Pa. GLC and NMR data were identical with those for an authentic racemic sample [10]. The enantiomeric excess was determined by NMR with tris(3-trifluoroacetyl-D-camphorato)europium(III),  $\text{Eu}(\text{facam})_3$ , utilising the methyl signal. For yields see Table 1. When lithium (phenyl) (*S*)-2-(1-dimethylaminoethyl)phenyl cuprate [3] was added to 4-(2-pyridyl)-

3-buten-2-one [12] in ether at  $-45^{\circ}\text{C}$  the 4-phenyl-4-(2-pyridyl)-2-butanone was obtained in 30% yield after distillation, but with low rotation,  $[\alpha]_{\text{D}} = 1.1^{\circ}$  (*c* 0.15, ethyl acetate).

*5-Phenyl-5-(2-pyridyl)-2,2-dimethyl-3-pentanone*

The product was distilled at  $130^{\circ}\text{C}/50$  Pa and isolated in 70% yield,  $[\alpha]_{\text{D}} = 0.1^{\circ}$  (*c* 0.15, ethyl acetate).

MS (40 eV): *m/e* 267 ( $M^{+}$ ), 266, 252, 210(100%), 182, 168. ( $M - 1$ ) 266.154  $\pm$  0.003.  $\text{C}_{18}\text{H}_{20}\text{NO}$ : 266.154.  $^1\text{H}$  NMR (270 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  (ppm) 8.41 (m, 1H), 7.36–6.56 (m, 8H), 4.88 (dd, 1H, *J* 5.5 and 8.9 Hz), 3.89 (dd, 1H,  $J_{\text{vic}}$  8.9,  $J_{\text{gem}}$  17.4 Hz) 2.92 (dd, 1H,  $J_{\text{vic}}$  5.5,  $J_{\text{gem}}$  17.4 Hz), 0.98 (s, 9H). The enantiomeric excess was barely detectable with  $\text{Eu}(\text{facam})_3$ .

*Ethyl 3-phenyl-3-(2-pyridyl)propanoate*

Distillation at  $130^{\circ}\text{C}/50$  Pa gave the product in 60% yield,  $[\alpha]_{\text{D}} = 12.8^{\circ}$  (*c* 0.15, ethyl acetate). GLC and NMR data were identical with those for an authentic racemic sample [10].

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