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Zinc(II) Catalysed Conjugate Addition of Grignard Reagents to α,β-Unsaturated Ketones

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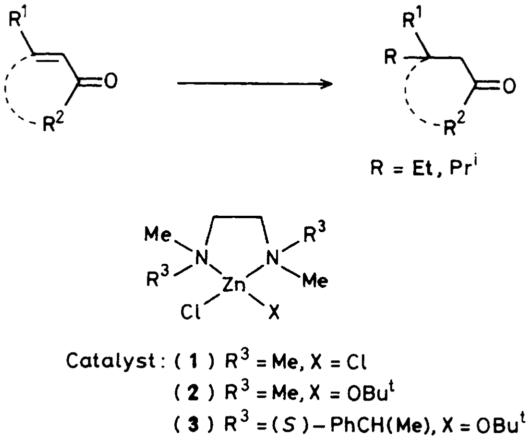
Zinc(II)–diamine complexes are efficient catalysts for the conjugate additions of Grignard reagents to various α,β-unsaturated ketones.

The conjugate addition of organocuprates,[1] and more recently organozincates[2] derived from Grignard and organolithium reagents, to α,β-enones comprises useful synthetic methodology. Considerable progress has been achieved in the use of organozincates with non-transferable ligands[2,3,4] and in enantioselective conjugate additions with organocuprates[5] and chiral copper catalysts.[6] Despite the fact that powerful copper(I) catalysed 1,4-additions have been developed[1,6] the zinc(II) catalysed addition of organometallic reagents has hardly been investigated.† We report herein the conjugate addition of Grignard reagents to α,β-enones catalysed by diamine–zinc(II) complexes.

In order to study the effect of zinc complexes in conjugate addition reactions the reaction of ethyl- and isopropyl-magnesium bromide with α,β-unsaturated ketones using 0.1 mol% of tetramethylethylenediaminezinc dichloride [(tmeda)$ZnCl_2$] (**1**) or (tmeda)Zn(OBu^t)Cl (**2**) was examined (Scheme 1). In a typical experiment Pr^iMgBr (10.5 mmol) in diethyl ether under a N_2 atmosphere was added to a solution of (**1**) or (**2**) (0.01 mmol) in tetrahydrofuran (THF). Cyclohexenone (10 mmol) was slowly added (5 min) and after 30 min the product was isolated using standard procedures.

The results of the conjugate addition with various enones are summarized in Table 1.

Several effects were observed using *catalytic amounts* (0.1 mol%) of zinc complexes at 0 °C. The isolated yields of 1,4-adducts increase substantially in all cases (Table 1). The amount of condensation products, as observed in the uncata-



Scheme 1. *Reagents and conditions*; RMgBr, THF, 0 °C, catalyst (0.1%) (**1**), (**2**), or (**3**).

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† 1,4-Additions of diethylzincate catalysed by a Ni^{II} complex have recently been reported.[10]

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Table 1. Conjugate addition of Grignard reagents to enones using (**1**) and (**2**) as catalysts.

Entry	Grignard (R in RMgBr)	Enone[a]	Catalyst (**1**)[b] 1,4/1,2 (%)[d] ratio[c]	Catalyst (**2**)[b] 1,4/1,2 (%)[d] ratio[c]
1[e]	Pr^{i}	(**4**)	[3 (25)]	
2[e,f]	Pr^{i}	(**4**)	[4.6 (25)]	
3	Pr^{i}	(**4**)	5.7 (81)	19 (88)
4	Et	(**4**)	1.0 (36)	1.4 (50)[g]
5	Pr^{i}	(**5**)	8.1 (34)	9.0 (51)
6	Et	(**5**)	0.9 (37)	1.0 (48)
7	Pr^{i}	(**6**)	7.3 (83)	13.4 (87)
8	Et	(**6**)	49 (89)	49 (91)[g]
9	Pr^{i}	(**7**)	5.7 (42)	6.1 (60)

[a] Enones: (**4**), cyclohexenone; (**5**), but-1-en-3-one; (**6**), 1-phenylbut-1-en-3-one; (**7**), cyclopentenone. [b] 0.1 mol% in all cases. [c] Ratios determined by g.l.c. [d] Isolated yields of 1,4-adduct; all compounds showed correct i.r., ^{1}H and ^{13}C n.m.r., and high resolution mass spectral data. [e] No zinc complex catalyst used. [f] Pr^{i}MgBr, tmeda, KOBu^{t}. [g] The isolation of 22% and 57% 1,4-adduct from the Grignard addition to (**4**) and (**6**) has been reported.[7]

lysed case, is consequently drastically decreased (entry 1). The regioselectivity towards the 1,4-adduct (1,4/1,2 ratio) is considerably increased in all cases using even this small amount of zinc complex; however in some cases (entries 4, 6) improvement is still required for synthetic purposes. Both the isolated yields of 1,4-adducts and the regioselectivity increase further when (tmeda)Zn(OBu^{t})Cl (**2**) is used instead of (tmeda)ZnCl$_2$ (**1**) as a catalyst.

We have previously observed a similar effect of an alkoxide as a non-transferable ligand in the stoicheiometric conjugate addition of organozincates.[3] On the basis of the results presented here it is reasonable to assume that a tmeda–dialkyl zincate in the case of (**1**) and a tmeda–monoalkylzinc-t-butoxide complex in the case of (**2**) act as the actual catalytically active species. Surprisingly the isolated yields of 1,4-adducts using catalyst (**2**) are only slightly lower than the reported results using stoicheiometric trialkylzincates[2] or mono-alkoxide substituted dialkylzincates.[3]

The preliminary results of the enantioselective catalytic conjugate addition of Pr^{i}MgBr to cyclohexenone using the chiral zinc complex (**3**) are in line with these observations. Complex (**3**) is prepared from (*S*,*S*)-*N*,*N*′-dimethyl-*N*,*N*′-bis(1-phenylethyl)-1,2-ethylenediamine.[3,8] With 1 mol% of (**3**) at 0 °C we obtained 3-isopropylcyclohexanone with an enantiomeric excess (e.e.) of 8%.‡ The e.e. was determined by ^{13}C n.m.r. of the diastereoisomeric (2*R*,3*R*)-(−)-butane-2,3-diyl acetal.[11] This result provides additional support for the catalytic role of the zinc complexes. In conclusion we have observed, as far as we know, the first conjugate addition of Grignard reagents catalysed by zinc complexes.

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‡ The optical yield compares favourably with stoicheiometric additions using a monoalkyl zinc complex derived from the same ligand[3] and with zincate additions using a chiral co-solvent.[9]