Tetrahedron Letters, Vol. 33, No. 26, pp. 3715-3716, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Preparation and Reactions of Chiral Propargylic Amines

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Abstract: *Exposure of chiral amino aldehydes (1) to dimethyl diazophosphonate (4) affords propargylic amines (2) of high optical purity. Chain extension of these intermediates is readily accomplished via hydrozirconation of the acetylene moiety and subsequent Ni(II) catalyzed Michael addition to a variety of Michael acceptors.*

Substituted chiral allylic amines are not only useful synthetic intermediates,[1] but also potentially useful peptide isosteres.[2] Herein, we report a protocol to convert amino aldehydes directly into substituted, chiral allylic amines via the intermediacy of propargylic amines[3,4] of high optical purity.

The amino aldehydes (1) were prepared via the method of Castro.[5] Thus, exposure of N-substituted amino acids to N,O-dimethyl hydroxylamine in the presence of a variety of activating agents affords the corresponding amide, which in turn is converted into the starting N-blocked amino aldehyde by low temperature LAH reduction. The propargylic amines (2) are prepared in high yield (see Table 1) in one step from the amino aldehydes (1) by exposure to dimethyl diazophosphonate (4)[6] (Scheme I). The optical purity of the resulting acetylenes (2) was assessed by measurement of NMR nonequivalence of the corresponding diastereomeric Mosher's amides[7] and the optical purities of these targets ranged from 93% to 97%. It is interesting to note that the diazophosphonate addition occurs without racemization. The optical purity of the starting aldehydes, as assessed by rotation, and the optical purity of the blocked propargyl amines, as assessed by NMR analysis of Mosher's amides, were essentially identical; therefore, the diazophosphonate addition occurs without racemization.

The blocked acetylenes are very useful synthetic intermediates, that readily undergo chain extension. For example, exposure of 2 to the Schwartz[8] reagent, which was prepared via the *in situ* procedure developed by Lipshutz,[9] provides the *trans* vinyl zirconium species. The organometallic is either quenched with iodine affording the *trans* vinyl iodide[10] (**3a-3d**, Scheme I, Table 1) or, alternatively, the vinyl zirconium intermediate is chain extended by Ni(II) catalyzed conjugate addition to both cyclic and acyclic Michael acceptors (see Table 1, entries **3e-3h**).[11]

Scheme I. Preparation and Hydrozirconation of Chiral Propargyl Amino Compounds.

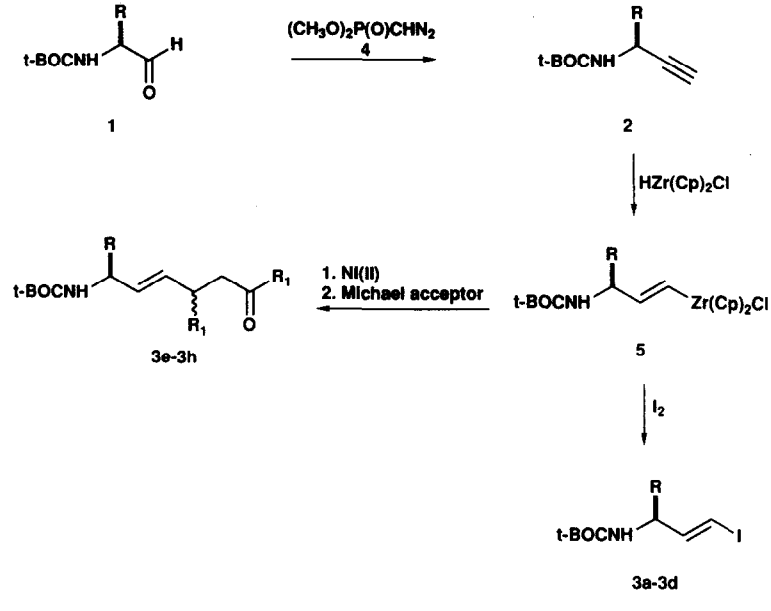
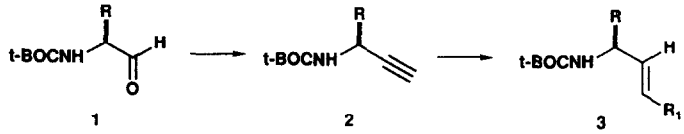


Table I. Diazophosphonate Addition and Chain Extension of Aldehyde 1.



1 2 3

Compound No.	R	R_1	Yield (%)	[α]°	% ee	diastereomeric ratio
2a	CH_3	—	67	-71.0		
2b	$(CH_3)_2CH$-	—	76	-59.9	96	
2c	$C_6H_5CH_2$-	—	85	-14.1	96	
2d	-$(CH_2)_4$NHCBZ	—	73	-23.1		
2e	-$CH_2C_6H_4OCH_2C_6H_5$	—	73	-91.8		
2f	-$CH_2OCH_2C_6H_5$	—	77	-19.5	93	
2g	$(CH_3)_2CHCH_2$-	—	76	-55.7	97	
3a	CH_3-	I	40	-59.0		
3b	$(CH_3)_2CH$-	I	51	-54.7		
3c	$C_6H_5CH_2$-	I	46	-17.8		
3d	-$(CH_2)_4$NHCBZ	I	43	-35.0		
3e	$(CH_3)_2CH$-	-$CH(CH_3)CH_2C(O)CH_3$	38	—		1:1
3f	$(CH_3)_2CH$-	-$CHCH_2C(O)CH_2CH_2$]	51	—		2:1
3g	$(CH_3)_2CH$-	-$CHCH_2C(O)OCH_2CH_2$]	54	—		2:1
3h	-$(CH_2)_4$NHCBZ	-$CHCH_2C(O)OCH_2CH_2$]	20	—		1:1

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(Received in USA 15 January 1992; accepted 9 April 1992)