Catalytic enantioselective conjugate addition of dialkylzinc reagents to *N*-substituted-2,3-dehydro-4-piperidones†

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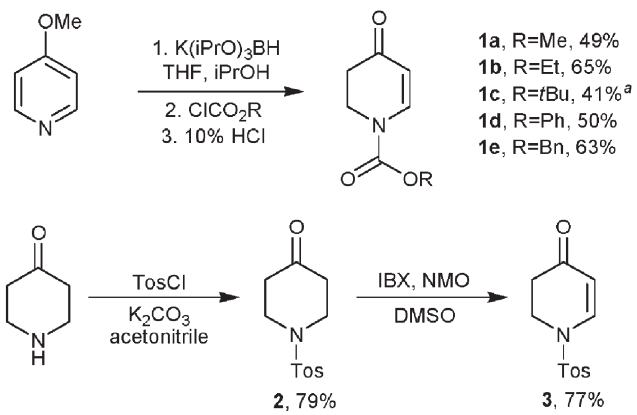
The first, highly enantioselective, copper/phosphoramidite-catalyzed conjugate addition of dialkylzinc reagents to *N*-substituted 2,3-dehydro-4-piperidones is described.

The stereoselective 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds represents exceptionally useful methodology for carbon–carbon bond formation.[1] Copper complexes based on homochiral BINOL-based phosphoramidites proved to be excellent catalysts for conjugate addition of dialkylzinc reagents to enones.[2] Recently, highly enantioselective copper-catalyzed additions of dialkylzinc reagents to α,β-unsaturated lactams were described.[3] Furthermore, Rh(I)/BINAP catalyzed asymmetric arylations of 2,3-dehydro-4-piperidones were reported by Hayashi.[4] Dehydropiperidones are versatile synthetic building blocks frequently used in alkaloid synthesis.[5] It is considered a major goal to establish effective catalytic procedure for their stereoselective functionalization, as the substituted chiral piperidone products are an important class of compounds.[6] Here we describe highly enantioselective copper/phosphoramidite-catalyzed alkylation of 2,3-dehydro-4-piperidones using dialkylzinc reagents.

N-Substituted-2,3-dehydro-4-piperidones, with carbamate protecting groups **1a–e**, were synthesized from 4-methoxypyridine in one step using the procedure of Comins *et al.*[7] Tosyl-protected 2,3-dehydro-4-piperidone **3** was prepared in two steps from 4-piperidone, *via* IBX-promoted oxidation[8] of piperidone **2**[9] (Scheme 1).



Scheme 1 Preparation of *N*-substituted-2,3-dehydro-4-piperidones. [a] In case of R = *t*Bu, Boc_2O was used with citric acid workup.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b417727d/

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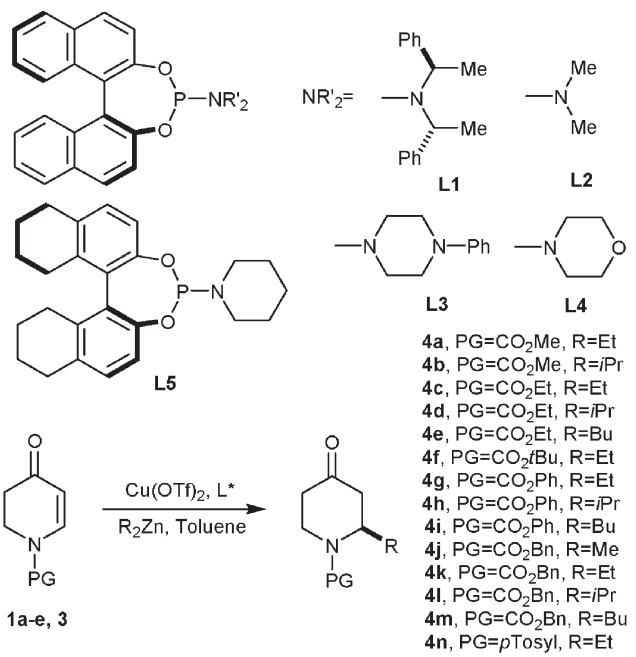
These *N*-protected-2,3-dehydro-4-piperidones were subjected to 1,4-addition using dialkylzinc reagents, employing copper complexes as catalysts generated *in situ* from $Cu(OTf)_2$ and homochiral phosphoramidite ligands **L1–5**[10] (Scheme 2). We suppose that the catalytic cycle is analogous to the one already proposed for conjugate addition of dialkylzinc compounds to enones.[11] It was already noted that 2,3-dehydro-4-piperidones are less reactive toward 1,4-addition than other enones such as 2-cyclohexen-1-one.[4] Our findings are consistent with these observations. In preliminary experiments using 2 mol% of copper catalyst, which gives complete conversion in 3 h with 2-cyclohexen-1-one as substrate,[11] it was not possible to obtain reasonable yields of desired products even at room temperature after 72 h. The enantioselectivity of the reaction, however, was high generating products with approximately 90% ee.

Encouraged by this promising enantioselectivity, careful optimization of the reaction conditions was performed. The best solvent for the 1,4-addition proved to be toluene. In other solvents like hexane, CH_2Cl_2, Et_2O, or THF, enantioselectivities of the Et_2Zn addition to **1b** decreased. Results of the screening of chiral ligands and solvents are summarized in Table 1.

Usually ligand **L1** is superior to other phosphoramidites in copper-catalyzed conjugate addition reactions of organozinc



Scheme 2 Conjugate addition of R_2Zn to dehydropiperidones.

Table 1 Addition of Et_2Zn to **1b** and **1e** using ligands **L1–5** in various solvents

Substrate[a]	Ligand	Solvent	ee (%)[b]
1b	**L1**	Toluene	92
1b	**L1**	Hexane	66
1b	**L1**	Et_2O	55
1b	**L1**	THF	5
1b	**L1**	CH_2Cl_2	13
1e	**L1**	Toluene	94
1e	**L2**	Toluene	33
1e	**L3**	Toluene	—
1e	**L4**	Toluene	20
1e	**L5**	Toluene	23

[a] Additions to **1b** were performed using 2 mol% $Cu(OTf)_2$ at −25 °C and to **1e** with 5 mol% of $Cu(OTf)_2$ at −20 °C. [b] Determined by GC on a Chiraldex G-TA column or by HPLC on a Chiralpak AS column.

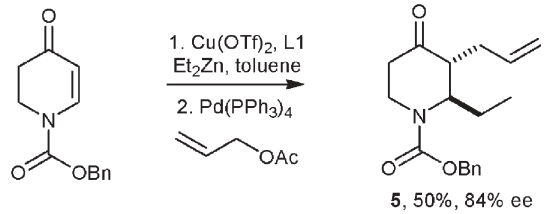
reagents.[12] We confirmed this by testing phosphoramidite ligands **L1–5** in the addition of Et_2Zn to enone **1e**, and all ligands were inferior to **L1** (Table 1).

In order to obtain acceptable yields of products we increased the amount of catalyst to 5 mol%. Under these conditions,[13] reactions with diethyl- and diisopropylzinc usually went to completion in 8 to 28 h, depending on the temperature. The resulting products were formed with excellent stereoselectivity, *e.g.* piperidones **4h** and **4k** were obtained with 97 and 94% ee, respectively. Me_2Zn proved to be quite unreactive towards *N*-substituted-2,3-dehydro-4-piperidones, which is in agreement with our previous findings with Me_2Zn addition to α,β-unsaturated lactams.[3] No methylated product could be obtained with Me_2Zn[14] at temperatures below 0 °C, but this does not constitute a problem as also at higher temperatures, product **4j** was obtained in 96% ee. Surprisingly, the addition of Bu_2Zn was problematic, both in terms of chemical yield and enantioselectivity. Results obtained with the optimized conditions (5 mol% of $Cu(OTf)_2$, 10 mol% of phosphoramidite **L1** and toluene as solvent) for several substrates and zinc reagents are given in Table 2.

Table 2 Addition of R_2Zn to *N*-protected-2,3-dehydro-4-piperidones **1a–e** and **3** using 5 mol% of $Cu(OTf)_2$ and 10 mol% of **L1**

Substrate	R	Time (h)	Temperature (°C)	Conversion/ Yield (%)[a]	ee (%)[b]
1a	Et	40	−25	95/20[c]	87
1a	*i*Pr	16	−25	100/79	94
1b	Et	16	−25	100/35[c]	94
1b	*i*Pr	16	−25	100/80	96
1b	Bu	16	−25	39/16	74
1c	Et	24	−20	83/58	91
1d	Et	16	−25	100/87	94
1d	*i*Pr	16	−25	100/84	97
1d	Bu	16	−25	36/22	82
1e	Me	24	0 → r.t.	80/44	96
1e	Et	8	0	100/69	91
1e	*i*Pr	8	0	100/54	94
1e	Et	28	−20	100/70	94
1e	*i*Pr	24	−20	100/68	95
1e	Bu[d]	48	0 → r.t.	20/12	59
3	Et	24	−20	64/50	81

[a] Conversions determined by ^1H NMR examination of the crude reaction mixture; isolated yield of pure piperidone. [b] Determined by GC on Chiraldex G-TA column or HPLC on Chiralpak AS or Chiralcel OD columns. [c] Low isolated yields due to difficult purification. [d] Addition of 1 equivalent of $Zn(OTf)_2$.



Scheme 3 Tandem 1,4-addition-allylation.

Concerning various N-protecting groups (substrates **1a–e**, **3**), it can be concluded that the nature of this group does not affect reactivity or enantioselectivity of the 1,4-addition significantly. Similarly, only minor influence of the temperature was observed.

The fact that the primary products of conjugate additions of dialkylzinc reagents are zinc enolates offers possibilities for further functionalization.[15] Indeed, the enolate formed from **1e** and Et_2Zn was trapped in catalytic allylation using 8 mol% $Pd(PPh_3)_4$ and allyl acetate. Allylated product **5** was obtained as a single (*trans*) diastereomer in 84% ee (Scheme 3).

In conclusion, we have shown that simple alkyl groups (Me, Et, *i*Pr and Bu) can be introduced with up to 97% ee in copper/phosphoramidite-catalyzed conjugate addition of dialkylzinc reagents to *N*-protected-2,3-dehydro-4-piperidones, providing valuable substrates for alkaloid synthesis. Preliminary results indicate that the procedure is also open to tandem reactions which enables construction of more complex heterocycles.

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13 *Typical procedure for dialkylzinc addition*: $Cu(OTf)_2$ (9 mg, 0.025 mmol) and ligand (0.050 mmol) were dissolved in anhydrous toluene (1 mL) and stirred for 40 min at room temperature. To this solution was added a solution of substrate (0.50 mmol) in toluene (2 mL). To the cooled mixture a solution of R_2Zn (1.50 mmol) was added dropwise. Progress of the reaction was followed by TLC analysis and, after quenching with sat. aq. NH_4Cl (see Table 2 for reaction times), the mixture was extracted with Et_2O, combined organic extracts washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography.
14 Methylation of **1d** was performed with Me_3Al at −50 °C, and the addition product was obtained in 80% yield and 89% enantioselectivity.
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