Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3161–3166

TETRAHEDRON:
ASYMMETRY

Copper-catalysed asymmetric 1,4-addition of organometallic reagents to 2-cyclohexenone using novel phosphine-phosphite ligands

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Received 22 June 2000; accepted 5 July 2000

Abstract

A series of novel non-symmetrical phosphine-phosphite ligands **1**–**10** have been tested in the copper-catalysed asymmetric addition of diethylzinc and triethylaluminium to 2-cyclohexenone. In all cases, excellent conversion and regioselectivities for the 1,4-product were found. Good enantiomeric excesses (up to 62%) were obtained when triethylaluminium was used as the alkylating reagent. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Catalytic asymmetric synthesis using organometallic reagents has become one of the most active areas of research in modern organic synthesis.[1] In this area, enantioselective conjugate addition of organometallic reagents to α,β-unsaturated compounds is a powerful tool to form carbon–carbon bonds and simultaneously introduce a new stereogenic centre in an organic molecule.[2] In most of these reactions, the addition of organolithium, Grignard and diorganozincs to enones is catalysed by copper complexes.[2] Although stoichiometric enantioselective additions have been widely studied,[2b] only a few catalytic systems have provided high enantioselectivities.[2]

Excellent enantioselectivities have been obtained in the copper-catalysed Michael addition of Grignard and diorganozinc reagents to enones and other α,β-unsaturated carbonyl compounds using phosphorus ligands[3–14] such as phosphorus amidites,[3–7] oxazoline–phosphite[8] and

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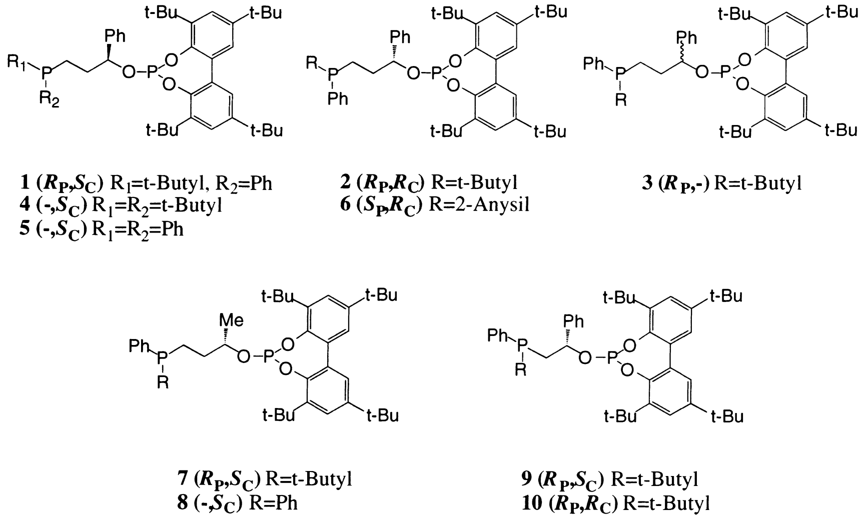
PII: S0957-4166(00)00262-7

phosphite ligands.[9–13] However, further investigations are required in order to understand how to obtain an efficient enantiocontrol in this reaction.

Van Leeuwen et al. have recently described the synthesis of a new class of chiral phosphine-phosphite ligands[15] and their successful use in asymmetric palladium-catalysed allylic alkylations (ee's up to 83%)[16] and rhodium-catalysed hydrogenations (ee's up to 99%).[17] It has also been shown that the use of these ligands, which contain different donor atoms viz. an electron-donating phosphine, an electron-withdrawing phosphite, affects the reactivity and selectivity of the catalyst.[15–17] Herein we report the use of this new class of phosphine-phosphite ligands (Fig. 1) in the enantioselective 1,4-addition of organocuprates to 2-cyclohexenone.



1 (R_P,S_C) R_1=t-Butyl, R_2=Ph
4 (-,S_C) R_1=R_2=t-Butyl
5 (-,S_C) R_1=R_2=Ph

2 (R_P,R_C) R=t-Butyl
6 (S_P,R_C) R=2-Anysil

3 (R_P,-) R=t-Butyl

7 (R_P,S_C) R=t-Butyl
8 (-,S_C) R=Ph

9 (R_P,S_C) R=t-Butyl
10 (R_P,R_C) R=t-Butyl

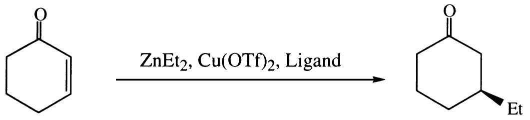
Figure 1.

This type of ligand has the advantage that many structural variations can be made that can provide information about the effects of the different stereocentres on the enantioselectivity. This study may give some insight into the origin of the stereochemistry of the reaction. The effect of the stereogenic phosphine moiety has been investigated by introducing different substituents at the phosphorus atom. The influence of the group attached to the stereogenic carbon next to the phosphite moiety and the size of the substituent have also been studied. Furthermore, we investigated the effect of the chain length using ligands **9** and **10**. To the best of our knowledge, this is the first example of the use of phosphine-phosphite ligands in the 1,4-addition of organocuprates to enones.

2. Results and discussion

We tested ligands **1**–**10** in the copper-catalysed conjugate addition of diethylzinc to 2-cyclohexenone: results are shown in Table 1. The catalytic system was generated in situ by adding 1 equivalent of the corresponding ligand to a dichloromethane solution of $Cu(OTf)_2$. Total conversions and excellent regioselectivities for the 1,4-product were found for all ligands. No 1,2-product was observed by gas chromatography.

Table 1
Catalytic conjugate addition reactions of $ZnEt_2$ to 2-cyclohexenone[a]



Entry	Ligand	T (K)	TOF[b]	%conv[c]	%1,4[d]	%ee[e]
1	(R_p,S_c)-**1**	253	660	100	100	17 (*S*)
2[f]	(R_p,S_c)-**1**	253	300	100[g]	100	17 (*S*)
3	(R_p,S_c)-**1**	273	912	100	98	11 (*S*)
4	(R_p,S_c)-**1**	298	1188	100	99	3 (*S*)
5	(R_p,S_c)-**1**	233	264	100	96	21 (*S*)
6	(R_p,R_c)-**2**	253	672	100	97	7 (*R*)
7	$(R_p,-)$-**3**	253	660	100	97	2 (*S*)
8	$(-,S_c)$-**4**	253	564	100	98	3 (*S*)
9	$(-,S_c)$-**5**	253	756	100	100	7 (*R*)
10	(S_p,R_c)-**6**	253	744	100	100	9 (*S*)
11	(R_p,S_c)-**7**	253	588	100	100	3 (*R*)
12	$(-,S_c)$-**8**	253	648	100	100	4 (*R*)
13	(R_p,S_c)-**9**	253	1164	100	99	21 (*R*)
14	(R_p,R_c)-**10**	253	1164	100	99	22 (*R*)

[a] Reaction conditions: $[Cu(OTf)_2]$ (0.025 mmol), CH_2Cl_2 (6 mL), $ZnEt_2$ (3.5 mmol), 2-cyclohexenone (2.5 mmol). [b] TOF in mol 2-cyclohexenone x mol Cu^{-1} x h^{-1} determined after 5 minutes reaction time by GC. [c]% Conversion of 2-cyclohexenenone determined by GC using undecane as internal standard after 30 minutes. [d] % Regioselectivity in 1,4-product. [e] % Enantiomeric excess measured by GC using a Lipodex A column. [f] $[Cu(OTf)_2]$ (0.05 mmol), 2-cyclohexenone (1.25 mmol) [substrate]/[Cu] = 25. [g] Conversion determined after 5 minutes reaction by GC.

The effect of the temperature and catalyst loading were studied using ligand **1**. Increasing the catalyst loadings increased the conversion but the regioselectivity for the 1,4-product and enantioselectivity were not affected (entries 1 and 2). In contrast to Cu–diphosphite catalysts,[13] better enantioselectivities were obtained at low temperature (entries 1, 3–5). Within the accuracy of these experiments, there was no change in the enantioselectivities over time. This agrees with the presence of the same aggregates during the reaction time.

By comparing the results obtained with the different substituted ligands **1**–**6**, we can conclude that the introduction of sterically demanding groups on the phosphine moiety has a negative influence on activities (TOF) (entries 1, 6–10). Using the (R_P,S_C) ligand **1** the (*S*)-product was obtained with 17% ee, whereas the diastereoisomeric (R_P,R_C) ligand **2** gave the opposite enantiomer in only 7% ee (entries 1 and 6). Apparently, both the configuration of the phosphine moiety and the configuration of the carbon next to the phosphite moiety are essential for enantiocontrol.

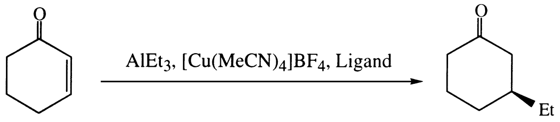
Changing the substituent of the stereogenic centre next to the phosphite influences both conversion and enantioselectivity. Ligands **7** and **8**, which contain a methyl substituent, gave lower conversions and enantioselectivities than ligands **1** and **5** with a phenyl substituent (entries 11 and 12 versus 1 and 9).

The influence of the chain length was also investigated with ligands **9** and **10**. Better conversions and enantioselectivities were observed for the more rigid ligands **9** and **10** (entries 13 and 14). Unexpectedly, and unlike the observed co-operative effect between phosphine and carbon next to the phosphite observed with related ligands **1** and **2**, changing the configuration of this stereocentre does not affect the enantioselectivity.

Although Michael additions of organolithium, Grignard and diorganozinc reagents to enones have been widely studied in the last decade,[2] very little attention has been paid to trialkylaluminium reagents.[18–20] Table 2 shows the results of the copper-catalysed conjugate addition of triethylaluminium to 2-cyclohexenone. It is noteworthy that better results have been obtained using $[Cu(MeCN)_4]BF_4$ instead of $Cu(OTf)_2$ as a catalyst precursor.

Table 2

Catalytic conjugate addition reactions of $AlEt_3$ to 2-cyclohexenone[a]



Entry	Ligand	T (K)	TOF[b]	%conv[c]	%1,4[d]	%ee[e]
1	(R_p,R_c)-**10**	253	1164	100	98	62 (*S*)
2	(R_p,R_c)-**10**	273	1200	100[f]	99	59 (*S*)
3	(R_p,S_c)-**9**	253	768	100	97	6 (*R*)
4	(R_p,S_c)-**1**	253	1200	100	100	4 (*S*)
5	(R_p,R_c)-**2**	253	1200	100	99	4 (*R*)

[a] Reaction conditions: $[Cu(MeCN)_4]BF_4$ (0.025 mmol), CH_2Cl_2 (6 mL), $AlEt_3$ (3.5 mmol), 2-cyclohexenone (2.5 mmol). [b] TOF in mol 2-cyclohexenone x mol Cu^{-1} x h^{-1} determined after 5 minutes reaction time by GC. [c] % Conversion of 2-cyclohexenenone determined by GC using undecane as internal standard after 30 minutes. [d] % Regioselectivity in 1,4-product. [e] % Enantiomeric excess measured by GC using a Lipodex A column. [f] Conversion measured after 5 minutes.

Using the (R_P,R_C) phosphine-phosphite ligand **10** excellent conversion and good enantioselectivity (up to 62%) were obtained (entry 1), whereas for the diastereoisomeric ligand **9** and related (R_P,S_C) ligand **1**, with one more carbon atom in the backbone, much lower enantioselectivities were obtained (entries 3 and 4). Moreover, by comparing the enantioselectivities from ligand **10** by using $ZnEt_2$ and $Cu(OTf)_2$ (Table 1, entry 14) and $AlEt_3$ and $[Cu(MeCN)_4]BF_4$ (Table 2, entry 1) we can conclude that for phosphine-phosphite ligands not only the configuration of the phosphine and the sterogenic centre next to the phosphite influence enantioselectivities, but that the catalyst precursor and the nature of the alkylating reagent are also important in determining enantioselectivity.

Encouraged by the promising behaviour using ligand **10**, further studies directed towards the development of an efficient ligand are in progress.

3. Experimental

3.1. Typical procedure for the catalytic conjugate addition of diethylzinc 2-cyclohexenone

In a typical procedure a solution of $Cu(OTf)_2$ (9 mg, 0.025 mmol) and phosphine-phosphite (0.025 mmol) in dichloromethane (3 mL) was stirred for 30 min at room temperature. After cooling to 273 K, diethylzinc (1 M sol. in hexanes, 3.5 mL, 3.5 mmol) was added. A solution of 2-cyclohexenone (0.24 mL, 2.5 mmol) and undecane as GC internal standard (0.25 mL) in dichloromethane (3 mL) was then added. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through flash silica gel. The conversion and enantiomeric excesses were measured by GC using a Lipodex-A column.

3.2. Typical procedure for the catalytic conjugate addition of triethylaluminium to 2-cyclohexenone

In a typical procedure triethylaluminium (1 M sol., 3.5 mL, 3.5 mmol) and enone (0.6 M sol. in CH_2Cl_2, 3.5 mL, 2.5 mmol) were introduced sequentially and in a dropwise manner over 10 min to a CH_2Cl_2 solution (3 mL) containing phosphine-phosphite (0.025 mmol) and $[Cu(MeCN)_4]BF_4$ (7.8 mg, 0.025 mmol) at 253 K. After 5 min the reaction was quenched with HCl (2 M) and undecane as GC internal standard (50 μL) was added. The organic layer was filtered twice through flash silica gel. The conversion and ee's were measured by GC using a Lipodex-A column.

Acknowledgements

We thank the Spanish Ministerio de Educación y Cultura and the Generalitat de Catalunya (CIRIT) for financial support (PB97-0407-CO5-01). Financial support from CW/STW is also gratefully acknowledged (project no. 349-3590).

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