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Use of an Ephedrine Alkoxide to Mediate Enantioselective Addition of an Acetylide to a Prochiral Ketone: Asymmetric Synthesis of the Reverse Transcriptase Inhibitor L-743,726.

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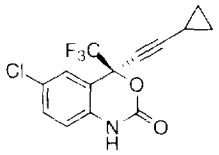
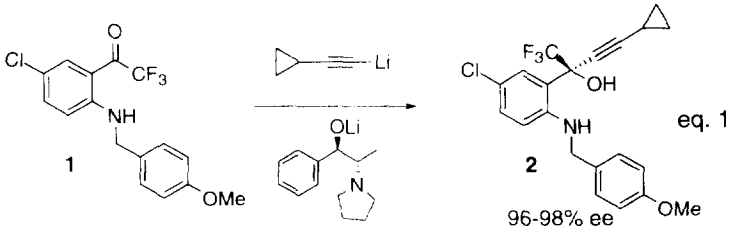
Abstract: The asymmetric synthesis of L-743,726 was achieved in six steps with an overall yield of 31%. The asymmetry was introduced using a lithiated ephedrine to mediate acetylide addition to a trifluoromethyl ketone with an enantiomeric excess of 96-98%.

The rapid development of viral resistance to nonnucleoside HIV-1 reverse transcriptase inhibitors (NNRTI) has necessitated more demanding screening methods to identify potential drug candidates. Recently, L-743,726 was chosen for development due to its potency against both wild-type HIV-1 and a panel of NNRTI-resistant mutant viruses in cell based studies.[1] In this paper we describe a highly enantioselective synthesis of L-743,726.

The key asymmetric bond forming step employs a lithium cyclopropylacetylide addition to trifluoromethyl ketone 1 in the presence of an ephedrine alkoxide, eq. 1. The stereocenter was formed with an enantiomeric excess of 96-98%. Our studies leading to the choice of ephedrine are described.



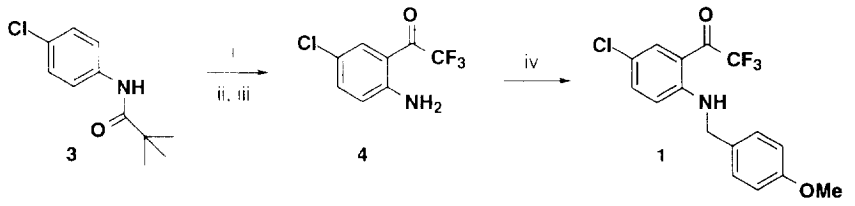
L-743,726



Ketone **1** was synthesized in four steps from N-(4-chlorophenyl) pivalamide **3**, Scheme 1. The pivalamide was ortho metallated under standard conditions[2] and the anion was quenched with ethyl trifluoroacetate.[3] The mixture, without purification, was dissolved in ethyl acetate and reacted with 1-2 equivalents of concentrated HCl at 60°C to effect pivalamide hydrolysis. As the hydrolysis proceeded, the aniline crystallized from the reaction mixture as the hydrochloride salt. Isolation by filtration afforded keto aniline **4** as the hydrochloride salt with a purity of 99%. The salt was liberated in water by adjusting the pH to 6-7.

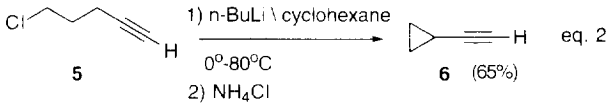
We discovered that the aniline nitrogen could be benzylated with 4-methoxybenzyl chloride using silica gel, molecular sieves or basic alumina in toluene. A procedure was developed which used basic alumina to catalyze the N-benzylation. Thus, the keto aniline **4** and basic alumina were suspended in toluene. To this mixture was added 4-methoxybenzyl chloride. The N-benzylation was complete in 4 hours at room temperature with an assay yield of 85%. After filtering the alumina and crystallization, the protected aniline **1** was isolated in 78% yield.

SCHEME 1



(i) n-BuLi / THF then ethyl trifluoroacetate. (ii) Ethyl acetate / conc. HCl (iii) adjust pH to 6-7 in water (65% from 3) (iv) 4-methoxybenzylchloride (1.1 eq.) / basic alumina / toluene (78%)

Cyclopropylacetylene was synthesized in one step from 5-chloro-1-pentyne, eq 2. All previously reported procedures to prepare cyclopropylacetylene require at least two steps.[4] Many of these reports use corrosive reagents such as PCl_5 and were not reproducible in our hands.

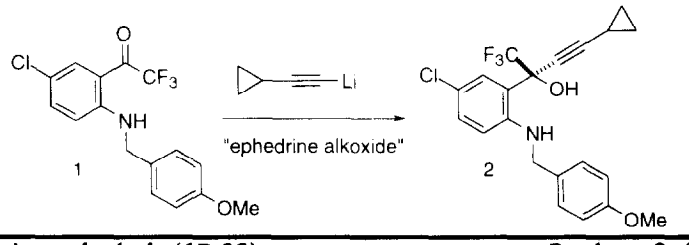


Using the precedent set by Huffman and Yasuda[5,6] we attempted to add lithium cyclopropylacetylide to ketone **1** (or **4**) in the presence of lithiated cinchona alkaloids (quinine and quinidine). Typically, these reactions were conducted by low temperature lithiation of both the acetylene and amino alcohol (at -50 C), followed by addition of ketone **1**. Under these conditions, using cinchona alkaloids, the enantiomeric excess of alcohol **2** was only in the range of 50-60%. Since the lithiated cinchona alkaloids provided only moderate levels of asymmetric induction, we turned toward ephedrine alkaloids as another class of readily accessible amino alcohols. Using commercially available N-methyl ephedrine we obtained the

addition product with a moderate ee of 55%. The work on asymmetric alkylzinc additions to aldehydes in the presence of amino alcohols, reported by Soai,[7] clearly demonstrates that the ephedrine nitrogen substituents can play an important role in the % ee of the products. We thus explored whether changes in the ephedrine nitrogen substituents would also help in our case. The results shown in Table 1 show a significant role for the ephedrine nitrogen substituents. The best ligand by far, was 1-phenyl-2-(1-pyrrolidinyl)propan-1-ol[7] (entry 5) which mediated the addition affording the product alcohol in 82% ee.

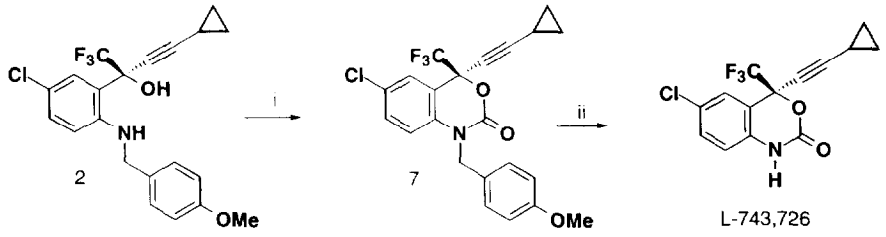
Upon optimizing the use of this amino alcohol, we noticed that lithiations performed at 0°C and then cooled to -50°C prior to adding the ketone, gave alcohol **2** of 96-98% ee. These observations were reproduced several times. *The asymmetric addition now routinely affords alcohol **2** with an optical purity of 96-98%.* Upon isolation by crystallization, the optical purity was further enriched to >99.5%.[8,9] The yield of isolated alcohol **2** was 80%.

TABLE 1 Amino Alcohol Mediated Addition to Ketone 1



Entry	Amino alcohol (1R,2S)	Product 2 (% ee)
1.	N-Methyl ephedrine	53
2.	2-(N,N-Diethylamino)-1-phenylpropan-1-ol	70
3.	2-(N,N-Di-n-propylamino)-1-phenylpropan-1-ol	59
4.	2-(N,N-Di-n-butylamino)-1-phenylpropan-1-ol	60
5.	1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol	82 (96-98 optimized: see text)
6.	1-Phenyl-2-(1-piperdinyl)propan-1-ol	72
7.	N-Methyl pseudoephedrine	35
8.	2-(1-Pyrrolidinyl)-1,2 diphenylethanol	61

The benzoxazinone was formed in 96% yield using phosgene in the presence of potassium carbonate. The product was crystallized from hexane and toluene to afford analytically pure benzoxazinone 7.



i) Phosgene / K_2CO_3 / THF (96%) ii) Ceric ammonium nitrate / CH_3CN / H_2O (85%)

The p-methoxybenzyl group was removed using ceric ammonium nitrate in acetonitrile and water. The product was purified by recrystallization from hexane and toluene to afford optically pure L-743,726 in 80% overall isolated yield from benzoxazinone **7**.

In conclusion, we have developed a highly enantioselective acetylide addition based on N-pyrrolidinyl norephedrine. We are currently studying the unusual temperature effect on the enantioselectivity of this reaction and will report our results in due course.

References

1. Young, S. D. *Perspectives in Drug Discovery and Design*, 1 **1993**, 181. Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carrol, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I.-W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrobial Agents and Chemotherapy*, submitted for publication.
2. Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, 1133.
3. Begue, J.-P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, 3207.
4. Schoberth, W.; Hanack, M. *Synthesis* **1972**, 703. Hudson, C. E.; Bauld, N. L. *J. Am. Chem. Soc.* **1972**, 1158. Salaun, J. *J. Org. Chem.* **1976**, 1237. Militzer, H.-C.; Schömenauer, S.; Otte, C.; Puls, C.; Hain, J.; Bräse, S.; de Meijere, A. *Synthesis* **1993**, 998.
5. Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, 1590.
6. Asymmetric acetylide additions to *aldehydes* have been reported previously: Mukaiyama, T.; Suzuki, K., *Chemistry Letters* **1980**, 255. Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chemistry Letters* **1979**, 447. Ye, M.; Logaraj, S.; Jackman, L.M.; Hillegass, K.; Hirsh, K.A.; Bollinger, A.M.; Grosz, A.L.; Mani, V. *Tetrahedron* **1994**, 6109.
7. Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, 4264. Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. I* **1990**, 993.
8. **Experimental Conditions:**
The (1R,2S)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (33 g, 161 mmol) was dissolved in dry THF (140 mL) and cooled to -15°C. To the mixture at -15°C under N_2 was added neat cyclopropyl-acetylene (15.0 mL at ca, 90% purity, 160 mmol) and n-butyllithium (2.5M in hexanes, 125 mL, 312 mmol) dropwise. The mixture was aged at -5° to 0°C for 30 minutes, then cooled to -55°C. The ketone (25 gm, 72.8 mmol) in THF (60 mL) was added to the lithiated mixture over 5 minutes. The resulting light orange solution was stirred at -55°C for 1 hour and quenched by adding 1M citric acid (125 mL) and ethyl acetate (180 mL). The reaction was warmed to ambient temperature and the layers were separated. The organic layer was washed with 1M citric acid (125mL). The product was shown to be 96% ee by chiral HPLC.
   Chiral HPLC conditions [Chiralpak AD column, hexane:isopropanol 85:15 isocratic elution, flow=1.0 ml/min, UV detection at 252 nm] st. material t_R=4.9 min., major enantiomer t_R=5.5 min., minor enantiomer t_R=25.0 min
The batch was concentrated in vacuo and recrystallized from hexane:ethyl acetate (10:1) to afford 24 g (80%) of an off white crystalline free flowing powder. This solid had an enantiomeric excess of >99.5% ee.
9. The reaction was tolerant of changes in the acetylide structure. Thus, 1-hexyne, phenylacetylene and TMS acetylene all underwent the asymmetric addition to ketone **1**. The optical purities were greater than 90% in these cases. However, addition to benzaldehyde or trifluoroacetophenone afforded alcohols in the range of 50-70% ee.

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