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Synthesis of Enantioenriched Propargylic Alcohols Related to Polyketide Natural Products. A Comparison of Methodologies

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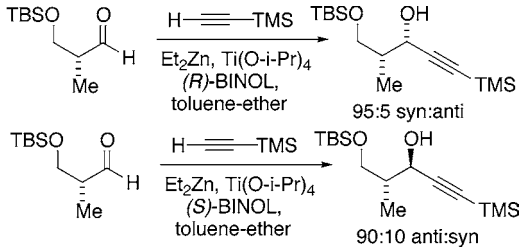
ABSTRACT



Applications of methodology for the synthesis of propargylic alcohols related to polyketide natural products were examined. Noyori's asymmetric transfer hydrogenation of α-chiral alkynones was found to be highly selective and catalyst controlled. Additions of TMS acetylene to α-chiral aldehydes, catalyzed by a Ti(*O-i*-Pr)$_4$–BINOL complex, were diastereoselective but substrate dependent.

In connection with a projected synthesis of polyketide natural products in the cytostatin family,[1] we required methodology to access enantiopure propargylic alcohols as illustrated in Figure 1 (**A**→**B** and **C**→**D**). Although a number of highly promising methods for enantioselective additions of alkynes to achiral aldehydes have recently appeared,[2−5] the important issue of substrate/reagent matching and mismatching has not been examined for these reactions. Accordingly, we initiated a study on the applicability of recently reported methodology for the addition of alkynes to various 3-alkoxy-2-methylpropanal derivatives (**1**) and several homologues.

Initial studies were conducted with the (*R*)-OTBS aldehyde **1a**[6] and TMS acetylene. The addition of TES and TMS

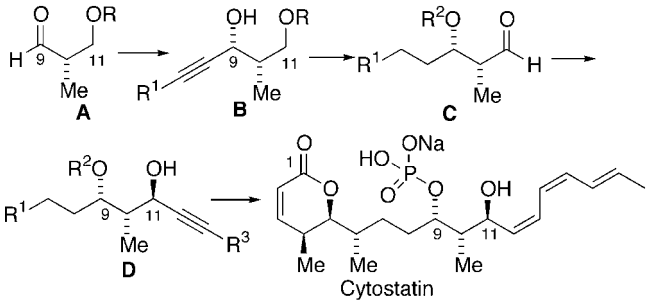


Figure 1. Synthetic plan for cytostatin and related polyketide natural products.

(1) Structure and Isolation: Amemiya, M.; Ueno, M.; Osono, M.; Masuda, T.; Kinoshita, N.; Nishida, C.; Hamada, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 536. Synthesis: Bialy, L.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1748.

(2) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605.

(3) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855. Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143. Xu, M.-H. Pu, L. *Org. Lett.* **2002**, *4*, 4555.

(4) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336.

(5) Braga, A. L.; Appelt, H. R.; Silveira, C. C.; Wessjohann, L. A.; Schneider, P. H. *Tetrahedron* **2002**, *58*, 10413.

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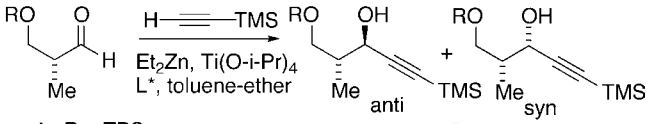
acetylene to cyclohexanecarboxaldehyde in the presence of $Zn(OTf)_2$ and (+)-*N*-methylephedrine has been reported by Carreira and co-workers to proceed in 85−90% yield to afford the (*R*)-adduct of 95−96% ee.[2] However, when we applied this procedure to aldehyde **1a**, no product could be detected; only starting aldehyde was recovered. The use of the enantiomeric ligand, (−)-*N*-methylephedrine, afforded no improvement, thus ruling out the possibility of a significant substrate/reagent mismatch. We also examined the use of THF and methylene chloride as solvents and Hunig's base as a replacement for triethylamine without success. In contrast, we were able to effect addition to cyclohexanecarboxaldehyde in 80% yield to afford the propargylic alcohol adduct of 90% enantiopurity. As the Carreira methodology has been found to succeed with α-branched aldehydes and TIPS-protected *β*-oxygenated aldehydes, we are unable to explain our lack of success.

We next examined the BINOL-based methodology of Pu et al.[3] Treatment of aldehyde **1a** with (*S*)-BINOL (40 mol %), $Ti(OiPr)_4$ (1 equiv), Et_2Zn (4 equiv), and TMS acetylene (4 equiv) afforded the adduct in 73% yield as a 90:10 mixture of the anti and syn isomers **2a** and **3a**, respectively (Table 1, entry 1). The same reaction with (*R*)-BINOL as the chiral

Table 1. Additions of TMS Acetylene to Aldehydes **1a** and **1b** Catalyzed by (*S*)- and (*R*)-Binol



entry	R	L*	yield, %	anti:syn
1	TBS (**1a**)	(*S*)-BINOL	73	90:10
2	TBS (**1a**)	(*R*)-BINOL	67	5:95
3	TBS (**1a**)	none	45	40:60
4	PMB (**1b**)	(*S*)-BINOL	73	85:15
5	PMB (**1b**)	(*R*)-BINOL	63	12:88

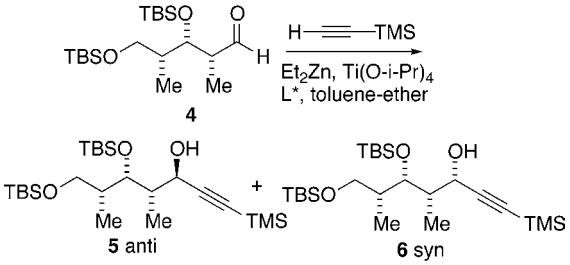
ligand gave a 5:95 mixture of these two adducts in 67% yield (entry 2). When this addition was conducted in the absence of BINOL, a 40:60 mixture of anti and syn adducts was obtained in 45% yield (entry 3). These ratios reveal a slight Felkin−Anh (syn) preference for additions to aldehyde **1a** with a resultant enhancement of the syn adduct in the matched pairing. The PMB-protected aldehyde **1b** showed similar, but slightly lower, diastereoselectivity. The stereochemistry of adducts **2** and **3** was deduced through *O*-methyl mandelic ester analysis.[7]

Additions to the stereotriad aldehydes **4** and **7** proved to be less selective.[8] In the case of the syn,syn aldehyde **4**, the

(6) Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817.

(7) Latypov, S. K.; Seco, J. M.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.

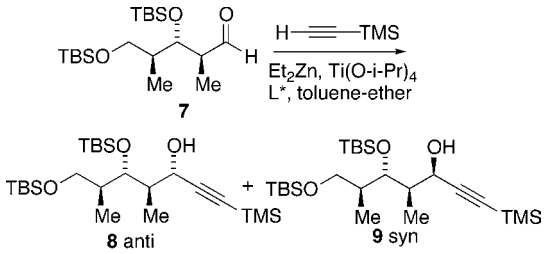
Table 2. Additions of TMS Acetylene to the Syn,Syn Aldehyde **4** Catalyzed by (*S*)- and (*R*)-Binol



L*	yield, %	anti:syn
(*S*)-BINOL	92	60:40
(*R*)-BINOL	85	12:88
none	56	33:67

Felkin−Anh directing effect was more pronounced than that of aldehyde **1a** (Table 2). This effect might account for diminished reagent control seen in the mismatched addition with the (*S*)-BINOL ligand. However, the syn:anti ratio for the matched addition with the (*R*)-BINOL ligand was less than might be expected from consideration of the product ratio from the reaction without added BINOL. The anti,anti aldehyde **7** also showed relatively modest diastereoselectivity for the alkyne additions (Table 3). However, in all cases,

Table 3. Additions of TMS Acetylene to the Anti,Anti Aldehyde **7** Catalyzed by (*S*)- and (*R*)-Binol



L*	yield, %	anti:syn
(*S*)-BINOL	59	25:75
(*R*)-BINOL	59	85:15
none	71	55:45

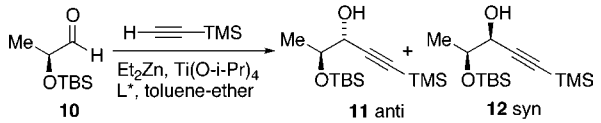
the major adducts were the result of reagent control in which the (*S*)-BINOL-mediated additions favored the formation of the (*R*)-propargylic alcohol and vice-versa. As before, the alcohol stereochemistry was verified by analysis of the *O*-methyl mandelates.[7]

Although not directly related to our current objective, we also examined additions to the OTBS-protected (*S*)-lactic aldehyde **10** (Table 4).[9] In this case, a significant stereodifferentiation was noted. The addition with the (*S*)-BINOL

(8) Preparation of these aldehydes is described in Supporting Information.

(9) Marshall, J. A.; Chobanian, H. R. *J. Org. Chem.* **2000**, *65*, 8357.

Table 4. Additions of TMS Acetylene to the Lactic Aldehyde **10** Catalyzed by (*S*)- and (*R*)-Binol

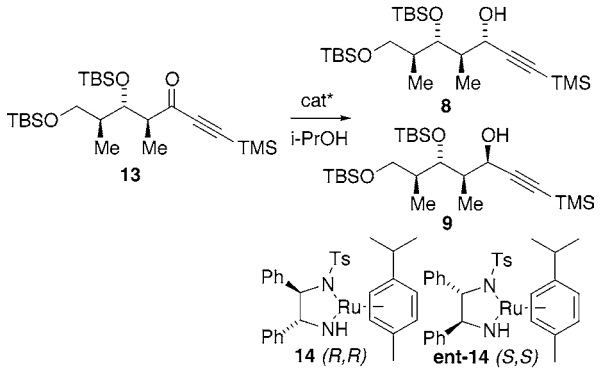


L*	yield, %	anti:syn
(*S*)-BINOL	55	45:55
(*R*)-BINOL	60	92:8
none	45	85:15

ligand afforded a nearly 1:1 mixture of anti and syn adducts **11** and **12**, respectively, whereas with the (*R*)-BINOL ligand a 92:8 mixture favoring the anti adduct was formed. As expected, the addition reaction strongly favored the anti adduct **11** in the absence of BINOL. These results are consistent with a Felkin−Anh transition state in which substrate control is dominant.

To complete these studies, we explored Noyori's asymmetric transfer hydrogenation[10] of the alkynyl ketones **13** and **21** related to our intended application. The former ketone was prepared by oxidation of the previously obtained mixtures of alcohols **8** and **9**. Reduction of ketone **13** with the (*R*,*R*)-catalyst **14** afforded the syn alcohol **9** as the sole detectable stereoisomer in 76% yield (Table 5). The use of

Table 5. Noyori Asymmetric Transfer Hydrogenation of Ketone **13** Leading to Alcohols **8** and **9**



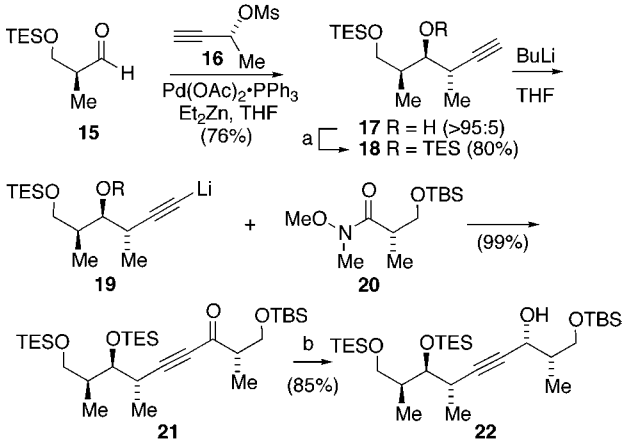
catalyst*	yield, %	**8**:**9**
14	76	<5:95
ent-**14**	73	>95:5

the (*S*,*S*)-catalyst led to the anti alcohol **8** with equally high diastereoselectivity.

A more complex application of the Noyori methodology, and one more closely related to our cytostatin target, is the reduction of ketone **21**. This substrate was prepared by addition of the lithio alkyne **19**, derived from the allenylzinc

(10) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

Scheme 1. Synthesis of Ketone **21** and Its Reduction to the Syn Alcohol **22**[a]



[a] Reaction conditons: (a) TESOTf, 2,6-lutidine, CH_2Cl_2 (80%); (b) **14** (5 mol%), *i*-PrOH (85%).

adduct **18**, to the known Weinreb amide **20**[11] as shown in Scheme 1. Transfer hydrogenation, as before, in the presence of the (*R*,*R*)-catalyst **14** afforded the syn alcohol **22** as the sole product in 85% yield. This reduction and those depicted in Table 5 represent some of the most structurally complex applications of the Noyori reduction yet reported.[12]

Our findings suggest that the Noyori asymmetric transfer hydrogenation of chiral alkynyl ketones is not highly sensitive to substrate stereochemistry, even with relatively complex ketones such as **13** and **21**. The BINOL−Ti(*O*-*i*-Pr)$_4$-catalyzed additions, on the other hand, are significantly substrate dependent. Even so, the major isomers formed in both the matched and mismatched additions are those expected from reagent control. In contrast, the alkynyl reagents involved in the Zn(OTf)$_2$-*N*-methylephedrine-catalyzed additions appear to be markedly less reactive. The reactivity differences between the two alkynyl reagents may be related to the nature of the respective metal−alkyne complexes. The latter reaction proceeds by alkyne transfer to the aldehyde from an alkynylzinc complex, whereas the former involves an alkynyltitanium intermediate.[4]

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Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034918H

(11) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.

(12) Previous applications have been directed to the 1,3-diol segments of taurospongin A and fostriecin: Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624. Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667. Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733.