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Tetrahedron: *Asymmetry* 15 (2004) 2575–2578

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Highly enantioselective copper-catalyzed 1,4-conjugate addition of diethylzinc to cyclic enones and α,β-unsaturated lactones

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Received 11 June 2004; accepted 8 July 2004

Abstract—A significant improvement in enantioselectivity has been achieved in the 1,4-additions of diethylzinc to 2-cyclopentenone, 2-cyclohexenone and 5,6-hydro-2H-pyran-2-one (up to 93%, 98% and 94% ee, respectively) by using a chiral diphosphite–copper catalyst under suitable reaction conditions.

1. Introduction

The enantioselective 1,4-addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds has recently become an important method for asymmetric carbon–carbon bond formation.[1,2] The stereocontrol in these reactions is of particular interest in the synthesis of biologically active compounds.[3] A number of P–N and P–O type chiral ligands have been used in the copper-catalyzed 1,4-conjugate additions of dialkylzinc reagents to enones.[4–6] Excellent enantioselectivities have been obtained using phosphorus ligands, such as phosphoramidites, oxazoline-phosphite, peptide-based phosphine and phosphite ligands and other chiral ligands (Fig. 1).[4–9] However, the application of these catalysts to the conjugate addition of dialkylzinc to 2-cyclopentenone has been less successful. The asymmetric conjugate addition of diethylzinc reagents to α,β-unsaturated lactones is also less studied.

We have recently developed a series of aryl diphosphite ligands for catalytic 1,4-conjugate addition reactions.[7] In a previous study, we found that (*R*,*R*,*R*)-**6** afforded moderate to high enantioselectivity in the 1,4-addition of diethylzinc to cyclic enones and lactones in toluene.[7a] Herein we report the improvement of this ligand through simple modifications of reaction conditions. The effects of solvent, reaction temperature, reaction procedure and loading of catalyst on enantioselectivity are studied in detail with much improved enantioselectivities being achieved.

2. Results and discussion

The Cu(OTf)$_2$ complex of ligand **6** was used as the catalyst in the conjugate addition of diethylzinc to cyclic enones and lactones (Scheme 1).

The enantioselectivity was found to be not only dependent on the order of the addition of reactants, but also strongly dependent on the choice of solvent. Initially, 2-cyclopentenone **8a** and 2-cyclohexenone **8b** were used as standard substrates to explore the optimal reaction conditions with the results listed in Table 1. The different orders of the addition of reagents in toluene gave noticeable difference in ee (Table 1, entries 1–4). However, this effect was found to be less significant in diethyl ether. Furthermore, the results obtained from using an ether solvent were consistently better than those from using toluene (Table 1, entries 5–8).

The reaction between diethylzinc and 2-cyclohexenone **8b** was further studied to find the optimal reaction conditions. In the absence of a catalyst, no ethyl transfer from diethylzinc to 2-cyclohexenone **8b** was observed.

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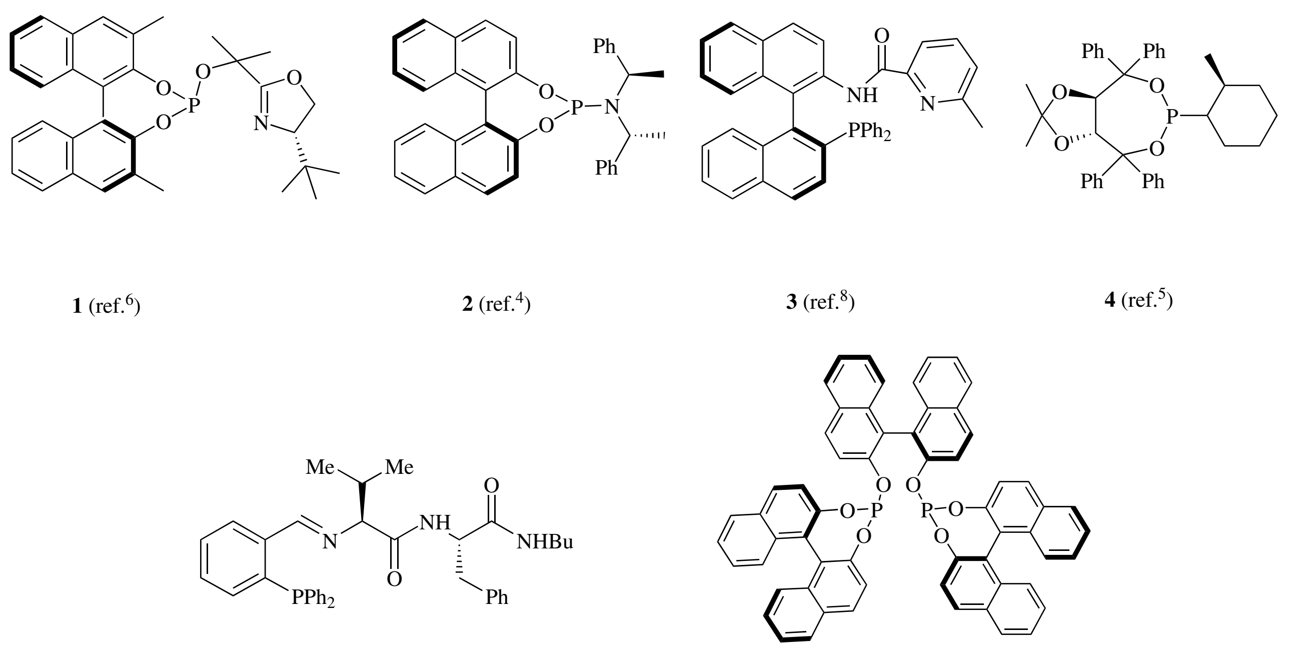
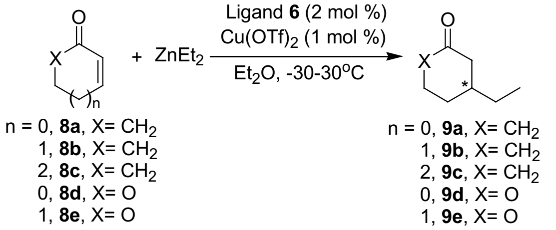
doi:10.1016/j.tetasy.2004.07.012



1 (ref.[6]) **2** (ref.[4]) **3** (ref.[8]) **4** (ref.[5])

5 (ref.[9]) **6** (ref.[7a-c])

Figure 1.



Scheme 1. Enantioselective conjugate addition of Et_2Zn to enones **8a**–**e** catalyzed by $Cu(OTf)_2$/(*R*,*R*,*R*)-**6**.

The effect of a copper source on enantioselectivity and reaction rate was significant. Using CuI as the copper source gave a much lower rate and enantioselectivity than those from using $Cu(OTf)_2$. No 1,2-addition product and other by-products were obtained. A variety of solvents were examined with diethyl ether being found to give the best results. The influence of reaction temperature on the enantioselectivity was also noticeable. At −30 °C, 98% ee was obtained (Table 2, entry 9).

By applying the improved conditions to the 1,4-addition of diethylzinc to a variety of other enones and α,β-unsaturated lactones, we found consistently better results than those previously obtained.[7a,b] The representative data obtained in the 1,4-conjugate addition of diethylzinc to 5,6-dihydro-2H-pyran-2-one, 2(5H)-furanone, 2-cyclopenten-1-one, and 2-cyclohepten-1-one, are summarized in Table 3.

In order to study further the effects of solvents and nucleophiles on the enantioselectivity of the reactions, we also carried out the conjugate addition reactions of different organometallic reagents such as $ZnMe_2$, $AlMe_3$ and $AlEt_3$ to substrates **8a**,**b** and **8c** in different reaction media (Et_2O and toluene), with the preliminary results summarized in Table 4. Combining the results in Tables 1, 2 and 4, it can be seen that diethyl ether is the pre-

Table 1. The 1,4-addition of diethylzinc to **8a** and **8b** under different conditions

Entry	Enones	Operating procedure[a,b]	Solvents	Conv.[c] (%)	Ee[c,d](%)
1	**8a**	1	Toluene	93	79
2	**8a**	2	Toluene	91	73
3	**8b**	1	Toluene	92	92
4	**8b**	2	Toluene	>99	87
5	**8a**	1	Et_2O	>99	89
6	**8a**	2	Et_2O	>99	90
7	**8b**	1	Et_2O	>99	94
8	**8b**	2	Et_2O	>99	95

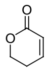
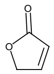
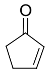
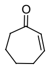
[a] Operating procedure 1 (adding order): catalyst Cu-**6**, solvent, substrate, Et_2Zn; operating procedure 2: catalyst Cu-**6**, solvent, Et_2Zn, substrate.
[b] The reactions were carried out at 0 °C for 3 h (copper/ligand/substrate/Et_2Zn = 0.01:0.02:1:1.5–2).
[c] The conversions and the ee values of **9a** were determined by GC with a Chiraldex A-TA column (50 m × 0.25 mm).
[d] The absolute configuration was determined to be *R* in all cases by comparison with previously established data.

Table 2. The effect of reaction conditions on the enantioselectivity of the 1,4-addition of diethylzinc to 2-cyclohexenone catalyzed by Cu-**6** complex

Entry	Copper source	Amount of catalyst (Cu/L)	Solvent	Temp. (°C)	Conv. (%)	Ee (%) (conf.)
1	—	—	Toluene	0	—	—
2	$Cu(OTf)_2$	—	Toluene	0	65	0
3	$Cu(OTf)_2$	1 (1:2)	Toluene	0	>99	92 (*R*)
4	CuI	1 (1:2)	Toluene	0	43	38 (*R*)
5	$Cu(OTf)_2$	1 (1:2)	Et_2O	0	>99	96 (*R*)
6	$Cu(OTf)_2$	1 (1:2)	CH_2Cl_2	0	>99	83 (*R*)
7	$Cu(OTf)_2$	1 (1:2)	Hexane	0	89	41 (*R*)
8	$Cu(OTf)_2$	1 (1:2)	Et_2O	−60	>99	92 (*R*)
9	$Cu(OTf)_2$	1 (1:2)	Et_2O	−30	>99	**98** (*R*)
10	$Cu(OTf)_2$	1 (1:2)	Et_2O	30	>99	95 (*R*)
11	$Cu(OTf)_2$	0.5 (1:1)	Et_2O	−30	90	95 (*R*)
12	$Cu(OTf)_2$	0.5 (1:2)	Et_2O	−30	>99	97 (*R*)

(1) The reactions were carried out in: enone/Et_2Zn = 1:1.5. (2) No 1,2-addition product was obtained. (3) The conversions and ee values of **9b** were determined by GC with a Chiraldex A-TA column (50 m × 0.25 mm).

Table 3. The enantioselective conjugate addition of cyclic enones and lactones catalyzed by the $Cu(OTf)_2$-**6** complex

Entry	Substrate	Temp. (°C)	Amount of ligands (mol%, Cu/L = 1/2)	Time (h)	Conv. (%)	Ee (%)
1		−50	1	24	95	94[a]
2		−30	1	28	70	87
3		−30	1	6	98	93[b]
5		−30	2	3	>99	88[c]

All reactions were carried out in Et_2O solvent; substrate/copper/**6**/Et_2Zn = 1:0.01:0.02:1.5.

[a] The conversions and the ee values of the adducts were determined by GC with a Chiraldex A-TA column (30 m × 0.25 mm).

[b] The conversions and the ee values of the adducts were determined by GC with a Chiraldex A-TA column (50 m × 0.25 mm).

[c] The conversions and the ee values of the adducts were determined by GC with a Chiraldex Diol column (30 m × 0.25 mm).

ferred solvent for the reaction when diethylzinc is used as the nucleophile.[7a,b] The reaction carried out in diethyl ether appeared to give better results than those carried out in toluene when trialkylaluminiums were used as nucleophiles. However, more experimental results are needed for a firm conclusion to be drawn.

3. Conclusion

We have demonstrated the effectiveness of Cu-**6** in the asymmetric 1,4-addition of diethylzinc to 2-cyclohexen-1-one, 2-cyclopenten-1-one, 2-cyclohepten-1-one, 5,6-dihydro-2H-pyran-2-one and 2(5H)-duranone. Using ether as the solvent significantly increased the enantioselectivity in the 1,4-conjugate addition of diethylzinc to a variety of cycloenones and lactones. The enantioselective 1,4-addition of diethylzinc to 5,6-dihydro-2H-pyran-2-one and 2(5H)-furanone has been achieved with over 94% ee and 87% ee, respectively. To the best of our knowledge, these are the best ee values achieved for these reactions to date.

4. Experimental section

Toluene and diethyl ether were distilled from sodium/benzophenone. Dichloromethane (CH_2Cl_2) was distilled over CaH_2. Triethylamine was distilled from CaH_2. PCl_3 was distilled before use. (*R*)-BINOL was dried azeotropically with toluene before use. $Cu(OTf)_2$, CuI and neat Et_2Zn were purchased from Aldrich and were without further purification. All reactions were carried out under a nitrogen atmosphere. ^{31}P, ^{1}H and ^{13}C NMR spectra were recorded on a Varian AS500 spectrometer. Mass analyses were performed on a Finnigan Model Mat 95 ST Mass spectrometer. Optical rotations were measured on a Perkin–Elmer Model 341 polarimeter. GC analyses were performed on an HP 5890 apparatus equipped with a FID.

Table 4. 1,4-Conjugate addition of dimethylzinc and trialkylaluminium to **8a**,**b** and **8e**

Entry	Substrates	Solvents	Reaction reagents	Temp. (°C)/h	Conv. (%)	Ee (%)
1	**8a**	Toluene	$AlEt_3$	10/24	95	75
2	**8a**	Et_2O	$AlEt_3$	10/24	78	46
3	**8b**	Toluene	$AlEt_3$	10/24	98	31
4	**8b**	Et_2O	$AlEt_3$	10/24	97	67
5	**8e**	Toluene	$AlMe_3$	Rt/6	72	81[a]
6	**8e**	Et_2O	$AlMe_3$	Rt/6	60	78
7	**8e**	Toluene	$ZnMe_2$	Rt/24	53	60
8	**8e**	Et_2O	$ZnMe_2$	Rt/24	60	85

[a] The conversion and ee of the products were determined by GC with a Chiraldex A-TA column (50 m × 0.25 mm).

All catalytic reactions were performed under an N_2 atmosphere on a 0.5 mmol scale. The catalysts were prepared in situ by stirring 1–2 mol% of $Cu(OTf)_2$ and 2 mol% of ligand in 3–4 mL of dry solvent for 20–30 min. The substrate (1.0 equiv) and 1.0–1.5 equiv of neat Et_2Zn were added sequentially. At the end of the reaction, the mixture was quenched with saturated NH_4Cl solution and the organic phase rinsed with water and then dried over $MgSO_4$. The conversions and ee values were directly analyzed by GC using the reaction mixture.

4.1. A typical procedure for the catalytic conjugate addition

A solution of $Cu(OTf)_2$ (0.005 mmol) and 0.01 mmol of **6** in 3 mL of diethyl ether was stirred under a nitrogen atmosphere at ambient temperature for 0.5 h. The substrate (e.g. 2-cyclohexen-1-one, 1 mmol) was added and the mixture cooled to −30 °C at which point 1.5–2.0 mmol of neat diethylzinc was added. Stirring was then continued at −30 °C for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution. The reaction solution was filtered through a thin layer of silica gel and the filtrate washed with water and then dried over $MgSO_4$. The filtrate was analyzed by GC using methods reported in the text for the determination of conversions and ee values.

Acknowledgements

We thank the Hong Kong Research Grants Council (Project number PolyU 5185/00P) and the Hong Kong Polytechnic University ASD fund for financial support of this study.

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