COMMUNICATION

ChemComm
www.rsc.org/chemcomm

BINOL catalyzed enantioselective addition of titanium phenylacetylide to aromatic ketones

Pier Giorgio Cozzi* and Silvia Alesi
Dipartimento di Chimica "G. Ciamician", Via Selmi 2, 40126 Bologna, Italy.
E-mail: piergiorgio.cozzi@unibo.it; Fax: +39 0512099456; Tel: +39 0512099511

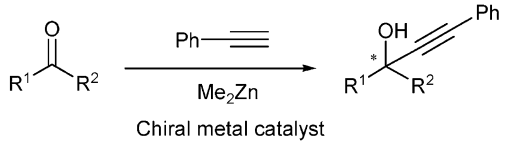
Received (in Cambridge, UK) 9th June 2004, Accepted 18th August 2004
First published as an Advance Article on the web 21st September 2004

An enantioselective addition of titanium phenylacetylide to ketones, promoted by BINOL, is described; this new enantioselective protocol gives high enantiomeric excess (up to 90% ee) with aromatic ketones using a simple procedure without pyrophoric or expensive reagents.

The enantioselective addition of organometallic reagents to ketones is complicated by their low reactivity, compared to aldehydes, and by the difficulties in performing efficient stereocontrol.[1] Therefore, only a few successful studies, concerning the enantioselective addition of diethylzinc and allylstannane to ketones, have been published.[2,3] Recently, we have reported an enantioselective alkynylation of ketones based on Zn(Salen),[4] while Chan described an efficient enantioselective alkynylation using camphorsulfonamide ligands in the presence of a strong Lewis acid $Cu(OTf_2)$.[5] In both of these methods, the alkynyl zinc species are obtained *in situ* by combining an excess of Me_2Zn with phenylacetylene (Scheme 1). Unfortunately, Me_2Zn is highly pyrophoric and expensive so that the addition of alkynides based on the use of Me_2Zn has a limited applicability.

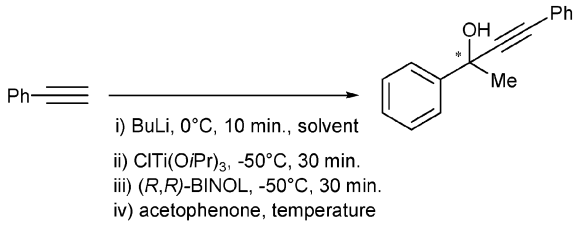
In searching for other organometallic reagents able to perform the addition of alkynides to ketones in the presence of chiral ligands, we were attracted by pioneering studies, reported by Seebach,[6] on alkynyl titanium reagents. Alkynyl titanium reagents are reactive compounds, stable at −50 °C or in the presence of coordinating electrophiles at higher temperatures, and able to react with ketones. Alkynyl titanium reagents are simply obtained by the transmetalation of lithium alkynyl derivatives with $ClTi(OiPr)_3$ at −50 °C. As mechanistic studies demonstrated the catalytic cycle involved in addition of alkyl titanium reagents to aldehyde[7] we reasoned that chiral titanium BINOL (BINOL = 1,1′-bi-2-naphthol) complexes could be used to transfer the titanium alkynyl compound to a ketone enantioselectively.

The reaction of phenylacetylene with acetophenone, taken as the model reaction, was optimized by varying different reaction parameters (Table 1). To avoid filtration at low temperatures, the alkynyl titanium reagent was prepared and used in the presence of salt (LiCl) derived from the transmetalation, and the catalytic active titanium complex was obtained by adding BINOL to the reaction mixture containing the alkynyl titanium reagent. When we had established the general procedure, the use of different solvents was investigated, performing the reaction with acetophenone at 0 °C. Based on the enantiomeric excess obtained, toluene was chosen as the solvent. The transmetalation temperature was carefully investigated. It is important to add the solution of $ClTi(OiPr)_3$ in toluene to the flask containing the lithium acetylide at −50 °C. Lower temperatures caused a partial reaction with $ClTi(OiPr)_3$, giving variable results in the enantiomeric excess recorded. Higher temperatures cause variable amounts of decomposition, while, if the addition of $ClTi(OiPr)_3$ is performed at 0 °C, the alkynyl titanium reagent decomposes instantaneously.



Scheme 1 Addition of phenylacetylene to ketone promoted by chiral catalysts.

Table 1 Enantioselective alkynylation of acetophenone catalyzed by BINOL



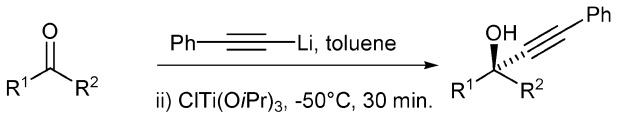
Entry[a]	*t*, hours	*T*, °C[b]	Ee %[c]	Yield[d]
1[e]	10	0	47(*S*)	98
2[e]	10	−15	62(*S*)	50
3[f]	10	0	60(*S*)	95
4[g]	10	0	64(*S*)	91
5[h]	10	0	76(*S*)	95
6[h]	10	−15	86	80
7[h]	24	−30	**89**	70
8[h]	40	−50	74	75
9[h]	40	−50	28[i]	74
10[h]	20	−15	74	74
11[h]	10	−15	43[j]	95

[a] The reactions were run using 22 mol% BINOL. [b] Reaction temperature in °C. [c] Determined by HPLC analysis. Absolute configuration was assigned according to ref. 5. [d] Conversion was measured by HPLC on the crude reaction mixture. [e] Reaction performed in THF. [f] Reaction performed in Et_2O. [g] Reaction performed in hexane. [h] Reaction performed in toluene. [i] 10 mol% BINOL was used. [j] 150 mol% $ClTi(OiPr)_3$ was used.

The formation of the active catalytic complex is obtained by stirring the titanium alkynide with BINOL (22 mol%) at −50 °C for 30 minutes. We observed the formation of an intense orange solution after 20–30 minutes. Using a co-solvent and performing the reaction at lower concentrations decreased the enantiomeric excess of the product. The use of other BINOL or TADDOLs derivatives was investigated, but similar or lower enantiomeric excess was obtained.[8] We have also briefly investigated other protocols (*i.e.* the addition of titanium–BINOL complexes prepared in another flask to the titanium alkynides, using different titanium sources) for the preparation of the active titanium complex, but the enantiomeric excess obtained in the model reactions was not improved.[9] The titanium alkynyl reagent is remarkably reactive with acetophenone, and the use of 1.3–1.6 equivalents is sufficient to ensure good conversions. The rapid background reaction required the use of 20–30 mol% BINOL as chiral ligand. Lower enantiomeric excess is recorded if this amount is decreased (Table 1, entry 9). The addition could also be performed at a lower temperature (−50 °C), but this led to a decrease in the enantiomeric excess. The results obtained in the reaction between phenylacetylene and a variety of aromatic ketones

DOI: 10.1039/b408654f

Table 2 Enantioselective alkynylation of aromatic ketones



Entry[a]	R^1	R^2	T, °C	PhCCTi(O*i*Pr)$_4$[b]	Yield[c]	ee [%][d]
1	4′-ClPh	Me	−15	1.3	48[e]	90
2	4′-ClPh	Me	−15	1.5	60[e]	86
3	4′-ClPh	Me	−45	1.8	53	88
4	4′-FPh	Me	−15	1.5	80	84
5	4′-FPh	Me	−30	1.6	84	86
6	4′-BrPh	Me	−30	1.5	28	84
7	4′-BrPh	Me	−30	1.8	50	83
8	4′-MePh	Me	−30	1.3	45[f]	85
9[e]	4′-MePh	Me	−30	1.6	62[g]	75
10	4′-MePh	Me	−30	1.8	85	71
11	4′-*t*BuPh	Me	−30	1.6	62	81
12	2′-ClPh	Me	−30	1.8	66	86
13	4′-FPh	CH_2Cl	−30	1.8	40	53
14	4′-FPh	CH_2Cl	−45	1.8	30	50
15	4′-ClPh	CH_2Br	−30	1.8	63	51

[a] All reactions were performed at the indicated temperature using 25 mol% (*R*,*R*)-BINOL as chiral ligand for 40 hours. [b] Equivalent of titanium phenylacetylides used. [c] Yields refer to product amounts after flash chromatography. [d] Determined by HPLC analysis using a chiral column. [e] Reaction time 14 hours. [f] Reaction time 20 hours. [g] Reaction time 60 hours.

catalyzed by BINOL are presented in Table 2.† Although aliphatic ketones are reactive using the present system, lower enantiomeric excess, with respect to aromatic ketones was obtained.[10] On the other hand, a variety of substituted aromatic ketones provide good results both in terms of yields and enantiomeric excess.[11] The present method is also applicable to α-halo ketones, giving access to highly functionalized building blocks, although the enantiomeric excess obtained is still not satisfactory. The reaction of aliphatic terminal titanium alkynilides with acetophenone also gave unsatisfactory enantiomeric excess (42% ee when using trimethylsilylacetylene).

To summarize, we have described a conceptually new, catalytic enantioselective addition of terminal acetylenes to ketones using titanium reagents and BINOL as the chiral ligand, through a simple procedure. The system is quite reactive, works at low temperatures and uses inexpensive, commercially available reagents. Furthermore, the use of pyrophoric zinc reagents is avoided. Further studies, in order to increase the enantiomeric excess and scope of our method through the use of different titanium catalysts, are in progress, and will be reported in due course.

P. G. Cozzi wishes to thank CNR (Rome), MIUR (Rome) "Progetto Stereoselezione in Chimica Organica. Metodologie ed Applicazioni", FIRB "Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi", and the University of Bologna "Funds for selected research topics" for the financial support of this research.

Notes and references

† **General procedure for the addition of phenylacetylene to ketone.** BuLi (1.5 mmol) was added to a solution of phenylacetylene (1.6 mmol) in toluene (1 mL) at 0 °C. Lithium phenylacetylide started to precipitate immediately. The white slurry was stirred for 10 minutes, then the flask was cooled at −50 °C. A 1 M solution of Cl(TiO*i*Pr)$_3$ in toluene (1.5 mmol) was added drop-wise to the reaction mixture. The resulting yellow solution containing un-dissolved LiCl was stirred for 30 minutes maintaining the reaction temperature between −55 °C and −50 °C. BINOL (0.25 mmol) was directly added to the mixture and the reaction was stirred for 30–45 minutes maintaining the temperature between −55 °C and −50 °C. Gradually the color of the reaction mixture turned orange. A solution of ketone (1 mmol) in toluene (0.5 ml) was slowly added drop-wise at −50 °C, and then the mixture was warmed up to −30 °C (−45 °C) and the flask was stirred at the same temperature for 40 hours. The reaction was quenched by adding water at a low temperature. The reaction mixture was diluted with Et_2O (5–8 mL) and stirred for 15 min, then it was filtered through a glass septum. The collected phases were separated and the aqueous layer was extracted with Et_2O (3 × 3 mL). The organic phases were reunited and dried over sodium sulfate. After removal of the solvent under reduced pressure, the resulting yellow oil was purified by chromatography on SiO_2.

1 (*a*) K. Fuji, *Chem. Rev.*, 1993, **93**, 2037; (*b*) E. J. Corey and A. Guzman-Perez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388; (*c*) J. Christoffers and A. Mann, *Angew. Chem., Int. Ed.*, 2001, **40**, 4591; (*d*) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2004, **43**, 284.
2 (*a*) D. J. Ramón and M. Yus, *Tetrahedron*, 1998, **54**, 5651; (*b*) P. I. Dosa and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 445; (*c*) C. García and P. J. Walsh, *Org. Lett.*, 2003, **5**, 3641; (*d*) C. García, L. K. LaRochelle and P. J. Walsh, *J. Am. Chem. Soc.*, 2002, **124**, 10970; (*e*) E. F. DiMauro and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2002, **124**, 12668; (*f*) E. F. DiMauro and M. C. Kozlowski, *Org. Lett.*, 2002, **4**, 3781; (*g*) K. Funabashi, M. Jachmann, M. Kanai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2003, **42**, 5489.
3 (*a*) S. Casolari, D. D'Addario and E. Tagliavini, *Org. Lett.*, 1999, **1**, 1061; (*b*) H. Hanawa, S. Kii and K. Maruoka, *Adv. Synth. Catal.*, 2001, **343**, 57; (*c*) A. Cunningham and S. Woodward, *SynLett*, 2002, 43; (*d*) K. M. Waltz, J. Gavenonis and P. J. Walsh, *Angew. Chem., Int. Ed.*, 2002, **41**, 3697.
4 P. G. Cozzi, *Angew. Chem., Int. Ed.*, 2003, **42**, 2895.
5 G. Lu, X. Li, X. Jia, W. L. Chan and A. S. C. Chan, *Angew. Chem., Int. Ed.*, 2003, **42**, 5057.
6 N. Krause and D. Seebach, *Chem. Ber.*, 1987, **120**, 1845.
7 J. Balsells, T. J. Davis, P. Carrol and P. J. Walsh, *J. Am. Chem. Soc.*, 2002, **124**, 10336.
8 Other BINOL derivatives give the following enantiomeric excesses in the reaction with acetophenone: 3,3′-dibromoBINOL (−15 °C, 7 hours, 63% yield, 62% ee); 6,6′-dibromoBINOL (−15 °C, 18 hours, 86% yield, 75% ee); 5,5′,6,6′,7,7′,8,8′-octahydroBINOL (−15 °C, 18 hours, 72% yield, 30% ee). TADDOL can also be used as active ligand, however, the enantiomeric excess recorded in the model reaction with acetophenone was inferior (−15 °C, 18 hours, 60% yield, 43% ee).
9 The mechanism of the present reaction probably involves a bimetallic titanium complex, in which titanium BINOL complex acts as a chiral Lewis acid coordinating ketones. For related studies, see: (*a*) K.-H. Wu and H.-M. Gau, *Organometallics*, 2004, **23**, 580; (*b*) K.-H. Wu and H.-M. Gau, *Organometallics*, 2003, **22**, 5193; (*c*) P. J. Walsh, *Acc. Chem. Res.*, 2003, **36**, 739.
10 Methyl cyclohexyl ketone (−30 °C, 40 hours, 71% yield, 40% ee); allyl methyl ketone (−50 °C, 70 hours, 60% yield, 32% ee).
11 Other aromatic ketones reacted in moderate to high yield and moderate enantioselectivity with our method: butyrophenone (−45 °C, 58% yield, 64% ee); tetralone (−30 °C, 92% yield, 60% ee); 4′-nitroacetophenone (−30 °C, 37% yield, 70% ee); 3′-cyanoacetophenone (−30 °C, 60% yield, 60% ee); acetylfuran (−30 °C, 86% yield, 35% ee).