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Acceleration of the Conjugate Addition of Diethyl Zinc to Enones by either $Cu(OTf)_2$ or Trivalent Phosphorus Ligands

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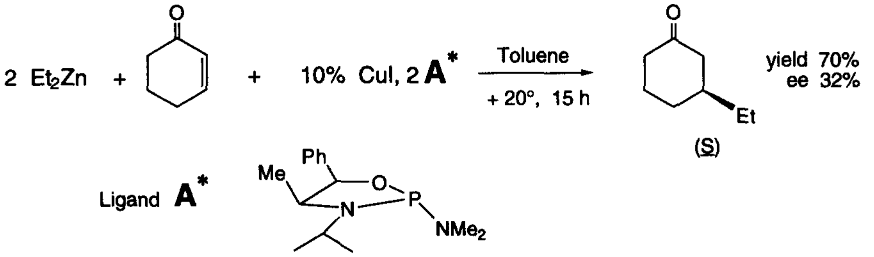
Abstract : The conjugate addition of diethyl zinc to enones under copper catalysis occurs well with copper (II) triflate. Other copper salts need a phosphine or phosphite ligand to be efficient. The best combination is copper (II) triflate and triethyl phosphite. A very small amount of copper (II) triflate (0.5%) and triehtyl phosphite (1%) are enough for high yields. © 1997 Elsevier Science Ltd.

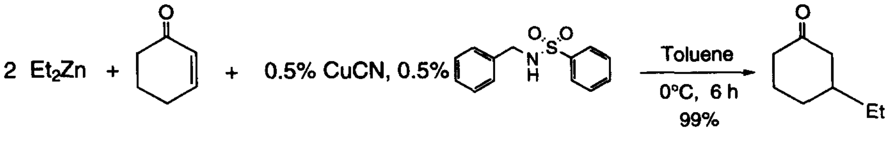
The conjugate addition reaction, an important synthetic transformation, is usually best carried out with organocopper reagents.[1] Although other organometallic reagents also promote this reaction, catalytic amounts of transition metals are usually added to improve the rate and the chemical efficiency.[2] The Cu^I catalyzed Grignard conjugate addition is the most prominent example. The fact that organozinc reagents are compatible with several functionalities makes them particularly attractive from a synthetic point of view.[3] Although their uncatalysed reaction is known,[4] Ni[5] as well as Cu[3,6] catalysis has found some synthetic applications.

In 1993, we reported the CuI catalysed conjugate addition of Et_2Zn to cyclohexenone, which, in the presence of a chiral phosphorus ligand, gave a moderate asymmetric induction (eq. 1).[7]



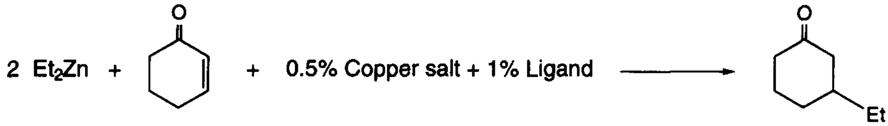
eq. 1

We were therefore astonished by the recent paper by Noyori *et al*[8] which reported that CuI (as well as other Cu salts) did not catalyse the reaction, unless a small amount of a sulfonamide was added (eq. 2).



eq. 2

The success of the reaction in our hands was probably due to the addition of a phosphorus ligand. To check this point, we undertook a study with different copper salts and various phosphorus ligands (eq. 3).



eq. 3

As shown in Table I a small amount (0.5%) of uncomplexed CuI, CuBr, CuCl or $CuCl_2$ does not catalyse the conjugate addition of Et_2Zn to cyclohexenone, in toluene solvent. However CuCN and $Cu(OTf)_2$ gave a good yield of 3-ethyl cyclohexenone after 5 h at 0°C. This is in contrast to Noyori's report.[8a] In the presence of $P(NMe_2)_3$ and, better, PBu_3 or $P(OEt)_3$ the $Cu(OTf)_2$ catalyzed reaction is over in ~ 10 min *with only 0.5% of copper salt and 1% phosphorous ligand !* Although slower, the other Cu^I salts (CuI, CuBr, CuCN) did catalyse the reaction when 1% $P(OEt)_3$ was added.

Table I : Cu catalysed (0.5%) conjugate addition of diethyl zinc to cyclohexen-2-one.

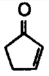
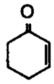
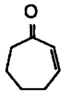
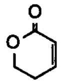
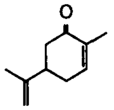
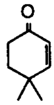
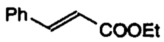
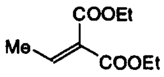
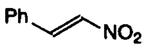
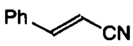
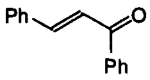
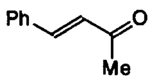
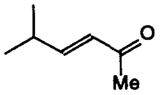
Entry	Cu salt	Ligand	Solvent	10 min 0°C^a	1 h 0°C^a	5 h 0°C^a	12 h +20°C^a
1	CuI	-	Toluene	-	-	-	-
2	CuCl	-	”	-	-	-	-
3	$CuCl_2$	-	”	-	-	-	-
4	CuCN	-	”	-	21	77	100#
5	$Cu(OTf)_2$	-	”	-	28	78	100#
6	CuCN	A*	”	52	88	100	
7	$Cu(OTf)_2$	”	”	100			
8	”	$P(NMe_2)_3$	”	74	94	100	
9	CuCN	$P(OEt)_3$	”	20	30	50	100#
10	CuOTf	”	”	67	100 (90)		
11	$Cu(OTf)_2$	PBu_3	”	100 (96)			
12	”	$P(OEt)_3$	”	100 (98)			
13	”	”	CH_2Cl_2	100 (97)			
14	”	”	Et_2O	100 (95)			
15	”	”	THF	41	100 (96)		
16	”	”	CH_3CN	23	30	36	80#
17	”	”	” + 2 TMSCl	16	27	100 (62)	

a) G.C. yields using n-decane as internal standard. Isolated yield in parenthese. # about 15-20% of aldol condensation was detected.

This dramatic acceleration may be ascribed to the solubilisation of the copper salt by the phosphine ligand, or to a different aggregation state of the transient organocopper species. The best copper salt in our hands was $Cu(OTf)_2$ (more practical and easy to handle than CuOTf) and the most convenient ligand $P(OEt)_3$. In the last entries (12-16) of Table I we compared the various solvent in which the reaction was carried out. In non coordinating solvents, such as toluene or CH_2Cl_2 and in moderately coordinating solvents such as Et_2O the reaction was over in 10 min. In more coordinating solvents, such as THF, the reaction required 1 h for completion, whereas in CH_3CN, 12 h were required. Addition of TMSCl had an accelarating effects in this latter case.

The reaction conditions disclosed above proved efficient with several other substrates (Table II).

Table II : Cu catalysed (0.5% $Cu(OTf)_2$+1% $P(OEt)_3$) conjugate addition of diethylzinc to various enones.

Entry	Substrate	Conversion	Reaction time	Additive	Isolated yield %
1		100	1 h	Ph-CHO	67
2		100	10 min	-	98
3		100	45 min	-	95
4		-	-	-	-
5		75	4 h		61
6		65	6 h	-	52
7		0	-	-	-
8		100	20 min	-	95
9		100	25 min	-	66
10		0	-	-	-
11		100	20 min	-	95
12		100	10 min	-	98
13		100	30 min	-	91

Cyclic as well as acyclic substrates smoothly undergo conjugate addition of diethylzinc. Although esters are not reactive enough, alkylidene malonates react perfectly well. Nitrostyrene is also a very good candidate. The lack of reactivity of cinnamonitrile is rather unexpected. Cyclopentenone was a particularly difficult case. The ethylation product could not be isolated in more than 20% yield despite the total disapearance of the starting material. It seems that the zinc enolate formed after conjugate addition is prone to react again with the starting enone. Addition of one equivalent of benzaldehyde *together* with cyclopentenone gave the desired mixed aldol in 67% isolated yield (as a 50:50 mixture of isomers).[8a]

With only 0.5% copper salt, the experimental protocol described herein[9] is among the most efficient conjugate addition procedures. In addition, the ligand accelerating effect offers very promising expectations for the asymmetric version of this reaction with very small amounts of chiral catalyst.

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9. Typical procedure : In a three-necked flask, containing dry toluene (5 mL), are added successively $Cu(OTf)_2$ (9 mg, 0.025 mmol) and $P(OEt)_3$ (9 µL, 0.05 mmol). The mixture is stirred for 30 min at room temperature to obtain a colourless solution. After cooling to -20°C, Et_2Zn (1M sol. in hexanes, 5mL, 5 mmol) is added followed by cyclohexen-2-one (0.48 mL, 5 mmol). The reaction is allowed to warm to 0°C (then room temperature after 6 h) and monitored by G.C. After completion, the mixture is hydrolysed with aqueous 5N HCl, extracted with Et_2O (2 x 15 mL); the organic phase is dried over $MgSO_4$ and concentrated in vacuo. The crude product is purified by column chromatography on SiO_2 (eluent Et_2O / pentane : 80 / 20).

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