Pergamon

Tetrahedron Letters 39 (1998) 7869–7872

TETRAHEDRON
LETTERS

Asymmetric Conjugate Addition of Diethyl Zinc to Enones with Chiral Phosphorus Ligands Derived from TADDOL

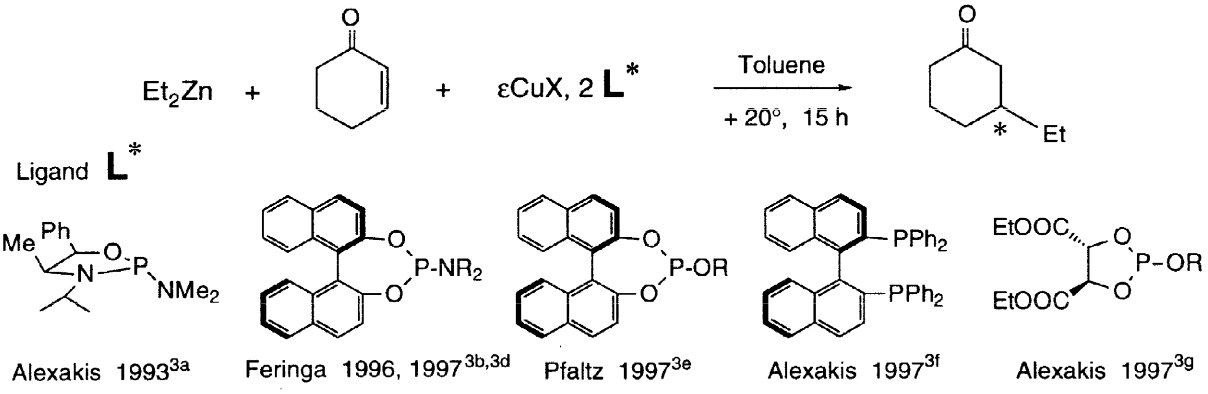
A. Alexakis*, J. Vastra, J. Burton, C. Benhaim and P. Mangeney

Département de Chimie Organique, UMR 7611 CNRS, Université Pierre et Marie Curie,
4, Place Jussieu, Tour 44-45, 2^{e} étage, Boîte 183, 75252 Paris Cedex 05, France.

Received 27 July 1998; accepted 21 August 1998

Abstract : The asymmetric conjugate addition of diethyl zinc to cyclohexen-2-one, chalcone and benzalacetone was studied with 0.5% copper (II) triflate and 1% chiral phosphorus ligands derived from TADDOL. Among the several ligand tested, the cyclic phosphite obtained with 1S,2R phenyl-cyclohexanol gave up to 96% ee of conjugate adduct to cyclohexenone. © 1998 Published by Elsevier Science Ltd. All rights reserved.

The asymmetric conjugate addition of organocopper reagents is an actively studied topic.[1] Despite several successful examples with stoichiometric chiral auxiliaries, there is a strong effort to develop catalytic version of this reaction, particularly with chiral external ligands. In these cases, the primary organometallic is either a Grignard reagent[2] or a dialkyl zinc reagent.[3] This latter possibility, introduced by us in 1993, has found an increasing popularity, and several chiral ligands have been developped since then by other authors.

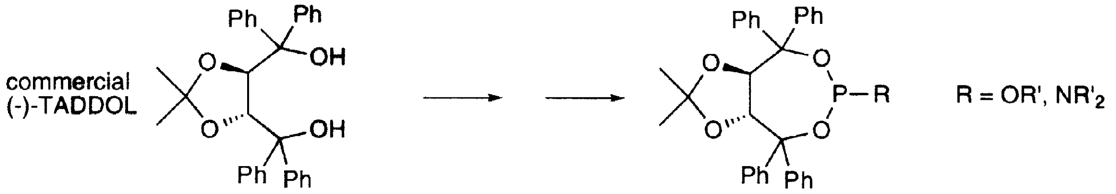


Although in our first report[3a] we used CuI as the copper source, we later found that $Cu(OTf)_2$ was a superior catalyst.[4] In addition, we showed that a trivalent phosphorus ligand had a strong accelerating effect. Hence the possibility of a *ligand accelerated asymmetric catalysis* arises when a chiral trivalent phosphorus ligand is employed. As little as 0.5% of copper salt and 1% of chiral ligand are enough for a high yield of conjugate adduct. The reaction is fast in non-coordinating solvents such as toluene or dichloromethane.[4]

As the chiral trivalent phosphorus ligand is concerned, we became also interested by another class of C2 symmetrical diols, the TADDOL's. These chiral auxiliaries were first used by Seebach's group with several impressive applications in asymmetric synthesis.[5] (-)-TADDOL is easily prepared from tartaric acid esters,[6] it is more than 10 times cheaper than chiral binaphthol,[7] and its trivalent phosphorus derivatives are

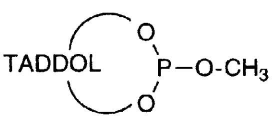
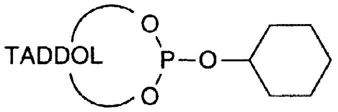
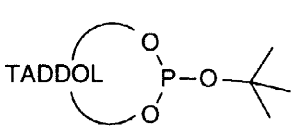
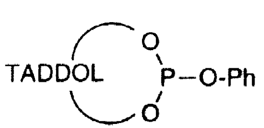
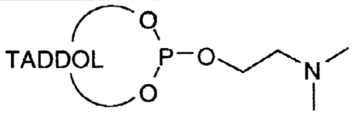
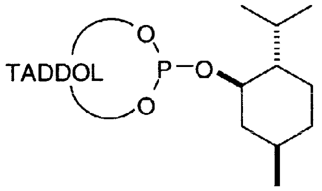
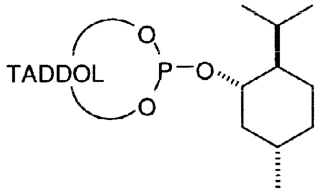
0040-4039/98/$ - see front matter © 1998 Published by Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)01761-4

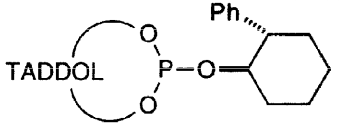
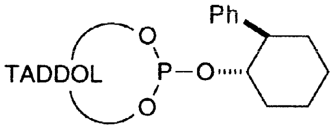
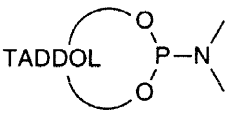
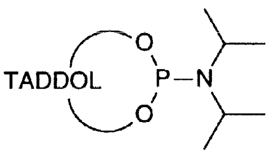
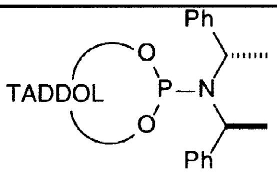
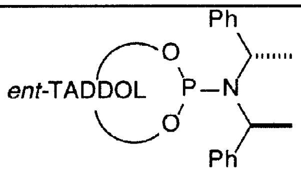
very stable towards moisture and oxidation.[8] All the ligands used in this study have the same basic skeleton. We have varied the exocyclic substituent from alcohols, to amine derivatives.



All the experiments have been performed under the same conditions, in CH_2Cl_2 as solvent, which usually affords slighly higher enantiomeric excesses than toluene. Typically, three enones were tested : cyclohexenone as representative of cyclic enones, benzalacetone as representative of acyclic s-trans enones and chalcone, the most tested one but a very atypical enone. The results are shown in the Table.

TABLE. Conjugate addition of diethylzinc with 0.5% $Cu(OTf)_2$ and 1% TADDOL phosphorus derivatives.

Entry	Ligand	Enone	Conditions	Yield[a] %	ee[b] %	Abs. Conf.
1a		cyclohexen-2-one	-20° to -10°, 3 h	93	4	S
1b		benzalacetone	-20° to -10°, 5 h	80	3	R
2a		cyclohexen-2-one	-20°, 1 h	86	18	S
3a		cyclohexen-2-one	-15°, 2 h	86	16	S
3b		benzalacetone	-10°, 9 h	<20	4	R
4a		cyclohexen-2-one	0° to r.t. 1 h	97	8	S
4b		benzalacetone	-20° to 0°, 2 h	97	5	R
5a		cyclohexen-2-one	-20° to -10°,3 h	95	13	R
5b		benzalacetone	-20° to r.t. 8 h	98	15	R
6a		cyclohexen-2-one	-20° to 10°, 1 h	95	5	S
6b		chalcone	-20° to -10°, 2 h	64	0	-
6c		benzalacetone	-20° to -10°, 7 h	<20	20	R
7a		cyclohexen-2-one	-20° to 10°, 1 h	95	50	S
7b		"	-20°, 1 h	90[c]	40[c]	S
7c		chalcone	-20° to 10°, 3 h	51	21	R
7d		benzalacetone	-10°, 6 h	<20	0	-

8a		cyclohexen-2-one	-30° to r.t. 16 h	82	0	-
8b		benzalacetone	-10° to r.t. 16 h	27	0	-
9a		cyclohexen-2-one	-30°, 3 h	92%	60	S
9b		"	-30°, 1 h	95%[c]	96[c]	S
9c		benzalacetone	-10° to r.t. 16 h	20	0	-
10a		cyclohexen-2-one	-20°, 1 h	98	35	R
10b		chalcone	-20°, 4.5 h	60	3	S
10c		benzalacetone	-20°, 4.5 h	51	10	R
11a		cyclohexen-2-one	-20°, 1 h	94	17	S
11b		chalcone	-20° to -10°, 6 h	37	13	R
11c		benzalacetone	-20° to 10°, 5 h	60	8	R
12a		cyclohexen-2-one	-20°, 1.5 h	98	15	S
12b		benzalacetone	-20° to 0°, 5 h	91	0	-
13a		cyclohexen-2-one	-20°, 50 mn	98	17	R

a. Yield of isolated adduct. For a Typical Procedure see ref. 3f or 3g.
b. Ee determined on G.C. with chiral capillary column (Lipodex E-0.2 μm, 50m, 0.25 mm).
c. Reaction performed in Toluene instead of CH_2Cl_2.

With simple, achiral, alcohol derivatives in the exocyclic position, the chirality is imposed by the TADDOL framework alone. The comparison between entries 1 and 2 or 3 shows that a bulky alcohol increases slighly the enantioselectivity. A phenoxy group gave no significant result (entry 4). In all these cases the absolute stereochemistry of the conjugate adduct is the same. With benzalacetone, all these ligands gave poor ee's. This is in striking contrast to the functionalized aminoalcohol (entry 5) which greatly enhances the rates of the reaction and the chemical yield. In addition, the ee is somewhat better with benzalacetone. Noteworthy is the *inversion* of the absolute stereochemistry of the conjugate adduct with cyclohexenone.

A more complex ligand may be prepared by combining (-)-TADDOL with a chiral exocyclic alcohol. Hence, a possibility for a matched or mismatched pair arises. Both have been tested, with menthol and phenyl-cyclohexanol, an excellent chiral auxiliaries usually much better than menthol.[9] The mismatched pairs (entries 6 and 8) gave poor ee's, whereas the matched pairs (entries 7 and 9) displays the best ee's obtained in this study (**96%**). In contrast to our previous results, the best result was obtained in toluene (entry 9a versus 9b). We ascribe this fact to a better solubilization of this particular Cu/ligand complex in toluene.

The last class of ligands examined have an amine moiety in the exocyclic position. The aim was to compare the behaviour of these ligands with the same ones, having a chiral binaphthol framework instead of TADDOL.[3b,3c] Clearly, these ligands are much less efficient and contrast strongly to their binaphthol analogues. With TADDOL, the smallest exocyclic amine gave the best ee (entry 10a). In addition, a reversal of the absolute configuration is observed. Bulky amines, the most successful in the binaphthol case,[3c] gave the lowest ee. However, all these ligands display a higher reactivity and the chemical yields are excellent.

In conclusion, we disclosed a new family of chiral phosphorus ligands, based on cheap (-)-TADDOL, which are as good (**ee 96%**) as those based on binaphtol (ee 63-98%) for the conjugate addition of diethylzinc to cyclohexenone. Work is in progress to improve and generalize these results.

References

1. (a) Rossiter, B.E.; Swingle, N.M. *Chem. Rev.* **1992**, *92*, 771. (b) Alexakis A. in *Organocopper Reagents, a practical approach*, Ed. R.J.K. Taylor, Chapt. 8 p. 159-183. Oxford University Press, **1994**. (c) Krause, N. *Ang. Chem. Int. Ed. Engl.* **1998**, *37*, 283-285.
2. (a). Villacorta, G.M.; Rao, C.P.; Lippard, S.J. *J. Am. Chem. Soc.*, **1988**, *110*, 3175-3182. (b). Ahn, K.H.; Klassen, R.B.; Lippard, S.J. *Organometallics*, **1990**, *9*, 3178-3181. (c) Lambert, F.; Knotter, D.M.; Janssen, M.D.; van Klaveren, M.; Boersma, J.; van Koten, G. *Tetrahedron : Asymmetry*, **1991**, *2*, 1097-1100. (d). Knotter, D.M.; Grove, D.M.; Smeets, W.J.J.; Spek, A.L.; van Koten, G. *J. Am. Chem. Soc.*, **1992**, *114*, 3400-3410. (e) Kanai, M.; Tomioka, K. *Tetrahedron Lett.*, **1992**, *33*, 4275-4278. (f) Kanai, M.; Tomioka, K. *Tetrahedron Lett.*, **1995**, *36*, 4273-4274. (g) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron Lett.*, **1993**, *34*, 7725-7728. (h) Stangeland, E.L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503-16510.
3. (a) Alexakis, A.; Frutos, J.C.; Mangeney, P. *Tetrahedron : Asymmetry*, **1993**, *4*, 2427-2430. (b) de Vries, A.H.M.; Meetsma, A.; Feringa, B.L. *Ang. Chem. Int. Ed. Engl.* **1996**, *35*, 2374-2376. (c) de Vries, A.H.M.; Hof, R.P.; Staal, D.; Kellog, R.M.; Feringa, B.L. *Tetrahedron: Asymmetry*, **1997**, *8*, 1539-1543. (d) Feringa, B.L.; Pineschi, M.; Arnold, L.A.; Imbos, R.; de Vries, A.H.M. *Ang. Chem. Int. Ed. Engl.* **1997**, *36*, 2620-2623. (e) Knöbel, A.K.H.; Escher, I.H.; Pfaltz, A. *Synlett* **1997**, 1429-1431. (f) Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, P. *Tetrahedron: Asymmetry*, **1997**, *8*, 3193-3196. (g) Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. *Tetrahedron: Asymmetry*, **1997**, *8*, 3987-3990.
4. Alexakis, A.; Vastra, J. Mangeney, P. *Tetrahedron Lett.*, **1997**, *38*, 7745-7748.
5. (a) Dahiden, R.; Beck, A.K.; Seebach, D. In *Encyclopedia of Reagents for Organic Synthesis*, (Paquette L.A. Ed.Wiley, Chichester, **1995** 2167. (b) Seebach, D.; Jaeschke, G.; Pichota, A.; Audergon, L. *Helv. Chim. Acta* **1997**, *80*, 2515-2519 and references cited therein.
6. Seebach, D.; Beck, A.K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954-974.
7. Acros Organics 98-99 : (+)-Binaphthol 713 FF / 1g; (-)-TADDOL 105 FF / 5g.
8. (a) Seebach, D.; Hayakawa, M.; Sakaki, J.I.; Schweizer, B. *Tetrahedron* **1993**, *49*, 1711-1724. (b) Sakaki, J.I.; Schweiser, W.B.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2654-2665.
9. Whitesell, J.K. *Chem. Rev.* **1992**, *92*, 953-964.