Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5347–5349

TETRAHEDRON LETTERS

Enantioselective phenylacetylene addition to aldehydes induced by *Cinchona* alkaloids

Rajesh M. Kamble and Vinod K. Singh*

Department of Chemistry, Indian Institute of Technology, Kanpur-208 016, India

Received 25 March 2003; revised 27 April 2003; accepted 9 May 2003

Abstract—Enantioselective addition of phenylacetylene to various aldehydes was studied in the presence of inexpensive and commercially available *Cinchona* alkaloids. A maximum of 85% ee was obtained using cinchonidine in the presence of $Ti(O^iPr)_4$.

Optically active propargyl alcohols are important precursors for the synthesis of many organic compounds.[1] One of the ways to synthesize these alcohols is via enantioselective addition of metalated terminal alkynes to carbonyl compounds.[2] Thus, the addition of alkynylzinc to aldehydes in an enantioselective manner is considerable.[3] Recently, Carreira and co-workers discovered a mild and efficient method for the enantioselective addition of terminal alkynes to aldehydes using stoichiometric[4a] or catalytic[4b] amounts of $Zn(OTf)_2$ and *N*-methylephedrine. The catalytic method is suitable only for the alkynylation of aliphatic aldehydes. Ishizaki and Hoshino found that diarylaminoethanols efficiently catalyzed the addition of alkynylzinc to both aromatic as well as aliphatic aldehydes.[2c] Subsequent to this work, various efforts have been made in this field to increase the enantioselectivity using various chiral amino alcohols.[5] Chan has reported high enantioselectivity for the addition of alkynylzinc to aliphatic and aromatic aldehydes using H_8-BINOL[6] in the presence of $Ti(O^iPr)_4$ and self assembled titanium catalysts.[7] Very recently, promising results were obtained in this area by using BINOL and its derivatives.[8] Although high enantioselectivity has been obtained by the above methods, there remains a need for inexpensive, commercially available chiral ligands for any enantioselective reaction. Herein, we disclose the enantioselective addition of phenylacetylene to aromatic and aliphatic aldehydes using cinchonidine in the presence of $Ti(O^iPr)_4$.

During our initial studies, a number of chiral ligands (Fig. 1) were examined for alkynylzinc addition to benzaldehyde in the presence and absence of $Ti(O^iPr)_4$. The amino alcohol **1** and the diol **2** gave an enantiomeric excess of 10% in the presence of $Ti(O^iPr)_4$. Under the same condition, Taddol **3** gave 60% ee (Table 1, entry 3). However, the absence of $Ti(O^iPr)_4$ decreased the enantioselectivity drastically (Table 1, entry 4). The *Cinchona* alkaloids, quinidine **4** and cinchonidine **5** were also examined for the above reaction in the presence and absence of $Ti(O^iPr)_4$. These gave a maximum of 45% and 66% ee, respectively (Table 1, entries 5 and 7). Again in the absence of $Ti(O^iPr)_4$, the enantioselectivity decreased (Table 1, entries 6 and 8). In all cases, the enantioselectivity was enhanced in the presence of $Ti(O^iPr)_4$.

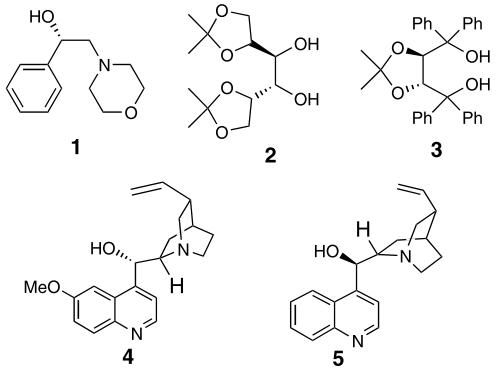


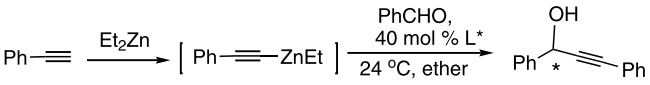
Figure 1.

Keywords: enantioselective addition; phenylacetylene; cinchonidine; aldehydes.

* Corresponding author. Fax: +91-512-597436; e-mail: vinodks@iitk.ac.in

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01196-1

Table 1. Enantioselective phenylacetylene addition to benzaldehyde



Entry	Ligand (L*)	Conditions[a]	Yield (%)	Ee (%)[b,c]
1	**1**	Et_2Zn, $Ti(O^iPr)_4$	78	10
2	**2**	Et_2Zn, $Ti(O^iPr)_4$	84	10
3	**3**	Et_2Zn, $Ti(O^iPr)_4$	85	60
4	**3**	Et_2Zn	56	4
5	**4**	Et_2Zn, $Ti(O^iPr)_4$	91	45
6	**4**	Et_2Zn	70	24
7	**5**	Et_2Zn, $Ti(O^iPr)_4$	70	66
8	**5**	Et_2Zn	60	14

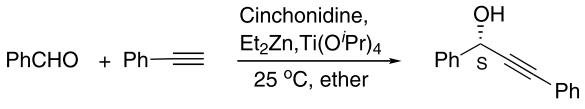
[a] Molar ratio of PhCHO:PhCCH:Et_2Zn:$Ti(O^iPr)_4$ = 1:4:4:1.
[b] % ee was determined by HPLC on chiralcel OD column.
[c] The absolute stereochemistry of the alcohol was *R* for entries 1–6, and *S* for entries 7 and 8. It was assigned by comparing its rotation.

Based on the above studies we decided to use cinchonidine as a chiral ligand for the enantioselective alkynylation of aldehydes as it is commercially available, inexpensive, stable, recoverable, and catalyzes a vast array of synthetically useful organic transformations with high enantioselectivity.[9] The addition of phenylacetylene to benzaldehyde was studied in ether under various conditions and the results are summarized in Table 2. It was observed that varying the amount of cinchonidine from 40 mol% to stoichiometric amount did not affect the enantioselectivity much (Table 2, entries 1–3). However, varying the amount of reagent did play some role. A maximum of 72% ee was obtained using 3 equiv. of the reagents and 2 equiv. of the Lewis acid (Table 2, entry 6). Lowering the temperature increased the selectivity to 77% ee (Table 2, entry 11). Addition of phenol as an additive[10] was not of any help (Table 2, entry 10). Performing the reaction in dichloromethane at −20°C increased the enantioselectivity marginally to 79% (Table 3, entry 1). So, a variety of aldehydes were subjected to alkynylation with 3 equiv. of the reagent in presence of 200 mol% of $Ti(O^iPr)_4$ at −20°C and the results are summarized in Table 3. A maximum of 85% ee was obtained in the case of 3-fluorobenzaldehyde (Table 3, entry 6). Isobutyraldehyde gave a maximum of 79% ee (Table 3, entry 11) while caprylic aldehyde gave a moderate enantioselectivity of 64% (entry 13). Further research to increase the catalytic activity and selectivity using modified cinchona alkaloids is currently under progress in our laboratory.

Acknowledgements

V.K.S. thanks DST for the Swarnajayanti fellowship project. R.M.K. thanks UGC for a research fellowship.

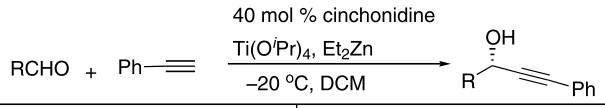
Table 2. Enantioselective phenyacetylene addition to benzaldehyde in the presence of cinchonidine and $Ti(O^iPr)_4$[a]

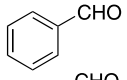
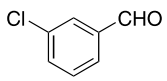
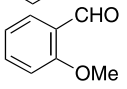
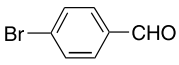
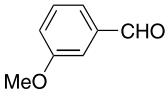
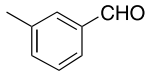
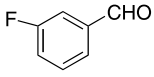
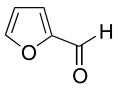
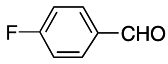
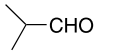
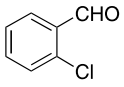


Entry	Et_2Zn:PhCCH[b]	$Ti(O^iPr)_4$ (mol%)	Cinchonidine (mol%)	Yield (%)	Ee (%)[c]
1	4:4	100	40	70	66
2	4:4	100	50	93	66
3	4:4	100	100	80	70
4	2:2	100	50	51	42
5	3:3	100	50	67	66
6	4:4	200	50	82	72
7	4:4	300	50	84	71
8	4:4	400	50	83	71
9	4:4	500	50	83	71
10	4:4	200	50	77	63[d]
11	3:3	200	40	69	77[e]

[a] A mixture of phenyacetylene (4 mmol) and Et_2Zn (4 mmol) in toluene (1 mL) was refluxed for 1 h. After cooling to rt, reaction mixture was diluted with ether (8 mL) followed by addition of cinchonidine (40 mol%) and $Ti(O^iPr)_4$ (1 mmol) and stirred for a further 1 h. Benzaldehyde (1 mmol) was added at 25°C and reaction stirred at 25°C for 6 h.
[b] Molar ratio with respect to benzaldehyde.
[c] % ee was determined by HPLC analysis using Chiralcel OD column.
[d] Phenol was used as an additive (50 mol%).
[e] Reaction carried out at −5°C.

Table 3. Enantioselective phenylacetylene addition to aldehydes in the presence of cinchonidine and $Ti(O^iPr)_4$[a]



Entry	Aldehyde	Yield (%)	ee (%)[b,c]	Entry	Aldehyde	Yield (%)	ee(%)[b,c]
1.		50	79	7.		64	80
2.		87	74	8.		23	62
3.		36	61	9.		51	79
4.		56	85	10.		75	81
5.		71	79	11.		57	79
6.		52	76	12.[d]		87	64

[a]Ratio of aldehyde:Phenylacetylene:Et_2Zn:$Ti(O^iPr)_4$ = 1:3:3:1. [b] ee was determined by HPLC using Chiralcel OD column. [c]Sense of enantioselectivity should be same as of benzaldehyde (yet to be proven). [d]Phenylacetylene:Et_2Zn:$Ti(O^iPr)_4$ in ratio 4:4:1 at 25 °C in ether for 6 h.

References

1. (a) Chun, J.; Byun, S.; Bittman, R. *J. Org. Chem.* **2003**, *68*, 348–354; (b) Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19–20; (c) Trost, B.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131–6141; (d) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 6457–6458; (e) Tombo, G. M. R.; Didier, E.; Loubinoux, B. *Synlett* **1990**, 547–548.
2. (a) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151–3152; (b) Jiang, B.; Feng, Y. *Tetrahedron Lett.* **2002**, *43*, 2975–2977; (c) Ishizaki, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1901–1904.
3. For reviews, see: (a) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, 101, 757–824; (b) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373–381.
4. (a) Frantz, E. D.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.
5. (a) Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524–1525; (b) Lu, G.; Li, X.; Zhou, Z.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2147–2152; (c) Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. *Synthesis* **1999**, 1453–1458; (d) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937–943.
6. Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002**, 172–173.
7. Li, X.; Kwok, H. W.; Chan, S. C. A. *J. Am. Chem. Soc.* **2002**, *124*, 12636–12637.
8. (a) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855–1857; (b) Gao, G.; Moore, D.; Xie, R.; Pu, L. *Org. Lett.* **2002**, *4*, 4143–4146; (c) Xu, M.; Pu, L. *Org. Lett.* **2002**, *4*, 4555–4557.
9. Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, *7*, 961–968.
10. Lu, G.; Li, X.; Chen, G.; Chan, W. L.; Chan, S. C. A. *Tetrahedron: Asymmetry* **2003**, *14*, 449–452.